



Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study.

Michael R Gold, Christophe Thébault, Cecilia Linde, William T Abraham, Bart Gerritse, Stefano Ghio, Martin St John Sutton, Jean-Claude Daubert

► To cite this version:

Michael R Gold, Christophe Thébault, Cecilia Linde, William T Abraham, Bart Gerritse, et al.. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study.. *Circulation*, 2012, 126 (7), pp.822-9. 10.1161/CIRCULATIONAHA.112.097709 . hal-00904448

HAL Id: hal-00904448

<https://hal.science/hal-00904448>

Submitted on 14 May 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Effect of QRS Duration and Morphology on Cardiac Resynchronization Therapy Outcomes in Mild Heart Failure: Results From the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Study
Michael R. Gold, Christophe Thébault, Cecilia Linde, William T. Abraham, Bart Gerritse, Stefano Ghio, Martin St. John Sutton and Jean-Claude Daubert

Circulation. 2012;126:822-829; originally published online July 10, 2012;
doi: 10.1161/CIRCULATIONAHA.112.097709

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2012 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/126/7/822>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>

Effect of QRS Duration and Morphology on Cardiac Resynchronization Therapy Outcomes in Mild Heart Failure Results From the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Study

Michael R. Gold, MD, PhD; Christophe Thébault, MD; Cecilia Linde, MD, PhD;
William T. Abraham, MD; Bart Gerritse, PhD; Stefano Ghio, MD;
Martin St. John Sutton, MD, FRCP; Jean-Claude Daubert, MD

Background—Cardiac resynchronization therapy (CRT) decreases mortality, improves functional status, and induces reverse left ventricular remodeling in selected populations with heart failure. We aimed to assess the impact of baseline QRS duration and morphology and the change in QRS duration with pacing on CRT outcomes in mild heart failure.

Methods and Results—Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) was a multicenter randomized trial of CRT among 610 patients with mild heart failure. Baseline and CRT-paced QRS durations and baseline QRS morphology were evaluated by blinded core laboratories. The mean baseline QRS duration was 151 ± 23 milliseconds, and 60.5% of subjects had left bundle-branch block (LBBB). Patients with LBBB experienced a 25.3-mL/m^2 mean reduction in left ventricular end-systolic volume index ($P < 0.0001$), whereas non-LBBB patients had smaller decreases (6.7 mL/m^2 ; $P = 0.18$). Baseline QRS duration was also a strong predictor of change in left ventricular end-systolic volume index with monotonic increases as QRS duration prolonged. Similarly, the clinical composite score improved with CRT for LBBB subjects (odds ratio, 0.530; $P = 0.0034$) but not for non-LBBB subjects (odds ratio, 0.724; $P = 0.21$). The association between clinical composite score and QRS duration was highly significant (odds ratio, 0.831 for each 10-millisecond increase in QRS duration; $P < 0.0001$), with improved response at longer QRS durations. The change in QRS duration with CRT pacing was not an independent predictor of any outcomes after correction for baseline variables.

Conclusion—REVERSE demonstrated that LBBB and QRS prolongation are markers of reverse remodeling and clinical benefit with CRT in mild heart failure.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00271154.

(*Circulation*. 2012;126:822-829.)

Key Words: bundle-branch block ■ pacing ■ cardiomyopathy ■ heart failure

Cardiac resynchronization therapy (CRT) improves functional status and cardiac function and decreases heart failure (HF) hospitalizations and mortality among HF patients with left ventricular (LV) systolic dysfunction and QRS prolongation.^{1–8} Initially, CRT was applied to patients with advanced HF, but more recent studies have shown similar benefit among patients with milder HF.^{9–11} Several studies have demonstrated that the hemodynamic response, extent of LV volumetric changes (ie, reverse remodeling), and clinical outcomes are affected by baseline or CRT-paced ECG characteristics.^{6,12–16} These studies suggest that patients with

longer intrinsic QRS duration, left bundle-branch block (LBBB) morphology, and greater QRS shortening with biventricular pacing have better outcomes. Conversely, those with non-LBBB morphology do not benefit from or may even worsen with CRT. However, a comprehensive evaluation of QRS duration and morphology on structural and clinical outcomes with CRT has not been performed previously. Accordingly, the present analysis was designed to evaluate the role of intrinsic and CRT-paced QRS characteristics on CRT in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study.

Received February 21, 2012; accepted June 20, 2012.

From the Medical University of South Carolina, Charleston (M.R.G.); Department of Cardiology, University Hospital, CIC IT, INSERM 642, Rennes, France (C.T., J.-C.D.); Karolinska University Hospital, Stockholm, Sweden (C.L.); Ohio State University, Columbus (W.T.A.); Medtronic Bakken Research Center BV, Maastricht, the Netherlands (B.G.); Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (S.G.); and University of Pennsylvania Medical Center, Philadelphia (M.S.J.S.).

Correspondence to Michael R. Gold, MD, PhD, Division of Cardiology, Medical University of South Carolina, 25 Courtenay Dr, ART 7031, Charleston, SC 29425-5920. E-mail goldmr@musc.edu

© 2012 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.112.097709

Clinical Perspective on p 829

Methods

The design and primary results of the REVERSE trial were published previously.^{9,17,18} Briefly, eligible patients had American College of Cardiology/American Heart Association stage C or New York Heart Association class I (previously symptomatic, currently asymptomatic) or class II (mildly symptomatic) HF for at least 3 months before enrollment. Patients were required to be in sinus rhythm with a QRS duration ≥ 120 milliseconds, an ejection fraction $\leq 40\%$, and an LV end-diastolic dimension ≥ 55 mm measured by transthoracic echocardiography. All patients were receiving optimal medical therapy for HF, including stable doses of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and a β -blocker.¹⁹ Patients requiring pacing were excluded. The ethics committee of each center approved the study protocol, and all patients gave written informed consent.

All patients underwent implantation of a CRT system (device and leads), with or without implantable cardioverter-defibrillator capabilities, on the basis of standard clinical criteria. Patients who had undergone successful implantation ($n=610$) were then randomly assigned in a 2:1 fashion to active CRT (CRT ON) or to a control group (CRT OFF). By study design, patients were followed up in their randomized arms for 12 months in North America and for 24 months in Europe. Those assigned to CRT ON were programmed to simultaneous biventricular pacing in the DDD mode at a lower rate of 35 bpm. Those patients randomized to CRT OFF were programmed to the DDI mode at a lower rate of 35 bpm.

Analyses were performed on 12-lead ECGs collected at baseline and after successful CRT implantation but before randomization to CRT ON or OFF by researchers at core laboratories who were blinded to randomization assignment and clinical outcomes. Consequently, patients had not received CRT before these measurements were made. Intrinsic QRS morphology and duration were measured, as well as CRT-paced QRS duration. Both intrinsic QRS duration and paced QRS duration were measured on a tracer table as the mean from 9 consecutive cycles in leads II, V_1 , and V_6 . The intraobserver and interobserver reproducibilities were evaluated by a second measurement of 50 randomly selected ECGs prepared by another expert interpreter. The intraobserver and interobserver coefficients of variability of the unpaced and paced QRS complexes were 1.6% and 1.4%, and 6.4% and 2.6%, respectively. Morphology was classified as LBBB, right bundle-branch block (RBBB), or nonspecific intraventricular conduction delay (IVCD) by World Health Organization criteria.^{20,21} LBBB was thus defined as QRS duration ≥ 120 milliseconds; QS or rS in lead V_1 ; broad R waves in leads I, aVL, V_5 , or V_6 ; and absent q waves in leads V_5 and V_6 . For the purpose of the present analyses, all other patients were combined as a non-LBBB cohort. In addition, analyses were performed with the non-LBBB cohort subdivided into subgroups of RBBB, IVCD, and narrow QRS (<120 milliseconds). In the overall study,⁹ each center interpreted the ECG and baseline echocardiography independently of the core laboratories to determine criteria for study entry, including QRS duration. Of note, core laboratory evaluation of QRS data was performed after enrollment; thus, some patients were classified as narrow QRS even though study inclusion criteria specified a QRS duration ≥ 120 milliseconds.

The primary end point of REVERSE was the clinical composite score (CCS).^{17,22} Using this end point, we classified patients into 1 of 3 response groups: worsened, unchanged, or improved. Patients were judged to be worsened if they died, were hospitalized for worsening HF, crossed over to or permanently discontinued double-blind treatment owing to worsening HF, or demonstrated worsening in New York Heart Association class or moderate to marked worsening of patient global assessment. Patients were judged to be improved if they had not worsened and had demonstrated improvement in New York Heart Association class and/or a moderate to marked improvement in patient global assessment. Patients who were not worsened or improved were classified as unchanged.

Echocardiograms were obtained at baseline and after 12 months of randomization. Data were analyzed in 1 of 2 core laboratories by researchers blinded to clinical data. LV dimensions were recorded with 2-dimensional directed M-mode echocardiography at the tips of the mitral valve leaflets. Echocardiograms were digitized to obtain LV volumes by the Simpson method of disks, as recommended by the American Society of Echocardiography,²³ from which LV ejection fraction was calculated. Change in LV end-systolic volume indexed by body surface area (LVESVi) was the predefined and independently powered secondary end point of REVERSE. Further details of the echocardiographic protocol have been published previously.²⁴

Data Analysis

Continuous variables are summarized with mean and standard deviation; categorical variables, with counts and percentages. Comparisons of baseline variables between patients with and without LBBB use the Student *t* test and Fisher exact test. Outcome parameters were analyzed with regression models that include some or all of QRS duration, LBBB, and study arm, with interactions. Effect estimates and *P* values were derived from contrasts. Interaction *P* values are reported to assess the difference of the effect of CRT between LBBB and non-LBBB. The CCS was analyzed as a 3-category ordinal variable by use of ordinal logistic regression. A reported odds ratio <1 indicates improvement; ie, patients are less likely to be in the worse categories. Echocardiographic parameters were analyzed with linear regression. Time-to-event analyses used Kaplan-Meier estimates and Cox proportional hazards regression to compute hazard ratios and to assess influence of covariates. Survival curves and rates were compared by the log-rank test. To assess possible confounding by baseline characteristics that differ between patients with and without LBBB, those characteristics with $P<0.10$ were added to the models to observe qualitative changes in the relation between outcome parameters and LBBB. The relation between QRS duration and outcomes is graphically illustrated with smooth curves fitted to the data using a cubic spline method. This technique extends the standard fitting of straight regression lines and finds a curve that optimally balances goodness of fit against minimal curvature.²⁵

The immediate QRS change is the difference between unpaced baseline QRS and biventricular paced QRS measured before permanent CRT programming. Normalized acute QRS change was calculated by subtracting the expected QRS change based on baseline QRS as calculated from a linear regression model.

A value of $P<0.05$ was considered statistically significant. *P* values were not adjusted for multiple comparisons.

Results**Patient Population**

All 610 patients randomized in REVERSE were included in this analysis. Demographic and other characteristics of the patient population are presented in Table 1. The mean age was 62.5 ± 11.0 years; 79% were male; and 55% had ischemic heart disease as the primary cause of HF. The mean ejection fraction was $26.7 \pm 7.0\%$. The intrinsic QRS duration could be determined by the core laboratory for 582 patients and was 151 ± 23 milliseconds. QRS morphology could be determined by the core laboratory for 593 patients. For 14 patients, the classification by the investigator is used in analysis. For the remaining 3 patients, QRS morphology remains unknown. Table 1 also shows the patient characteristics grouped by QRS morphology. There was no significant difference in the proportion of patients in the CRT ON versus OFF groups with LBBB (61.1% versus 59.2%, respectively). However, there are some important differences between the groups. Specifically, subjects with LBBB were less likely to be men,

Table 1. Baseline Patient Characteristics

	QRS Morphology*			P†
	All Patients (n=610)	LBBB (n=369)	Non-LBBB (n=238)	
Age, y	62.5±11.0	62.3±11.3	63.0±10.3	0.42
Male, n (%)	479 (79)	266 (72)	210 (88)	<0.0001
NYHA functional class II, n (%)	503 (82)	310 (84)	192 (81)	0.32
Ischemic, n (%)	333 (55)	160 (43)	173 (73)	<0.0001
Diabetic, n (%)	137 (22)	66 (18)	71 (30)	<0.001
Chronic obstructive pulmonary disease, n (%)	60 (10)	34 (9)	26 (11)	0.49
ACE inhibitors or ARBs, n (%)	590 (97)	359 (97)	228 (96)	0.36
β-blockers, n (%)	580 (95)	351 (95)	226 (95)	1.00
Intrinsic QRS duration, ms	151±23	159±18	139±23	<0.0001
LV ejection fraction, %	26.7±7.0	26.6±7.0	26.7±7.2	0.88
LV end-diastolic dimension, cm	6.7±0.9	6.7±1.0	6.6±0.7	0.19
Interventricular mechanical delay, ms	33.6±39.0	47.6±33.7	11.8±36.6	<0.0001
Minnesota Living With HF Score	27.6±20.6	26.2±19.1	29.7±22.7	0.055
6-min hall walk, m	395±127	408±122	374±132	0.001
CRT-D implanted, n (%)	508 (83)	292 (79)	213 (89)	<0.001

LBBB indicates left bundle-branch block; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LV, left ventricular; HF, heart failure, and CRT-D, cardiac resynchronization therapy with implantable cardioverter-defibrillator capabilities.

*For 3 patients, QRS morphology could not be classified.

†P values are for LBBB vs non-LBBB patients.

to have diabetes mellitus, or to have an ischemic type of HF. The LBBB group also had significantly longer intrinsic QRS duration with a mean of 159 milliseconds compared with 139 milliseconds in the non-LBBB group ($P<0.0001$) and better functional status as evidenced by quality-of-life scores and 6-minute hall-walk distances. The non-LBBB group consisted of 57 patients with narrow QRS (<120 milliseconds), 55 patients with RBBB, and 126 patients with IVCD.

Echocardiographic Changes

One of the hallmark findings of CRT is the reduction of LV volumes and the increase in LV ejection fraction as part of the reverse remodeling response. Paired baseline and 12-month echocardiographic data were available for 509 patients, with an overall LVESVi reduction of 18.3 ± 28.9 mL/m² in the CRT ON arm. The results for change in LVESVi at 12 months grouped by QRS morphology are shown in Table 2. There was a large reduction of LVESVi with CRT noted in

this study that was observed primarily in the LBBB cohort. For the LBBB group, there was a 25.3-mL/m² mean reduction in LVESVi ($P<0.0001$ versus CRT OFF), whereas in the non-LBBB group, this decrease was much smaller and nonsignificant (6.7 mL/m²; $P=0.18$). LV end-diastolic volume index showed a similar relationship with QRS morphology, as shown in Table 2. Finally, a significant increase in ejection fraction was observed only in the LBBB cohort. Lack of reverse remodeling is consistent among the non-LBBB subgroups, with an LVESVi reduction of 6.6 mL/m² in patients with narrow QRS, 2.8 mL/m² for RBBB, and 8.6 mL/m² for IVCD. Model-based estimates for CRT effect are shown in Table 3 with corresponding 95% confidence intervals.

To evaluate the impact of QRS duration on remodeling parameters, patients were divided into quartiles based on the intrinsic QRS duration. The changes in LVESVi are shown in Table 4. The reduction of LVESVi increased progressively

Table 2. Effect of QRS Morphology on Changes in Echocardiographic Parameters at 12 Months

	LBBB			Non-LBBB			P for Interaction*
	CRT OFF (n=99)	CRT ON (n=211)	P	CRT OFF (n=66)	CRT ON (n=131)	P	
LVESVi, mL/m ²	-1.7±25.8	-25.3±28.5	<0.0001	-1.5±19.7	-6.7±25.8	0.18	0.0003
LVEDVi, mL/m ²	-1.8±30.0	-25.7±31.5	<0.0001	-1.2±24.7	-8.5±30.5	0.11	0.0043
LVEF, %	0.8±6.9	6.9±9.7	<0.0001	0.7±6.3	0.9±7.2	0.88	0.0002

LBBB indicates left bundle-branch block; CRT OFF, group with no cardiac resynchronization therapy; CRT ON, group with cardiac resynchronization therapy; LVESVi, left ventricular end-systolic volume index; and LVEF, left ventricular ejection fraction.

*Assesses the difference of CRT effect between LBBB and non-LBBB.

Table 3. Cardiac Resynchronization Therapy Effect Estimates by QRS Morphology

	Non-LBBB (n=238)				
	LBBB (n=369)	RBBB (n=55)	IVCD (n=126)	Narrow QRS (n=57)	All
LVESVi change, mL/m ²	-23.7 (-29.9 to -17.4)	-3.5 (-19.1 to 12.0)	-7.8 (-18.3 to 2.6)	0.5 (-16.8 to 17.7)	-5.2 (-13.0 to 2.5)
LVEDVi change, mL/m ²	-23.9 (-31.1 to -16.8)	-4.5 (-22.3 to 13.3)	-10.5 (-22.5 to 1.5)	-0.3 (-20.1 to 19.5)	-7.3 (-16.2 to 1.6)
LVEF change, %	6.0 (4.1 to 8.0)	-0.2 (-5.0 to 4.7)	0.8 (-2.5 to 4.0)	-0.5 (-5.9 to 4.8)	0.2 (-2.2 to 2.6)
CCS, odds ratio	0.53 (0.35 to 0.81)	0.27 (0.10 to 0.77)	0.79 (0.40 to 1.57)	1.42 (0.46 to 4.34)	0.72 (0.44 to 1.20)
Composite end point, HR	0.48 (0.24 to 0.94)	0.083 (0.01 to 0.69)	0.60 (0.22 to 1.65)	2.21 (0.27 to 18.0)	0.53 (0.26 to 1.09)

LBBB indicates left bundle-branch block; RBBB, right bundle-branch block; IVCD, intraventricular conduction delay; LVESVi, left ventricular end-systolic volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; CCS, clinical composite score; and HR, hazard ratio. Values in parentheses are 95% confidence intervals.

with QRS prolongation in the presence of CRT ($P<0.0001$), with little change observed in the control population ($P=0.87$; P for interaction <0.0001). Figure 1 illustrates the continuous relationship between QRS duration and change in LVESVi using spline smoothing. The relationship in the CRT ON group is fairly linear and intersects the CRT OFF group and a 0 change at a QRS duration of ≈ 120 milliseconds.

When subgrouped by QRS morphology, the relationship between QRS duration and LVESVi noted above was due primarily to the LBBB cohort. Specifically, there was an estimated incremental decrease in LVESVi of 5.7 mL/m² for each 10-millisecond increase of the QRS duration by linear regression analysis among LBBB subjects ($P<0.0001$; Figure 2A). No significant relationship between QRS duration and LVESVi was observed in the non-LBBB cohort (0.13 mL/m²; $P=0.20$; Figure 2B). A similar interaction between QRS duration and morphology was observed for LV end-diastolic volume index. Specifically, an estimated incremental decrease in LV end-diastolic volume index of 6.1 mL/m² for each 10-millisecond increase in QRS duration was noted for LBBB subjects ($P<0.0001$), but no relationship between QRS duration and these volumetric changes was observed for non-LBBB subjects (0.39 mL/m²; $P=0.81$).

Clinical Response

The primary end point for REVERSE was the CCS.^{9,17} The results grouped by randomization and QRS morphology are summarized in Table 5. In the control arm (CRT OFF), the distribution of CCS was similar between the LBBB and non-LBBB groups ($P=0.12$). CRT had no significant effect for the non-LBBB group (for CRT ON relative to CRT OFF:

odds ratio, 0.724; $P=0.21$) but markedly improved the CCS for the LBBB group (odds ratio, 0.530; $P=0.0034$). However, the odds ratios for non-LBBB and LBBB were not significantly different (P for interaction $=0.35$). Of note, the response in the non-LBBB group was not homogeneous, with improved CCS for RBBB patients (odds ratio, 0.272; $P=0.014$) but not for IVCD or narrow QRS. Odds ratio estimates for all groups are provided in Table 3.

In addition to the CCS, we evaluated the commonly used composite end point of time to first HF hospitalization or all-cause death. In the LBBB group, the curves diverged early and more end point events were observed in the CRT OFF cohort (hazard ratio, 0.48; $P=0.028$; Figure 3A). Event rates were somewhat higher in the non-LBBB group and the curves also seemed to diverge, but this difference did not reach statistical significance (hazard ratio, 0.53; $P=0.081$; Figure 3B). The hazard ratios for LBBB and non-LBBB are not significantly different (P for interaction $=0.86$). A significant reduction of events was observed in RBBB patients (hazard ratio, 0.083; $P=0.0032$) but not in IVCD (hazard ratio, 0.60; $P=0.31$) or narrow QRS (hazard ratio, 2.21; $P=0.46$; see also Table 3).

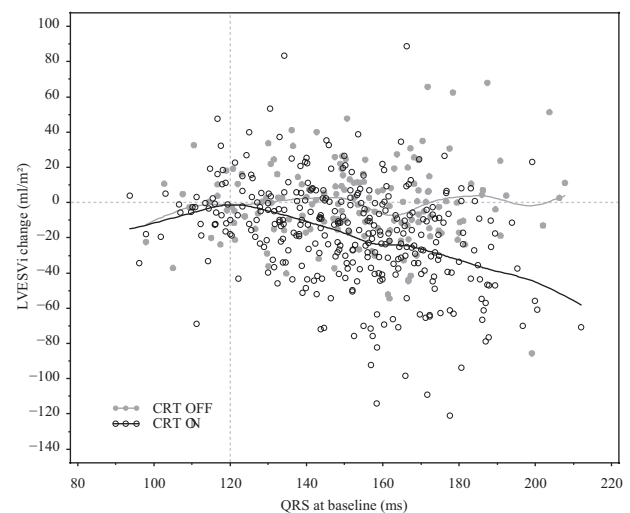


Figure 1. The absolute change in left ventricular end-systolic volume index (LVESVi) at 12 months. Each point represents data from 1 patient. The open symbols are for cardiac resynchronization therapy on (CRT ON) patients; closed symbols, control (CRT OFF) patients. The black line is the expected LVESVi change using spline smoothing for the CRT ON group; the gray line, the change for the CRT OFF group.

Table 4. Effect of Intrinsic QRS Duration on Left Ventricular End-Systolic Volume Index Change at 12 Months

QRS Duration, ms	CRT OFF (n), mL/m ²	CRT ON (n), mL/m ²
<134	-1.4 $\pm$ 17.5 (38)	-5.2 $\pm$ 20.5 (81)
134–152	3.5 $\pm$ 20.7 (38)	-12.3 $\pm$ 26.1 (88)
152–167	-7.7 $\pm$ 21.9 (41)	-23.0 $\pm$ 32.2 (82)
168–218	2.9 $\pm$ 27.1 (44)	-33.3 $\pm$ 29.2 (77)
All*	-0.7 $\pm$ 22.5 (161)	-18.1 $\pm$ 29.1 (328)

CRT OFF, group with no cardiac resynchronization therapy; CRT ON, group with cardiac resynchronization therapy.

*Baseline QRS and paired echocardiographic data are available for 489 patients.

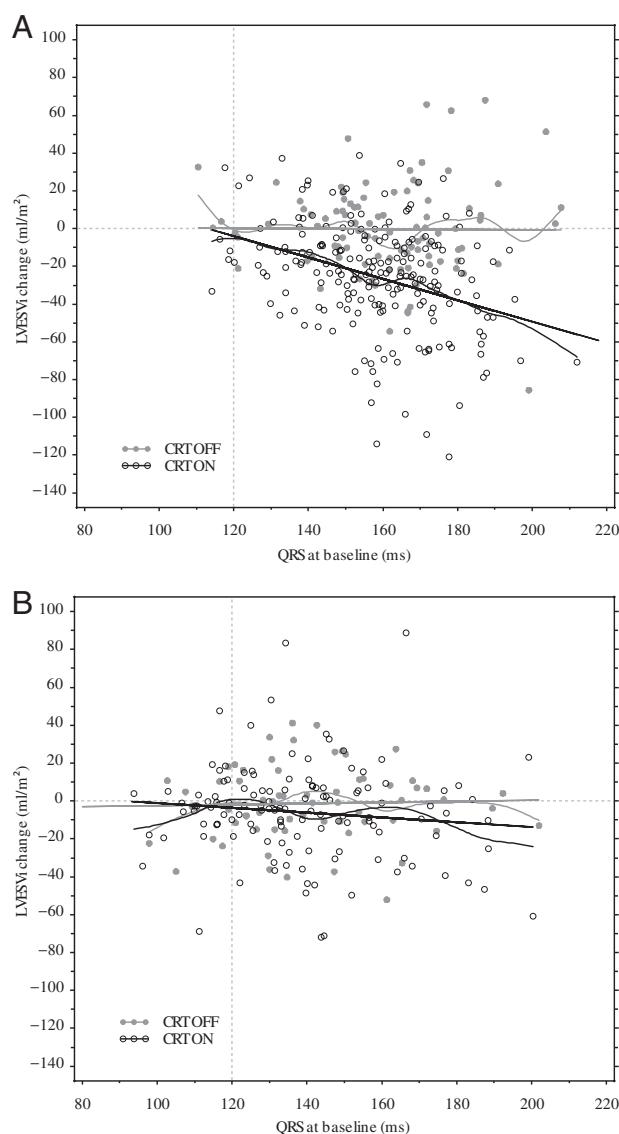


Figure 2. The absolute change in left ventricular end-systolic volume index (LVESVi) at 12 months. **A**, The left bundle-branch block (LBBB) group; **B**, the non-LBBB group. Each point represents data from 1 patient. The open symbols are for cardiac resynchronization therapy on (CRT ON) patients; the closed symbols, control (CRT OFF) patients. The curved black line is the expected LVESVi change using spline smoothing for the CRT ON group; the curved gray line, the change for the CRT OFF group. The straight black and gray lines are model-based regression lines.

The effect of QRS duration on CCS was also evaluated. In the control arm (CRT OFF), there was no relationship between CCS and QRS duration (odds ratio, 1.016 for each 10-millisecond increase in QRS duration; $P=0.79$). However, in the CRT arm, the association between CCS and QRS duration was highly significant (odds ratio, 0.831 for each 10-millisecond increase in QRS duration; $P<0.0001$), with improved response at longer QRS durations. This relationship is further illustrated in Figure 4. Spline smoothing is used to plot the percentage of patients improved (ie, responders) in relation to QRS duration for the 2 randomized groups. There is little change in response for the CRT OFF group, whereas the proportion of responders

Table 5. Clinical Composite Score Grouped by Randomization and QRS Morphology

	LBBB (%)		Non-LBBB (%)	
	CRT OFF	CRT ON	CRT OFF	CRT ON
Improved	50 (44.2)	154 (60.2)	26 (33.3)	73 (45.6)
Unchanged	42 (37.2)	76 (29.7)	32 (41.0)	46 (28.8)
Worsened	21 (18.6)	26 (10.2)	20 (25.6)	41 (25.6)
Odds ratio	0.530		0.724	
<i>P</i>	0.0034		0.21	

LBBB indicates left bundle-branch block; CRT OFF, group with no cardiac resynchronization therapy; and CRT ON, group with cardiac resynchronization therapy.

increases as baseline QRS duration is prolonged in the CRT ON group. The curves cross at a QRS duration of ≈ 115 milliseconds, suggesting a lack of benefit of CRT in patients with narrow QRS.

The observed relations between outcome parameters and LBBB were also present in multivariable models that in-

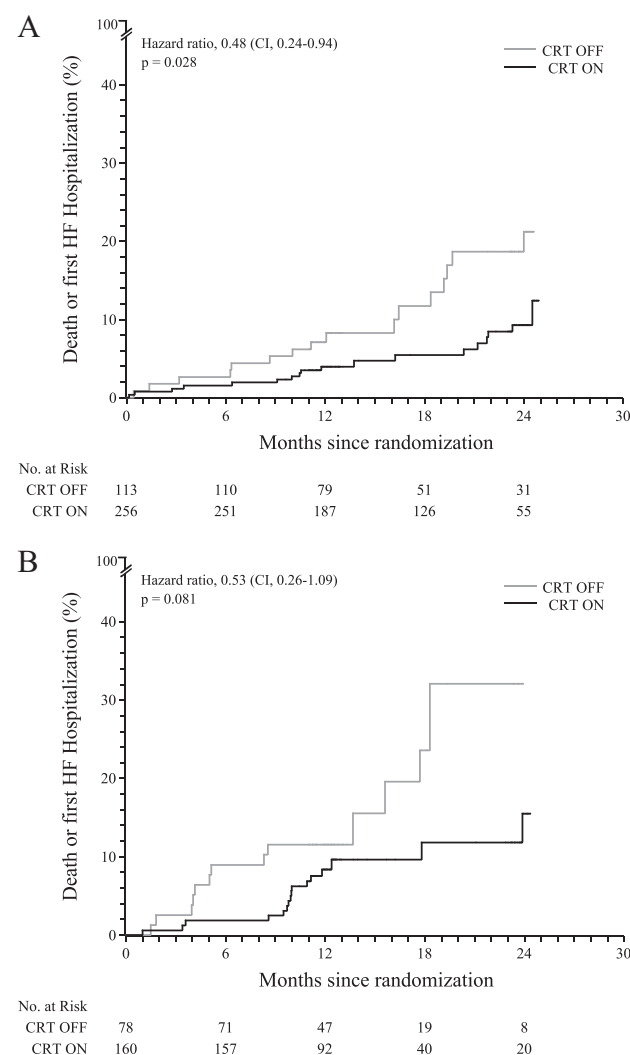


Figure 3. Kaplan-Meier curves showing time to the composite end point of first heart failure (HF) hospitalization or all-cause death. **A**, The left bundle-branch block (LBBB) group; **B**, the non-LBBB group.

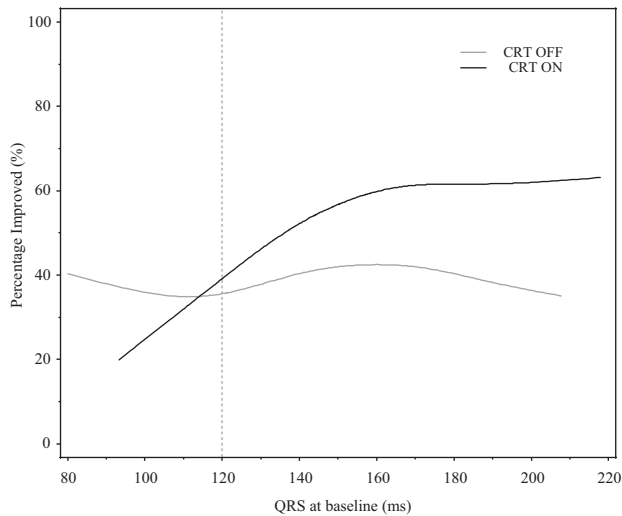


Figure 4. Effect of unpaced QRS duration on the proportion of patients with an improved clinical composite score. The curves use spline smoothing and are for the cardiac resynchronization therapy on (CRT ON) and control (CRT OFF) groups.

cluded the baseline characteristics that differed between patients with and without LBBB at $P < 0.10$.

Paced QRS Duration

The immediate change in QRS duration with pacing has been reported to predict outcomes with CRT.¹⁴ To evaluate this possibility in REVERSE, we analyzed the acute QRS change in the CRT ON group. Acute QRS change was -6 ± 26 milliseconds (LBBB, -13 ± 24 milliseconds; non-LBBB, 3 ± 26 milliseconds). For the primary end point, the association between CCS and acute QRS change is highly significant (odds ratio, 0.877 for each 10-millisecond additional acute decrease in QRS duration; $P = 0.0011$). To explore these observations further, the relationship between unpaced baseline QRS duration and acute QRS change was analyzed, showing a moderate correlation ($r = 0.46$, $P < 0.0001$), and normalized QRS change was calculated. In a multivariate model for CCS with baseline QRS duration and normalized acute QRS change as covariates, only baseline QRS was significant ($P < 0.0001$ in CRT ON arm versus $P = 0.20$ for normalized acute QRS change). Similar results were observed with other end points. Specifically, the association between LVESVi change and acute QRS change was highly significant ($P < 0.0001$). However, in the multivariate model, only baseline QRS was significant ($P < 0.0001$ versus $P = 0.14$ for normalized acute QRS change). Finally, in the CRT ON arm, the association between the incidence of death or HF hospitalization and acute QRS change was highly significant ($P = 0.0054$), but only baseline QRS was significant ($P = 0.0002$ versus $P = 0.39$ for normalized acute QRS change) in the multivariate model.

Discussion

The primary results of this analysis suggest that the benefit of CRT in mild HF is strongly dependent on QRS morphology and duration. Specifically, echocardiographic changes in volumes and ejection fraction were noted only in the LBBB

cohort, and the magnitude of this response was strongly dependent on baseline QRS duration. Similarly, improvement in the CCS with CRT was larger in the LBBB cohort, and again it was related strongly to baseline QRS duration. Finally, the change in QRS duration with pacing was not an independent predictor of outcomes.

The results of the present study are consistent with several previous studies of QRS morphology on CRT in both the advanced and mild HF populations. Specifically, subgroup analyses of multiple trials of New York Heart Association class III/IV subjects showed minimal or no benefit in the presence of RBBB.^{6,13,26} The results for REVERSE were mixed with regard to response in RBBB subjects. The echocardiographic measures of reverse remodeling were attenuated and nonsignificant in this subgroup, although there was an improvement in clinical outcomes. More recently, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT)¹¹ and the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT)¹⁶ evaluated the impact of QRS morphology on clinical response and noted benefit only in the LBBB subgroup, not in the composite of non-LBBB subjects.

The impact of QRS duration on outcomes has also been evaluated previously in CRT trials. Most commonly, QRS duration is dichotomized at 150 milliseconds for these analyses, with a smaller or no response observed among subjects with QRS duration < 150 milliseconds.^{10,11} However, transforming a continuous measure such as QRS duration into a dichotomous one may not be optimal for analysis. Accordingly, we subdivided the cohort into quartiles based on unpaced QRS duration and analyzed outcomes with regression models that include QRS duration as a continuous parameter.

We observed that the relationship between QRS duration and response to CRT is best treated as a continuous variable, with larger response rates as QRS is prolonged. Moreover, the curve for change in LVESVi with CRT intercepts 0 at a QRS duration of ≈ 120 milliseconds, and the curves for active CRT and control for the CCS cross at ≈ 115 milliseconds. These similar observations are intriguing and indicate a lack of benefit among patients with narrow QRS, as shown in the subgroup analyses of that cohort. This is consistent with other multicenter studies of CRT specifically addressing this issue.^{27,28}

Although the change in QRS duration with biventricular pacing was associated with clinical outcomes, this effect was no longer significant in a multivariate model that corrected for baseline QRS duration. These 2 parameters were correlated. Thus, QRS duration tends to shorten more with longer baseline QRS durations and may even be prolonged with shorter baseline QRS durations. Accordingly, the change in QRS duration with pacing reflects primarily the intrinsic QRS duration. Although the total paced QRS duration was not an independent predictor of response, we did not evaluate whether other properties of the paced complex predicted response, as reported recently.²⁹

There are several clinical implications of these data. First, CRT in mild HF patients may need to be restricted to those with LBBB. Second, we found a progressive incremental

response to CRT by increasing QRS duration but with no clear cutoff value for reverse remodeling or clinical benefit of CRT other than the conventional cutoff of 120 milliseconds. Thus, responses increase with increasing QRS prolongation but, importantly, with no response for QRS durations <115 to 120 milliseconds. Accordingly, CRT should be avoided in patients with narrow QRS, and the risks and benefits should be weighed carefully among subjects with only modest QRS prolongation or with non-LBBB morphology. Third, the change in QRS duration with pacing did not independently predict outcomes but rather was a reflection of intrinsic QRS duration.

This study should be interpreted in the face of several methodological limitations. First, randomization was not stratified on the basis of QRS morphology or duration, and many of these analyses were performed post hoc. Second, the study was not powered to detect any clinically relevant difference between QRS morphologies. Third, paired echocardiographic data were incomplete. However, this did not appear to affect the outcomes. The CCS is improved in 260 of 509 patients with complete echocardiographic data (51%) and in 44 of 89 patients without complete echocardiographic data who survived through 12 months (49%; $P=0.68$). Moreover, there is no observed difference in baseline LVESVi between patients with (99 ± 38 mL/m²) and without (103 ± 37 mL/m²) complete echocardiographic data ($P=0.51$). Finally, this study evaluated only subjects with mild HF, so the results may not necessarily apply to patients with more severe HF.

Conclusions

In a large cohort of patients with QRS prolongation, LV dilatation, but mild HF, CRT resulted in improved clinical response, fewer HF hospitalizations, and greater reverse remodeling. However, QRS morphology and duration had important impacts on these end points. Specifically, little remodeling or clinical benefit was observed in the absence of LBBB. Additionally, both remodeling and clinical responses increased progressively with increasing baseline QRS duration compared with little or no response in unpaced control subjects or QRS durations <120 milliseconds.

Sources of Funding

This work was supported by Medtronic Bakken Research Center BV, Maastricht, Netherlands and Medtronic, Inc, Minneapolis, MN.

Disclosures

Drs Gold, Linde, St. John Sutton, and Daubert served as consultants to and received research grants from Medtronic. Drs Gold and Linde served as consultants to and receive research grants from St. Jude Medical. Dr Linde reports honoraria payments from Biotronik and St. Jude. Dr Abraham reports consulting fees from Biotronik, Medtronic, and St. Jude. Dr Gold reports consulting fees from Biotronik, Sorin, and Boston Scientific. Dr Gerritse is an employee of Medtronic. Dr Thébault reports research grants from Medtronic. Dr Ghio reports no conflicts.

References

1. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001; 344:873–880.
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
3. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA*. 2003;289:2685–2694.
4. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC. Long-term benefits of biventricular pacing in congestive heart failure: results from the Multisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol*. 2002;40:111–118.
5. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol*. 2003;42:1454–1459.
6. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150.
7. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
8. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CARDiac RESynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J*. 2006;27:1928–1932.
9. Linde C, Abraham WT, Gold MR, St. John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834–1843.
10. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338.
11. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385–2395.
12. Stellbrink C, Breithardt OA, Franke A, Sack S, Bakker P, Auricchio A, Pochet T, Salo R, Kramer A, Spinelli J. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol*. 2001;38:1957–1965.
13. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, Freemantle N, Cleland JGF, Tavazzi L, Daubert C. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail*. 2009; 11:699–705.
14. Lecoq G, Leclercq C, Leray E, Crocq C, Alonso C, de Place C, Mabo P, Daubert C. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. *Eur Heart J*. 2005;26:1094–1100.
15. Bleeker GB, Schalij MJ, Molhoek SG, Verwey HF, Holman ER, Boersma E, Steendijk P, Van Der Wall EE, Bax JJ. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. *J Cardiovasc Electrophysiol*. 2004;15:544–549.
16. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P,

- Moss AJ; MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. 2011;123:1061–1072.
17. Linde C, Gold M, Abraham WT, Daubert JC; REVERSE Study Group. Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic left ventricular dysfunction with previous symptoms or mild heart failure: the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Am Heart J*. 2006;151:288–294.
 18. Daubert JC, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Török T, Linde C; REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial. *J Am Coll Cardiol*. 2009;54:1837–1846.
 19. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10:933–989.
 20. Willems JL, Robles de Medina EO, Bernard R, Coumel P, Fisch C, Krikler D, Mazur NA, Meijler FL, Mogensen L, Moret P, Pisa Z, Rautaharju PM, Surawicz B, Watanabe Y, Wellens HJJ. Criteria for intra-ventricular conduction disturbances and pre-excitation. *J Am Coll Cardiol*. 1985;5:1261–1275.
 21. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram, part III: intra-ventricular conduction disturbances a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53:976–981.
 22. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail*. 2001;7:176–182.
 23. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber of Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
 24. St. John Sutton M, Ghio S, Plappert T, Tavazzi L, Scelsi L, Daubert C, Abraham WT, Gold MR, Hassager C, Herre JM, Linde C; REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) Study Group. Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure. *Circulation*. 2009;120:1858–1865.
 25. Reinsch CH. Smoothing by spline functions. *Numerische Mathematik*. 1967;10:177–183.
 26. Egoavil CA, Ho RT, Greenspon AJ, Pavri BB. Cardiac resynchronization therapy in patients with right bundle branch block: analysis of pooled data from the MIRACLE and CONTAK CD trials. *Heart Rhythm*. 2005;2:611–615.
 27. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, Pires LA, Tchou PJ; RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med*. 2007;357:2461–2471.
 28. Leon AR, Niazi I, Herrman K, Stucky M, Galle E, Donahue T; ESTEEM-CRT Investigators. Chronic evaluation of CRT in narrow QRS patients with mechanical dyssynchrony from a multicenter study: ESTEEM-CRT. *Heart Rhythm*. 2008;5:S23–S24.
 29. Sweeney MO, van Bommel RJ, Schalij MJ, Borleffs CJW, Hellkamp AS, Bax JJ. Analysis of ventricular activation using surface electrocardiography to predict left ventricular reverse volumetric remodeling during cardiac resynchronization therapy. *Circulation*. 2010;121:626–634.

CLINICAL PERSPECTIVE

Cardiac resynchronization therapy (CRT) decreases mortality, improves functional status, and induces reverse left ventricular remodeling in selected populations with both mild and advanced heart failure. Despite these benefits of CRT, nearly one third of subjects are typically classified as nonresponders. Characteristics of the surface ECG have been shown to be important predictors of response in several previous studies. In the present analysis of the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, the impact of baseline QRS duration and morphology and the change in QRS duration with pacing on outcomes in mild heart failure with CRT were described. Patients with left bundle-branch block experienced large reductions in left ventricular volumes, whereas patients with non-left bundle-branch block had much smaller decreases. Baseline QRS duration was also a strong predictor of remodeling, with monotonic increases as QRS duration prolonged and no obvious threshold above 120 milliseconds. Similarly, clinical outcomes improved with CRT for left bundle-branch block subjects but not for non-left bundle-branch block subjects, and clinical outcomes increased as QRS duration prolonged. The change in QRS duration with CRT pacing was not an independent predictor of any outcomes after correction for baseline variables. These data indicate that left bundle-branch block and QRS prolongation are markers of reverse remodeling and clinical benefit with CRT in mild heart failure. However, the change in QRS duration with biventricular pacing is not a useful predictor of response independently of the baseline ECG characteristics. Finally, despite the relationship between QRS duration and outcomes, these results do not support the use of any arbitrary QRS duration cutoff >120 to 130 milliseconds for selecting CRT candidates.