
Effect of QRS Morphology and Duration on Clinical Outcomes After Cardiac Resynchronization Therapy
— Analysis of Japanese Multicenter Registry —

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Background: QRS duration (QRSd) and morphology are established response predictors of cardiac resynchronization therapy (CRT). However, evidence in Japanese populations is lacking.

Methods and Results: We retrospectively analyzed the Japanese multicenter CRT database. We divided patients according to their intrinsic QRSd and morphology, and assessed echocardiographic responses and clinical outcomes. The primary endpoint was a composite of all-cause death or hospitalization because of heart failure. A total of 510 patients were enrolled: 200 (39%) had left bundle branch block (LBBB) and QRSd ≥150 ms; 80 (16%) had LBBB (QRSd: 120–149 ms); 61 (12%) had non-LBBB (NLBBB) (QRSd: ≥150 ms); 54 (11%) had NLBBB (QRSd: 120–149 ms); 115 (23%), narrow (<120 ms). The proportion of echocardiographic responders was higher in LBBB (QRSd ≥150 ms) [74% vs. 51% vs. 38% vs. 52% vs. 50%, LBBB (QRSd ≥150 ms) vs. LBBB (QRSd 120–149 ms) vs. NLBBB (QRSd ≥150 ms) vs. NLBBB (QRSd 120–149 ms) vs. narrow, respectively, P<0.001]. During follow-up (3.2±1.5 years), the incidence of the primary endpoint was lowest in the LBBB group (QRSd ≥150) (28.6% vs. 42.3% vs. 45.9% vs. 55.6% vs. 55.3%, respectively, P<0.001). This difference was still significant after adjusting for other baseline characteristics.

Conclusions: In this Japanese patient population, LBBB intrinsic QRS morphology and prolonged QRSd (≥150 ms) exhibited the best response to CRT.

Key Words: Cardiac resynchronization therapy; Heart failure; Intrinsic QRS morphology; QRS duration; Treatment outcome
QRS morphology (LBBB or non-LBBB (NLBBB)) and duration of QRS complex (≥150 ms, 120–149 ms, or <120 ms) to investigate the proportion of echocardiographic responders and the 5-year clinical outcomes.

Methods

CUBIC Registry
This study was a retrospective analysis of cases in the CRT Utilization by Interventional Cardiologists registry (CUBIC). The CUBIC registry is a Japanese multicenter registry of 995 patients who underwent CRT-pacemaker (CRT-P) or CRT-defibrillator (CRT-D) implantation at 11 institutions. Originally, the CUBIC registry was established as part of the CUBIC trial, which investigated the differences in clinical outcomes and responses to CRT between patients with ischemic and those with non-ischemic cardiomyopathy (ICM). All patients who underwent CRT implantation and gave written informed consent for the CUBIC study were included. In principle, the CRT indication of each patient was determined on the basis of the degree of LV dysfunction, New York Heart Association (NYHA) functional class, QRSd and optimal pharmacological therapy. Exclusion for prospectively enrolled cases was at the discretion of the doctors. A total of 307 patients who underwent device implantation between May, 2008 and November, 2010 were prospectively enrolled and followed up for >1.5 years, and 688 patients who underwent device implantation between April, 2004 and September, 2008 were retrospectively enrolled and followed up for up to 5 years. The protocol was approved by the institutional review board at each participating center, and all patients gave informed consent for anonymous use of their data.

Patients
We identified 995 patients and included only those with available information of baseline ECG and complete echocardiographic datasets at 6–12 months after implantation (Figure 1). The echocardiographic data were analyzed in a core laboratory. Because of incomplete echocardiography dataset and baseline ECG, 321 patients were excluded. Additionally, 164 patients who underwent CRT following right ventricular pacing were also excluded. Based on the intrinsic QRS morphology, the remaining 510 patients were divided into groups with LBBB, right bundle branch block (RBBB), intraventricular conduction delay (IVCD), and narrow QRS complex (QRSd <120 ms). RBBB and IVCD were combined into NLBBB. Subsequently, based on QRSd, LBBB and NLBBB were further subdivided into LBBB with QRSd ≥150 ms, LBBB with QRSd: 120–149 ms, NLBBB with QRSd ≥150 ms, and NLBBB with QRSd: 120–149 ms.

The intrinsic QRS morphology in LBBB was defined by the following criteria: (1) broad, notched R-waves in lateral precordial leads (V5 and V6) and usually leads I and aVL, (2) small or absent initial r waves in the right precordial leads (V1 and V2) followed by deep S waves, (3) absent septal q waves in the left-sided leads, and (4) QRSd ≥120 ms. RBBB was defined with the following criteria: (1) broad, notched R-waves (rsr', rsR' or rsR' patterns) in the right precordial leads (V1 and V2), (2) wide
Proportion of Echocardiographic Responders and Clinical Outcomes of Each Group

We defined echocardiographic responders as patients with a relative reduction of left ventricular end-systolic volume (LVESV) ≥15% at 6–12 months after CRT implantation.24

<table>
<thead>
<tr>
<th>Intrinsic QRS morphology</th>
<th>LBBB*</th>
<th>LBBB</th>
<th>NLBBB*</th>
<th>NLBBB</th>
<th>Narrow</th>
<th>No. of patients</th>
<th>CRT-D, %</th>
<th>Female sex</th>
<th>Age, years</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>NYHA functional class III and IV</th>
<th>Non-ICM</th>
<th>Medical comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration (ms)</td>
<td>≥150</td>
<td>120–149</td>
<td>≥150</td>
<td>120–149</td>
<td>&lt;120</td>
<td>200</td>
<td>80</td>
<td>61</td>
<td>54</td>
<td>115</td>
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<td>154</td>
<td>Hypertension</td>
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<td>No. of patients</td>
<td></td>
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<td></td>
<td>129 (66%)</td>
<td>60 (75%)</td>
<td>44 (72%)</td>
<td>45 (83%)</td>
<td>95 (83%)</td>
<td>0.003</td>
<td>75 (38%)</td>
<td>24 (30%)</td>
<td>13 (21%)</td>
<td>11 (20%)</td>
<td>23 (20%)</td>
<td>0.004</td>
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<tr>
<td>Age, years</td>
<td>69±11.1</td>
<td>69±9.6</td>
<td>67±11.2</td>
<td>64±11.9</td>
<td>65±12.6</td>
<td>0.003</td>
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<td>Height, cm</td>
<td>158.9±9.5</td>
<td>157.7±19.9</td>
<td>159.9±22.5</td>
<td>163.3±8.2</td>
<td>161.4±8.3</td>
<td>0.10</td>
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<tr>
<td>Weight, kg</td>
<td>57.4±12.5</td>
<td>58.0±11.0</td>
<td>58.1±12.1</td>
<td>61.5±13.9</td>
<td>58.3±12.0</td>
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<td>BMI, kg/m²</td>
<td>22.5±3.5</td>
<td>22.6±3.5</td>
<td>21.9±3.6</td>
<td>22.9±4.1</td>
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<td>Systolic BP, mmHg</td>
<td>120.0±19.6</td>
<td>115.3±18.8</td>
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<td>117.4±21.6</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>68.1±12.0</td>
<td>67.3±13.6</td>
<td>66.6±11.8</td>
<td>70.7±15.5</td>
<td>68.9±13.7</td>
<td>0.45</td>
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<tr>
<td>NYHA functional class III and IV</td>
<td>149 (75%)</td>
<td>62 (78%)</td>
<td>44 (72%)</td>
<td>36 (67%)</td>
<td>90 (78%)</td>
<td>0.53</td>
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<td>Non-ICM</td>
<td>154 (77%)</td>
<td>54 (68%)</td>
<td>34 (56%)</td>
<td>36 (72%)</td>
<td>72 (63%)</td>
<td>0.010</td>
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</table>

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; AVN, atrioventricular node; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization-defibrillator therapy; HF, heart failure; ICM, ischemic cardiomyopathy; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MR, mitral regurgitation; NLBBB, non-left bundle branch block; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

and deep S waves in the left precordial leads (V5 and V6), and (3) QRSd ≥120 ms. IVCD was defined as a conduction disturbance that did not meet the criteria of LBBB or RBBB, and had QRSd ≥120 ms.20
Relative reduction of LVESV was estimated as follows: relative reduction of LVESV (%)=(LVESV (baseline)−LVESV (6–12 months))/LVESV (baseline)×100. We calculated the proportion of echocardiographic responders and relative reduction of LVESV in each group. We also analyzed the proportions of super-responders (reduction of LVESV ≥30%) and negative responders [decreased LV ejection fraction (LVEF)] to evaluate an improvement in HF symptoms, we analyzed changes in NYHA functional class 6 months after implantation. We analyzed the baseline patients’ characteristics of each group with univariate analysis. We performed survival analysis of the primary and secondary endpoints among the 5 subgroups. The primary endpoint was a composite of all-cause death or hospitalization because of HF. The secondary endpoints were significant at a prespecified P<0.05 in the univariate test. Adjusted multivariable Cox proportional hazards analysis was performed using the Kaplan-Meier method with log-rank test. All P-values reported are 2-sided with a prespecified significance of P<0.05. Analyses were performed using the MedCalc software version 15.8 (MedCalc Software, Ostend, Belgium).

### Results

**Patients**

A majority of the patients underwent implantation with CRT-D devices (n=370, 73%) and the remaining patients underwent implantation with CRT-P devices (n=140, 27%). The overall mean age was 67.8±11.5 years and 71% were men; 31% of the patients had ischemic heart disease as the primary etiology of HF and the severity in 75% was of NYHA functional class III or IV. At baseline, the mean LVEF was 27.7±9.4% and LVESV was 139.3±64.6 mL. In terms of intrinsic QRS morphology, 55% of the study population had LBBB, 11% had RBBB, and 11% had ICM. The mean QRS duration was 146.4±30.7 ms.

**Intrinsic QRS Morphology and QRS Duration**

The 510 patients were divided into groups with LBBB (QRS6≥150 ms), using multivariable Cox proportional hazards models adjusted for several clinical variables that were significant at a prespecified P<0.05 in the univariate analysis. Finally, we divided patients into ICM and non-ICM and groups, and performed a subanalysis of the primary endpoints among the 5 subgroups in the non-ICM and ICM cohorts.

### Statistical Analysis

In the univariate analysis of covariates between the groups, continuous variables were analyzed using one-way analysis of variance with Tukey’s post-hoc analysis, and categorical variables were analyzed using the chi-square test. For survival analysis, primary and secondary endpoints were identified using the Kaplan-Meier method with log-rank test. Adjusted multivariable Cox proportional hazards regression analyses were performed to assess the correlation between intrinsic QRS morphology and QRSd, and each outcome. The pool of variables considered were those found to be significant at a prespecified P<0.05 in the univariate analysis. All data are expressed as mean±standard deviation.
QRS Morphology and Duration Predict CRT Response

patients with NYHA functional class III or IV was not different among the 5 groups at baseline (75% vs. 78% vs. 72% vs. 67%, 78%, P=0.53). At 6 months after implantation, the percentage of NYHA III or IV was the lowest in the LBBB with QRSd $\geq 150$ ms group compared with the other groups (11% vs. 25% vs. 33% vs. 28% vs. 21%, respectively, P=0.006) (Table 2).

Clinical Outcomes of Each Group

During a mean follow-up of 3.2±1.5 years, the primary endpoints occurred in 211 (8.3% per year) of 510 patients, and the secondary endpoints of all-cause death, HF hospitalization, and VT/VF occurred in 106 (4.2% per year), 173 (6.8% per year), and 108 (5.4% per year) patients, respectively.

Figure 2. Kaplan-Meier estimates of cumulative probability of the primary and secondary endpoints in the 5 study groups. (A) Composite endpoint (all-cause death and hospitalization because of heart failure), (B) all-cause death, (C) hospitalization because of heart failure, and (D) VT/VF events. LBBB, left bundle branch block; NLBBB, non-LBBB; VF, ventricular fibrillation; VT, ventricular tachycardia.
respectively. The incidence of the composite endpoint was significantly different between the groups (28.6% vs. 42.3% vs. 45.9% vs. 55.6% vs. 55.3%, respectively, P<0.001) (Figure 2A). There were significant differences in the incidence of all-cause death (15.5% vs. 23.8% vs. 24.6% vs. 27.8% vs. 22.6%, respectively, P=0.047) and HF hospitalization (22.1% vs. 35.9% vs. 36.1% vs. 48.2% vs. 46.5%, respectively, P<0.001) (Figure 2B, C). The incidence of VT/VF was significantly different between the groups (28.6% vs. 42.3% vs. 42.3% vs. 48.2% vs. 48.2%, respectively, P<0.001) (Figure 2B).

Table 3 shows the results of the multivariable Cox hazards models adjusted for clinical variables found to be significant according to a prespecified P<0.05 in the univariate analysis (Table 1) such as age at enrollment, sex, CRT-D/CRT-P, ICM/non-ICM etiology, presence of old myocardial infarction, smoking, moderate-severe mitral regurgitation and atrioventricular nodal dysfunction. CI, confidence interval; CRT-P, cardiac resynchronization-pacemaker therapy; HR, hazard ratio; VT/VF, ventricular tachycardia/ventricular fibrillation. Other abbreviations as in Table 1.

### Discussion

**Major Findings**

We sought to investigate the effect of intrinsic QRS morphology and duration on echocardiographic response and clinical outcomes after CRT implantation in a Japanese population based on a multicenter database. Our major findings were: (1) patients with intrinsic LBBB QRS morphology and prolonged QRSd (≥150 ms) were most likely to be echocardiographic responders and super-responders, and the least likely to be negative responders, and (2) patients with intrinsic LBBB QRS morphology and wide QRS duration (≥150 ms) were consistently associated with the most favorable clinical outcomes (free from all-cause death or HF hospitalization).

**Background of CRT Recipients in Japan**

Few studies are available concerning the response to CRT stratified by intrinsic QRS morphology and QRSd in Asian patients. For the interpretation of the results of the current study, we would like to point out the epidemiological difference between Japanese and Western populations in the characteristics of CRT recipients. Compared with Western populations, East Asian populations generally have lower morbidity from CAD. In the Western world, morbidity of CAD has been reported to be 4–5-fold higher than in Japan. In our study population from a Japanese registry, only 30% of patients had an ICM etiology, whereas 70% of patients in prior Western studies had an ICM etiology. Thus, the majority of CRT recipients in the Japanese population had non-ICM etiology, which has been reported as a positive predictor for response to CRT. In the current study, the proportion of echocardiographic

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**Table 3. Unadjusted and Adjusted HRs of Clinical Outcomes in Overall Patients With Different Intrinsic QRS Morphologies and Duration**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of events</th>
<th>No. of patients</th>
<th>LBBB QRSd 120–149 ms</th>
<th>NLBBB QRSd ≥150 ms</th>
<th>NLBBB QRSd 120–149 ms</th>
<th>Narrow QRSd &lt;120 ms</th>
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<tr>
<td></td>
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<td>HR (95% CI) P value</td>
<td>HR (95% CI) P value</td>
<td>HR (95% CI) P value</td>
<td>HR (95% CI) P value</td>
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<td>Composite endpoint</td>
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<tr>
<td>Unadjusted analysis</td>
<td>211</td>
<td>506</td>
<td>1.99 (1.30–3.06) 0.002</td>
<td>2.10 (1.34–3.30) 0.001</td>
<td>2.72 (1.75–4.23) &lt;0.001</td>
<td>2.42 (1.69–3.46) &lt;0.001</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td>211</td>
<td>506</td>
<td>1.80 (1.17–2.78) 0.008</td>
<td>1.96 (1.23–3.13) &lt;0.001</td>
<td>2.77 (1.76–4.36) &lt;0.001</td>
<td>2.50 (1.72–3.63) &lt;0.001</td>
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<tr>
<td>All-cause death</td>
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<tr>
<td>Unadjusted analysis</td>
<td>106</td>
<td>510</td>
<td>1.97 (1.11–3.49) 0.020</td>
<td>1.86 (1.01–3.44) 0.049</td>
<td>2.19 (1.19–4.05) 0.013</td>
<td>1.59 (0.94–2.67) 0.083</td>
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<tr>
<td>Adjusted analysis</td>
<td>106</td>
<td>509</td>
<td>1.71 (0.95–3.05) 0.073</td>
<td>1.87 (0.98–3.55) 0.057</td>
<td>2.50 (1.32–4.74) 0.005</td>
<td>1.71 (1.00–2.94) 0.053</td>
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<td>HF hospitalization</td>
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<tr>
<td>Unadjusted analysis</td>
<td>173</td>
<td>506</td>
<td>2.15 (1.34–3.46) 0.002</td>
<td>2.11 (1.26–3.51) 0.004</td>
<td>3.01 (1.86–4.88) &lt;0.001</td>
<td>2.60 (1.74–3.87) &lt;0.001</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td>173</td>
<td>505</td>
<td>1.96 (1.21–3.15) 0.006</td>
<td>1.97 (1.16–3.34) 0.012</td>
<td>3.07 (1.87–5.05) &lt;0.001</td>
<td>2.72 (1.73–4.13) &lt;0.001</td>
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<td>VT/VF</td>
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<tr>
<td>Unadjusted analysis</td>
<td>108</td>
<td>502</td>
<td>1.10 (0.75–2.60) 0.29</td>
<td>1.11 (0.53–2.33) 0.78</td>
<td>1.75 (0.90–3.43) 0.10</td>
<td>3.14 (1.97–5.03) &lt;0.001</td>
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<tr>
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<td>108</td>
<td>501</td>
<td>1.30 (0.69–2.43) 0.42</td>
<td>1.02 (0.47–2.18) 0.97</td>
<td>1.34 (0.67–2.66) 0.41</td>
<td>2.90 (1.77–4.75) &lt;0.001</td>
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</table>
QRS Morphology and Duration Predict CRT Response

Individuals from Japan and the Western world exhibit differences in the basic characteristics between patients from Japan and the Western world. LBBB intrinsic QRS morphology and wide duration of QRS appear to universally indicate a beneficial response to CRT.

A debate has been ongoing regarding which is the more important regarding CRT response: intrinsic QRS morphology or QRSd. Dupont et al. stratified patients according to both QRS morphology and QRSd in the same way as we did, and concluded that QRS morphology was the more important baseline ECG determinant of CRT response. In our data, however, the clinical outcomes of patients with LBBB with QRSd ≥ 120–149 ms and those with non-LBBB with QRSd ≥ 150 ms were almost similar. Neither of these QRS criteria should be considered in isolation, as they both reflect the ability of CRT to address LV mechanical dyssynchrony only when considered together. At the moment, LBBB intrinsic QRS morphology is not involved in the Class I indication for CRT in the current JCS guidelines. Both of these QRS criteria should be considered in future guidelines on CRT recommendations.

CRT Response in Patients With Narrow QRS Complex

In our study, 115 patients with narrow QRS complex were enrolled and approximately 50% of them were echocardiographic responders. The proportion of super-responders in the narrow QRS group was higher than we expected. We speculate that correction of AV dyssynchrony and bradycardia by CRT, and optimal medication therapy might improve the response in this group. Correction of bradycardia also possibly allowed physicians to increase the dose of β-blocker. Although the echocardiographic response of the narrow QRSd group was not poor, the risk of HF hospitalization was the highest in those with narrow QRSd and NLBBB with QRSd 120–149 ms. Intriguingly, whereas CRT did not affect the risk of VT/VF in the 4 groups with

Effect of Intrinsic QRS Morphology and QRS Duration on CRT Effectiveness

Intrinsic QRS morphology refers to the areas of delayed activation resulting in mechanical dys synchrony, and duration of QRS refers to the severity of the activation delay. Typically, LBBB is associated with delayed activation of the lateral and posterolateral portions of the LV, so it is the target of LV lateral wall pacing. Prolonged QRSd implies a greater delay in activation, which needs to be corrected using biventricular pacing. Therefore, LBBB intrinsic QRS morphology and prolonged QRSd are of considerable importance in predicting the response to CRT. In the current study, Japanese patients with LBBB intrinsic QRS morphology and QRSd ≥ 150 ms were the most likely of all the study patients to become echocardiographic responders at 6–12-month follow-up and they exhibited the most favorable clinical outcomes even after adjustment for several covariates. In contrast, patients with NLBBB morphology and QRSd between 120 and 149 ms, and narrow QRS complex exhibited the poorest long-term prognoses. Although there are epidemiological differences in the basic characteristics between patients from Japan and the Western world, LBBB intrinsic QRS morphology and wide duration of QRS appear to universally indicate a beneficial response to CRT.

A debate has been ongoing regarding which is the more important regarding CRT response: intrinsic QRS morphology or QRSd. Dupont et al. stratified patients according to both QRS morphology and QRSd in the same way as we did, and concluded that QRS morphology was the more important baseline ECG determinant of CRT response. In our data, however, the clinical outcomes of patients with LBBB with QRSd 120–149 ms and those with non-LBBB with QRSd ≥ 150 ms were almost similar. Neither of these QRS criteria should be considered in isolation, as they both reflect the ability of CRT to address LV mechanical dys synchrony only when considered together. At the moment, LBBB intrinsic QRS morphology is not involved in the Class I indication for CRT in the current JCS guidelines. Both of these QRS criteria should be considered in future guidelines on CRT recommendations.
QRSd ≥120 ms, only patients with narrow QRS complex exhibited an increased risk of VT/VF. The pro-arrhythmic effects of CRT have been argued in several prior studies. Biventricular pacing could increase the dispersion of repolarization, and induce VT/VF in some patients. Before pacing, a narrow QRS duration could mean smaller activation delay compared with wide QRS duration. In patients with a narrow QRS complex, biventricular pacing might increase the activation delay and dispersion of repolarization. Several RCTs have failed to demonstrate the effectiveness of CRT in patients with a narrow QRS complex, regardless of the presence of LV dyssynchrony.

Clinical Implications
LBBB intrinsic QRS morphology and wide QRS duration (≥150 ms) had a close association with a beneficial response after CRT implantation in this Japanese cohort. These 2 ECG parameters should be taken into consideration together when discussing the indications for CRT in the Japanese population.

Study Limitations
This study should be interpreted after taking into account its methodological limitations. First, it was a post-hoc analysis and 69% of patients were retrospectively enrolled. Second, 32% of patients were excluded from the analysis because of incomplete data. Third, we compared clinical outcomes among 5 groups that were subdivided according to intrinsic QRS morphology and duration. Some of the baseline patient characteristics were different between groups. Fourth, because of the lack of a control group without CRT, we had to set the group with LBBB (QRSd ≥150 ms) as the reference group in our multivariate Cox regression analysis.

Conclusions
In this Japanese population, LBBB intrinsic QRS morphology and wide QRS duration (≥150 ms) had the strongest association with a beneficial response after CRT implantation.

Funding
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Acknowledgement of Grant Support
None.

Conflict of Interest
K. Inoue received honoraria for lecturing from Medtronic Japan, Inc.

References
QRS Morphology and Duration Predict CRT Response


