ORIGINAL RESEARCH

Interaction of Left Ventricular Size and Sex on Outcome of Cardiac Resynchronization Therapy Among Patients With a Narrow QRS Duration in the EchoCRT Trial

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***Background*—**Longer QRS duration (QRSd) improves, but increased left ventricular (LV) end-diastolic volume (LVEDV) reduces, efficacy of cardiac resynchronization therapy (CRT). QRSd/LVEDV ratios differ between sexes. We hypothesized that in the EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial enrolling patients with heart failure with QRSd <130 ms, those with larger LVEDV would deteriorate but those with the highest QRSd/LVEDV would *improve* with CRT.

***Methods and Results*—**Primary outcome in patients (n=787, 72% men, 93% New York Heart Association class III, QRSd <130 ms, LV ejection fraction ≤35%, LV dilation and dyssynchrony) randomized to CRT-ON or CRT-OFF and followed up for 19 months was compared according to LVEDV (height indexed) or QRSd/LVEDV ratio, in multivariable analysis. Structural remodeling was assessed echocardiographically 6 months after implantation. Patients with baseline LVEDV higher than or equal to median worsened with CRT (death/heart failure hospitalization: CRT-ON versus CRT-OFF, 35.2% versus 24.5% [hazard ratio, 1.64; 95% confidence interval, 1.11–2.42; *P*=0.012]), but those with LVEDV lower than median remained unaffected. Patients with the highest QRSd/LVEDV ratio improved with CRT (death/heart failure hospitalization in top quartile: 20.9% in CRT-ON [n=91] versus 28.3% in CRT-OFF [n=106] [hazard ratio, 0.64; 95% confidence interval, 0.34–1.24; *P*=0.188], versus the remaining quartiles: 31.7% in CRT-ON [n=300] versus 24.8% in CRT-OFF [n=290] [hazard ratio, 1.47; 95% confidence interval, 1.07–2.02; *P*=0.016], test for interaction *P*=0.046). QRSd and dyssynchrony were similar between groups. The 3-way test for interaction indicated no sex-specific effects. However, numerically, men with LVEDV higher than or equal to median accounted for worse outcomes of CRT-ON. Women, with the highest QRSd/LVEDV ratio exhibited significant reverse remodeling.

***Conclusion*—**CRT has opposite effects among patients with heart failure with QRSd <130 ms according to LV size: worsening outcomes in patients with larger LV, but inducing beneficial effects in those with smaller LV.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT00683696. **(*J Am Heart Assoc*. 2018;7: e009592. DOI: 10.1161/JAHA.118.009592.)**

Key Words: cardiac resynchronization therapy • left ventricle size • narrow QRS

Assessment of QRS duration (QRSd) is a key selection criterion for cardiac resynchronization therapy (CRT), recognizing that there is a spectrum of responses. Indications reflect the greatest probability for successful therapy with QRSd >150 ms, less (or no) effect for QRSd <150 ms, and futility (or possible harm) with QRSd <130 ms.[1] However,

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Clinical Perspective

What Is New?

- Although the overall results of the EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial indicated futility or even harm of using cardiac resynchronization therapy in patients with heart failure with QRS duration <130 ms, we discovered that the risk was concentrated among those with larger left ventricular dimensions; conversely patients with longer QRS duration and smaller left ventricular size appeared to benefit from cardiac resynchronization therapy.

What Are the Clinical Implications?

- The assessment of nonelectrical modulators (eg, left ventricular size, sex, and stature) in patients with heart failure may reveal a group with "narrow" QRS duration and smaller ventricles who benefit from cardiac resynchronization therapy.

there is increasing recognition that QRSd may be prolonged not only by reduced myocardial conduction velocity (His-Purkinje lesions) but also by increased left ventricular (LV) dimension acting to extend the "travel distance" of the propagating wavefront.[2] The distinction is important because the former is the target for CRT, but the latter (itself influenced by heart failure [HF] remodeling, sex, and body size/height[3,4]) limits CRT response.[5] Hence, any given QRSd reflects the sum effect of factors with opposite implications for CRT success, and this balance may differ among individuals with identical QRSd values. The ratio of QRSd/LV size may better index CRT substrate. When applied, this was superior to the unadjusted QRSd in predicting successful CRT measured by short-term hemodynamic effects or long-term remodeling among patients with left bundle branch block (LBBB).[3,6] Patients with a high index score (relatively large QRSd and small LV size) had higher probability of CRT response compared with those with a low index score (smaller QRS and large LV size) who could worsen with treatment. Interestingly, this calculation explained CRT inefficacy in some patients with LBBB and QRSd >150 ms (ie, meeting class I CRT indications) and conversely why others (principally women) with narrower QRSd (<150 ms) were successfully treated by CRT. These observations raise the intriguing notion that some patients with QRSd <130 ms, together with lower LV dimensions, may also benefit from CRT.

We tested this hypothesis post hoc in the EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial, which evaluated CRT effect among patients with QRSd <130 ms and LV dilatation,[7] hypothesizing that patients with larger LV end-diastolic volume (LVEDV) would deteriorate but those with the highest QRSd/LVEDV would *improve* with CRT. In addition, because among conventionally selected patients undergoing CRT (LBBB and LV ejection fraction [LVEF] <35%), men have greater LV dilation,[3,6] and numerically a higher all-cause mortality was reported in male patients randomized to CRT-ON in the EchoCRT trial,[8] we assessed interactions of sex with LV size and CRT effect.

Methods

Study Design and Conduct

The study was approved by an institutional review board at each participating site, and participants gave written informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The study protocol and main outcome results of the EchoCRT trial were reported previously.[7] In brief, patients with New York Heart Association class III or IV HF with LVEF of ≤35%, optimized medical therapy with QRSd <130 ms and LV end-diastolic diameter ≥55 mm, and echocardiographic evidence of LV dyssynchrony were randomized 1:1 to CRT-OFF (control) or CRT-ON. Device-implanting physicians and physicians involved in the follow-up were aware of the study group assignment, whereas patients, HF physicians, and study personnel completing the follow-up assessments were not. The trial was terminated early after interim analysis because of futility in reaching the primary end point and an observed overall increase in mortality in the CRT-ON group.

The current analysis was directed towards assessment of the impact of LV size and QRSd/LV size ratio on the effect of CRT in the EchoCRT trial cohort. QRSd was determined from a standard 12-lead ECG recorded at 25 mm/s before implantation, submitted to the ECG Core Laboratory (University of Glasgow, Glasgow, UK), and echocardiographic data from the Echo Core Laboratory (University of Pittsburgh Medical Center, Pittsburgh, PA). All readers were blinded to the treatment group assignment and any clinical data. Correlations between QRSd, LV size, and height were assessed. LV size was derived from preimplantation biplane LVEDV and indexed to height to account for influence of body size (indexed volumes [mL/m] are reported throughout this article). Then, enrolled patients were dichotomized by median LVEDV value ($LVEDV_{Median}$). Because LV size generally is larger in male CRT recipients,[3,6] and men were the driver for worse outcomes with CRT in the whole EchoCRT trial cohort,[8] we compared CRT effect according to LV size in each sex. We then assessed the quotient QRSd/LVEDV to test the hypothesis that patients with larger QRSd/LVEDV ratios benefited from CRT. Because LV enlargement was a criterion for inclusion (thus restricting the available patient population with

lower LVEDV), we compared CRT effects in patients stratified in the top quartile (ie, quartile 4 [Q4]; QRSd/$LVEDV_{Q4}$) versus the remainder (ie, quartile 1–quartile 3 [Q1–Q3]; QRSd/$LVEDV_{Q1–Q3}$). This permitted identification of the subgroup of patients with the least contribution of LV enlargement to QRS prolongation and evaluation of their outcome according to the randomized treatment.

Outcomes were assessed by the prespecified primary efficacy outcome (combination of death from any cause and first hospitalization for worsening HF) and secondary outcomes (ie, all hospitalizations for worsening HF throughout the study, all-cause mortality, and cardiovascular mortality).[7] In addition, we measured changes in echocardiographic structural remodeling from baseline to 6 months after implantation. The combination of LVEF increase of ≥5% and LV end-systolic volume decrease of ≥10% was used as a measure of positive CRT effect.[9] Results were compared between sexes.

Statistical Analysis

The study results were analyzed at the independent Statistical Centre at the Robertson Centre for Biostatistics, University of Glasgow. (One of us [N.V.] had full access to all the data in the study and takes responsibility for its integrity and the data analysis.) Baseline characteristics were reported as means and SDs for continuous variables and counts and percentages for categorical variables, and treatment group comparisons were based on 2-sample *t* test (or Mann-Whitney test) and χ^2 (or Fisher's exact) tests, as appropriate. For primary and secondary outcome analyses, interactions between treatment effects (CRT-ON and CRT-OFF) and selected groups (ie, dichotomized by $LVEDV_{Median}$ and QRSd/$LVEDV_{Q4}$ versus QRSd/$LVEDV_{Q1–Q3}$) were tested for in Cox proportional hazard models. These models included hazard ratios (HRs) with 95% confidence intervals (CIs) that included treatment (CRT-ON and CRT-OFF) adjustments for the following baseline characteristics: sex, country, walking distance, quality-of-life score, sitting systolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, and diuretic use. (The same characteristics, except sex, were used in independent male/female comparisons, followed by 3-way test for interaction.) Time-to-event curves were estimated using the Kaplan-Meier method with the log-rank test. Follow-up was censored at study closure, date of death, LV assist device implantation, heart transplant, withdrawal from the study, or unavailability for follow-up, whichever came first.

For structural remodeling analyses, the proportions of patients with events were compared among groups using a χ^2 test. Tests for interaction were analyzed using a logistic regression model with CRT randomized treatment and baseline LVEDV grouping included as explanatory variables along with an interaction term. Correlations were reported using the Pearson correlation coefficient.

All tests were 2 sided, with $P<0.05$ considered to be significant.

Results

A total of 809 patients were randomized in the EchoCRT trial (405 to CRT-OFF group [control] and 404 to CRT-ON group). The mean follow-up was 19.4 months for all patients and 19.8 months for surviving patients. The study visit compliance rate among patients was 95.5%. Overall patient characteristics in our substudy (n=796) did not differ from the whole trial cohort[7] (eg, age, 58±13 years; 72% men; New York Heart Association class III, 94%; LVEF, 27±6%; LV end-diastolic diameter, 66±8 mm; LVEDV [uncorrected], 190±59 mL; ischemic cardiomyopathy, 53%; hypertension, 66%; diabetes mellitus, 40%; chronic lung disease, 19%; chronic kidney disease, 13%; QRSd [Core Laboratory], 106±13 ms). Correlation (coefficient *r*) of QRSd with LVEDV was 0.32 ($P<0.001$); LVEDV/height, 0.32 ($P<0.001$); LVEF, 0.09 ($P<0.01$); height, 0.04 ($P=0.32$); and body mass index, 0.04 ($P=0.23$). Among patients with available 6-month follow-up echocardiograms (CRT-ON versus CRT-OFF, n=313 versus n=312), there was a larger proportion demonstrating improvement in LV function with CRT (36.4% versus 28.2%; $P=0.028$), but most patients in each group showed no change or deterioration.

LV Size and Outcome

This study group (796 patients with available echocardiographic studies; CRT-ON, n=398; and CRT-OFF, n=398) was dichotomized by $LVEDV_{Median}$/height (105.9 mL/m; interquartile range [IQR], 87.1–127.4 mL/m). Group characteristics are contrasted in Table 1. LV end-diastolic diameter was 11.6% and LVEDV (uncorrected) was 59.4% greater in $LVEDV_{\geq Median}$ versus $LVEDV_{<Median}$. Patients with $LVEDV_{\geq Median}$ were younger, were more frequently men (≈80%) with wider QRSd, had larger body mass index, had less diabetes mellitus, had lower LVEF, and less frequently had underlying ischemic cardiomyopathy. Groups did not differ for dyssynchrony (Table 1), lead position (Table 2), or % CRT pacing (97.7±4.85% versus 97.4±4.69%; $P=0.51$).

CRT did not affect any of the measured outcomes in patients with $LVEDV_{<Median}$ (Table 3). In contrast, among patients with $LVEDV_{\geq Median}$, the primary outcome was worsened significantly by CRT (Figure 1A) and there were more deaths, both overall ($P=0.002$) and attributable to cardiovascular causes ($P=0.001$; significant test for interaction $P=0.036$) (Table 3). When compared, LV structural

Table 1. Characteristics of Patients at Baseline by LVEDV/Height Grouping

Variable	Less Than Median, n	Less Than Median, statistic	Greater Than or Equal to Median, n	Greater Than or Equal to Median, statistic	*P* Value
Age, y	398	60.9 (11/43)	398	55.1 (13.31)	<0.001
Men	398	258 (64.82)	398	316 (79.40)	<0.001
QRS width (site) ms	398	102.9 (12.37)	398	107.6 (12.83)	<0.001
QRS width (core) ms	394	102.7 (12.00)	393	108.9 (12.36)	<0.001
Walking distance, m	390	310.8 (119.66)	390	339.7 (118.41)	<0.001
Quality-of-life score	395	51.1 (24.27)	398	51.4 (24.47)	0.830
NYHA classification					
I	398	1 (0.25)	398	4 (1.01)	*
II	398	4 (1.01)	398	15 (3.77)	
III	398	379 (95.23)	398	368 (92.46)	
IV	398	14 (3.52)	398	11 (2.76)	
BNP, pg/mL	201	240.0 (92.00–586.00)	189	281.0 (112.00–515.00)	0.284
NT-proBNP, pg/mL	184	915.0 (409.50–2331.0)	191	1250.0 (587.00–2373.0)	0.128
Sitting SBP, mm Hg	398	118.8 (18.80)	398	118.6 (20.01)	0.894
Sitting DBP, mm Hg	398	72.0 (11.48)	398	73.4 (12.42)	0.097
BMI, kg/m^2	397	29.2 (6.52)	398	32.5 (15.81)	<0.001
Height, cm	397	170.4 (10.1)	398	172.6 (13.9)	0.012
Ischemic cardiomyopathy	397	236 (59.45)	398	191 (47.99)	0.001
Myocardial infarction >3 mo ago	398	170 (42.71)	398	148 (37.19)	0.111
Percutaneous coronary intervention >3 mo ago	398	157 (39.45)	398	130 (32.66)	0.046
CABG >3 mo ago	398	86 (21.61)	398	63 (15.83)	0.037
Hypertension	391	271 (69.31)	398	256 (64.32)	0.137
Prior ischemic stroke or TIA	396	51 (12.88)	394	44 (11.17)	0.460
Diabetes mellitus	396	173 (43.69)	397	142 (35.77)	0.023
Chronic lung disease	395	72 (18.23)	394	74 (18.78)	0.841
Chronic kidney disease	394	56 (14.21)	396	49 (12.37)	0.446
LVEF biplane, %	398	28.7 (4.93)	398	25.2 (5.55)	<0.001
LV end-diastolic diameter, mm	398	62.7 (5.48)	398	70.0 (7.42)	<0.001
LVEDV, mL		145.7 (26.2)		232.2 (49.9)	<0.001
Qualified by TDI and/or radial strain dyssynchrony					
TDI only	397	111 (27.96)	398	85 (21.36)	0.061
Radial strain only	397	81 (20.40)	398	100 (25.13)	
TDI and radial strain	397	205 (51.64)	398	213 (53.52)	
Medication					
ACE inhibitor or ARB	398	374 (93.97)	398	382 (95.98)	0.194
Aldosterone antagonist	398	220 (55.28)	398	257 (64.57)	0.007
β Blocker	398	385 (96.73)	398	384 (96.48)	1.000
Diuretic agent	398	336 (84.42)	398	351 (88.19)	0.122

Categorical variable number (percentage) values are reported. Continuous variable mean (SD) values are reported, except for BNP and NT-proBNP, for which median (interquartile range) values are presented. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TDI, tissue Doppler imaging; and TIA, transient ischemic attack.
**P* value not reported because of small numbers.

Table 2. LV Lead Location, by Study Grouping

Location	Less Than Median (n=332)	Greater Than or Equal to Median (n=316)
Study grouping: LVEDV		
Basal	59 (17.8)	64 (20.3)
Mid	214 (64.5)	207 (65.5)
Apical	59 (17.8)	45 (14.2)
P=0.40		
	Q1–Q3 (n=481)	Q4 (n=160)
Study grouping: QRS/LVEDV		
Basal	93 (19.3)	30 (18.8)
Mid	315 (65.5)	101 (63.1)
Apical	73 (15.2)	29 (18.1)
P=0.68		

Data are given as number (percentage). LV indicates left ventricular; LVEDV, LV end-diastolic volume; and Q, quartile.

improvement was better with CRT-ON in $LVEDV_{<Median}$ than with CRT-OFF (38.8% [n=59] versus 27% [n=44]; *P*=0.025), but unchanged in $LVEDV_{\geq Median}$ (but interaction between the CRT treatment and the LVEDV grouping was nonsignificant: *P*=0.34).

Sexes were tested separately. Men had larger LVEDV than women (median, 109.6 [IQR, 91.2–130.6] versus 96.2 [80.8–116.3] mL/m; *P*<0.001). CRT in men with $LVEDV_{<Median(Men)}$ had no effect. In contrast, outcomes were significantly worsened by CRT in $LVEDV_{\geq Median(Men)}$ (Table 4; Figure 1B). The primary outcome was observed more frequently in this group (Figure 1B). Cardiovascular death and number of patients with HF hospitalizations increased significantly (Table 4). Thus, during the trial, 21 of 150 patients with $LVEDV_{\geq Median(Men)}$ (14%) in the CRT-ON group experienced cardiovascular death, compared with 4 of 137 (2.9%) in the CRT-OFF group (HR, 7.85; 95% CI, 2.17–28.32; *P*=0.002; significant test for interaction with $LVEDV_{<Median(Men)}$ *P*=0.034). The number of patients with HF hospitalizations increased with CRT: 46 of 150 patients with $LVEDV_{\geq Median(Men)}$ (30.7%) in CRT-ON group versus 25 of 137 (18.25%) in the control group (HR, 1.99; 95% CI, 1.17–3.38; *P*=0.011; test for interaction with $LVEDV_{<Median(Men)}$ *P*=0.039). No significant LV structural changes occurred at 6 months after implantation among men (n=450) with CRT-ON (n=231) versus CRT-OFF (n=219) in either $LVEDV_{\geq Median(Men)}$ or $LVEDV_{<Median(Men)}$.

In women, CRT did not worsen outcomes in $LVEDV_{\geq Median(Women)}$ compared with $LVEDV_{<Median(Women)}$, but analysis is limited by the relatively few patients in each group and paucity of events (Table 4; Figure 1C). Among women (n=175), CRT resulted in no change in $LVEDV_{\geq Median(Women)}$, but positive structural remodeling occurred in $LVEDV_{<Median(Women)}$ (46.5% versus 25% in CRT-OFF; *P*=0.03 [although test for interaction was nonsignificant {*P*=0.25}]).

A 3-way test of interaction to test whether sex influenced effects of LVEDV on the relationship between CRT and outcome found no difference between men and women for any of the end points.

Table 3. End Point Results by LVEDV Grouping, All Subjects

End Point	Subgroup	CRT-OFF	CRT-OFF, No. (%) With Event	CRT-ON	CRT-ON, No. (%) With Event	Fully Adjusted Hazard Ratio (95% Confidence Interval), *P* Value*	*P* Value for Interaction Between Randomized Treatment and Groupings
Death or HF hospitalization	Less than median	203	54 (26.60)	195	44 (22.56)	0.95 (0.62–1.44), 0.793	0.056
	Greater than or equal to median	196	48 (24.49)	202	71 (35.15)	1.64 (1.11–2.42), 0.012	
Death	Less than median	203	17 (8.37)	195	18 (9.23)	1.19 (0.58–2.44), 0.631	0.054
	Greater than or equal to median	196	9 (4.59)	202	26 (12.87)	3.71 (1.60–8.61), 0.002	
HF hospitalization	Less than median	203	44 (21.67)	195	36 (18.46)	0.96 (0.60–1.53), 0.857	0.149
	Greater than or equal to median	196	46 (23.47)	202	62 (30.69)	1.52 (1.01–2.27), 0.042	
CVD death	Less than median	203	11 (5.42)	195	13 (6.67)	1.37 (0.58–3.22), 0.477	0.036
	Greater than or equal to median	196	6 (3.06)	202	23 (11.39)	5.26 (1.93–14.30), 0.001	

CRT indicates cardiac resynchronization therapy; CVD, cardiovascular disease; HF, heart failure; and LVEDV, left ventricular end-diastolic volume.
*Hazard ratio (95% confidence interval) adjusted for country, sex, walking distance, quality of life, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, and diuretic use; *P* value from Wald test.

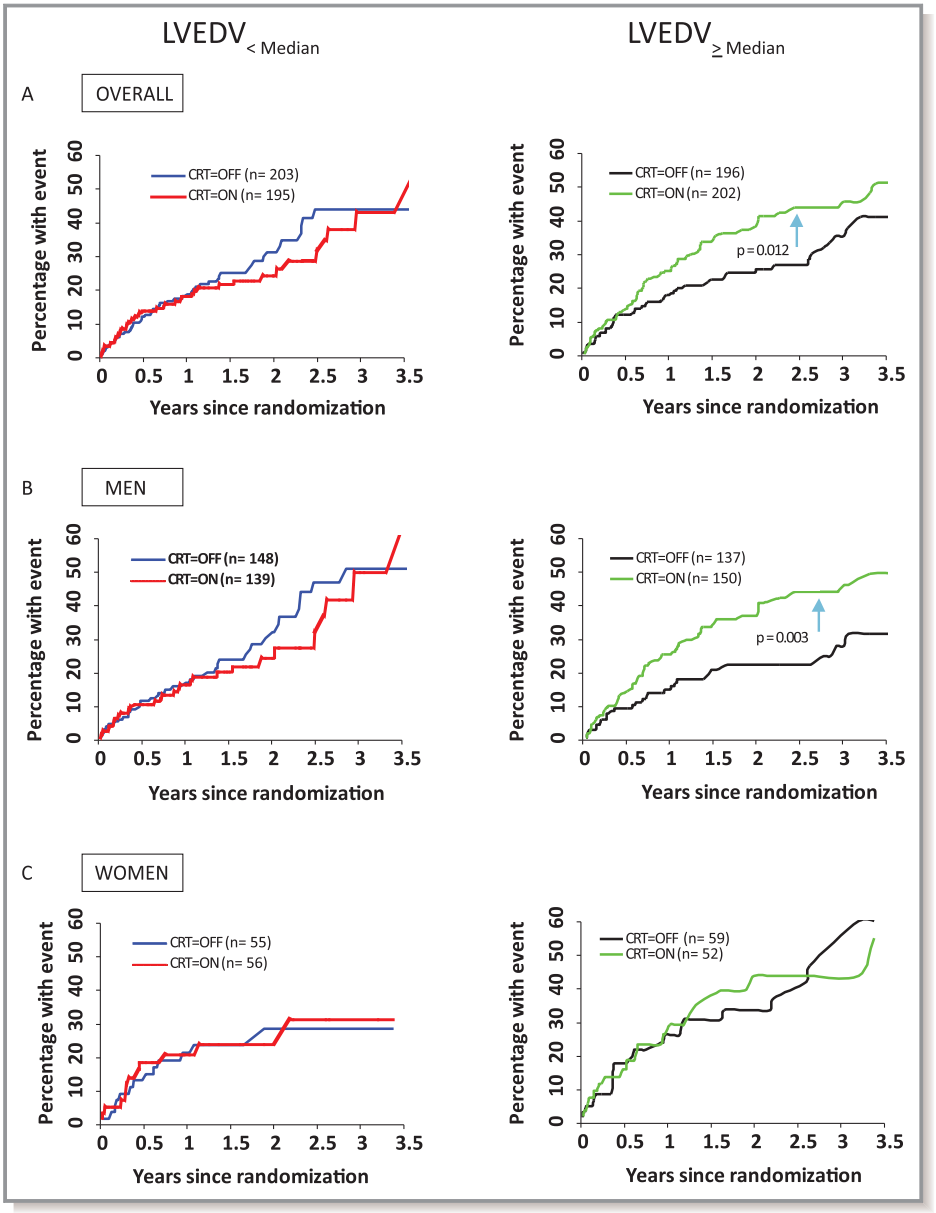

Figure 1. Cardiac resynchronization therapy (CRT) effect by left ventricular (LV) size: primary outcomes. Primary outcomes (death from any cause or hospitalization for worsening heart failure) are reported in patient groups dichotomized by median values of LV end-diastolic volume (LVEDV). A, Overall. Left panel: Among patients with LVEDV lower than median ($LVEDV_{<Median}$), CRT had no significant effect. Right panel: In contrast, among those patients with LVEDV is higher than or equal to median ($LVEDV_{\geq Median}$), the primary outcome occurred in 71 of 202 patients (35.2%) in the CRT-ON group vs 48 of 196 patients (24.5%) in the control group (hazard ratio with CRT, 1.64; 95% confidence interval [CI], 1.11–2.42; *P*=0.012). B, Men. Left panel: In $LVEDV_{<Median(Men)}$, CRT had no significant effect. Right panel: In $LVEDV_{\geq Median(Men)}$, the primary outcome occurred in 54 of 150 patients (36%) in the CRT-ON group vs 27 of 137 patients (19.7%) in the control group (hazard ratio with CRT, 2.14; 95% CI, 1.30–3.55; *P*=0.003; significant test for interaction with $LVEDV_{<Median[Men]}$ *P*=0.018). C, Women. CRT had no significant effect in women, with $LVEDV_{<Median(Women)}$ (left panel) or $LVEDV_{\geq Median(Women)}$ (right panel).

QRSd/LVEDV Ratio and Outcome

The QRS and LV size analysis population included 787 patients with core laboratory electrocardiographic analyses (396 in CRT-OFF and 391 in CRT-ON). Among 621 patients with available echocardiographic data (CRT-ON versus CRT-OFF, n=311 versus n=310), there was a larger proportion demonstrating improvement in LV function with CRT at 6 months after CRT (36.3% versus 27.7%; *P*=0.022).

QRSd/LVEDV ratio in the overall population was a median of 0.99 ms/mL per m (IQR, 0.83–1.19 ms/mL per

Table 4. End Point Results by LVEDV Grouping Separated by Sex

End Point	Subgroup	CRT-OFF	CRT-OFF, No. (%) With Event	CRT-ON	CRT-ON, No. (%) With Event	Fully Adjusted Hazard Ratio (95% Confidence Interval), *P* Value*	*P* Value for Interaction Between Randomized Treatment and Groupings
Men (n=574)							
Death or HF hospitalization	Less than median	148	41 (27.70)	139	31 (22.30)	0.95 (0.57–1.58), 0.838	0.018
	Greater than or equal to median	137	27 (19.71)	150	54 (36.00)	2.14 (1.30–3.55), 0.003	
Death	Less than median	148	14 (9.46)	139	15 (10.79)	1.32 (0.59–2.96), 0.498	0.084
	Greater than or equal to median	137	7 (5.11)	150	24 (16.00)	4.16 (1.57–11.04), 0.004	
HF hospitalization	Less than median	148	32 (21.62)	139	23 (16.55)	0.90 (0.50–1.62), 0.728	0.039
	Greater than or equal to median	137	25 (18.25)	150	46 (30.67)	1.99 (1.17–3.38), 0.011	
CVD death	Less than median	148	9 (6.08)	139	11 (7.91)	1.35 (0.51–3.61), 0.547	0.034
	Greater than or equal to median	137	4 (2.92)	150	21 (14.00)	7.85 (2.17–28.32), 0.002	
Women (n=222)							
Death or HF hospitalization	Less than median	55	13 (23.64)	56	12 (21.43)	0.61 (0.24–1.54), 0.295	0.530
	Greater than or equal to median	59	21 (35.59)	52	18 (34.62)	1.13 (0.53–2.44), 0.753	
Death	Less than median	55	3 (5.45)	56	3 (5.36)	0.70 (0.11–4.27), 0.699	0.841
	Greater than or equal to median	59	2 (3.39)	52	2 (3.85)	0.63 (0.03–12.19), 0.758	
HF hospitalization	Less than median	55	12 (21.82)	56	12 (21.43)	0.68 (0.27–1.76), 0.430	0.730
	Greater than or equal to median	59	21 (35.59)	52	17 (32.69)	1.08 (0.50–2.37), 0.838	
CVD death	Less than median	55	2 (3.64)	56	2 (3.57)	0.44 (0.04–5.48), 0.527	0.640
	Greater than or equal to median	59	2 (3.39)	52	2 (3.85)	0.63 (0.03–12.19), 0.758	

Three-way test of interaction of sex with effects of LVEDV/height on CRT effect for outcomes: death/HF hospitalization, *P*=0.23; death, *P*=0.52; HF hospitalization, *P*=0.19; and CVD death, *P*=0.47. CRT indicates cardiac resynchronization therapy; CVD, cardiovascular disease; HF, heart failure; and LVEDV, left ventricular end-diastolic volume.
*Hazard ratio (95% confidence interval) adjusted for country, walking distance, quality of life, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, and diuretic use; *P* value from Wald test.

m). QRSd/LVEDV$_{Q4}$ patients, when compared with QRSd/LVEDV$_{Q1–Q3}$ patients, were older and less tall, with a higher proportion of women, had higher LVEF, and more frequently had underlying ischemic cardiomyopathy, lower body mass index, and more diabetes mellitus (Table 5). LV end-diastolic diameter was 11.6%, and LVEDV (uncorrected) was 60.5% greater in QRSd/LVEDV$_{Q1–Q3}$ patients compared with QRSd/LVEDV$_{Q4}$ patients. There was no difference between groups for dyssynchrony, QRSd, LV lead position (Table 2), or %CRT pacing (97.5±4.88% versus 97.6±4.53%; *P*=0.87).

After a mean follow-up of 19.4 months, CRT elicited opposite effects in study groups (Table 6, Figure 2). In multivariable analysis, CRT-ON *increased* the proportion of patients reaching the primary end point in QRSd/LVEDV$_{Q1–Q3}$ (31.7% in CRT-ON [n=300] versus 24.8% in CRT-OFF [n=290]; HR, 1.47; 95% CI, 1.07–2.02; *P*=0.016), but *decreased* it in QRSd/LVEDV$_{Q4}$ (death/HF hospitalization, 20.9% in CRT-ON [n=91] versus 28.3% in CRT-OFF [n=106]; HR, 0.64; 95% CI, 0.34–1.24; borderline significant test for interaction *P*=0.046). Stronger differences were observed for all-cause mortality (test for interaction *P*=0.038). Reverse structural remodeling was increased in QRSd/LVEDV$_{Q4}$ (Figure 3A). Hence, patients in QRSd/LVEDV$_{Q4}$ gained benefit from CRT.

Effects in each sex were evaluated separately. QRSd/LVEDV ratio was greater in women (median, 1.1 [IQR, 0.9–1.3] ms/mL) versus men (median, 1.0 [IQR, 0.8–1.2] ms/mL; *P*<0.001). Among men, primary or secondary outcomes were unaffected by CRT in QRSd/LVEDV$_{Q4\ Men}$ but significantly worsened in QRSd/LVEDV$_{Q1–Q3\ Men}$ (Table 7). In women, outcomes were unaffected by CRT in QRSd/LVEDV$_{Q1–Q3\ Women}$ or QRSd/LVEDV$_{Q4\ Women}$ (Table 7). A 3-way test of interaction to test whether sex influenced effects of QRSd/LVEDV on the relationship between CRT and outcome found no difference between men and women for any of the end points. (However, the few female patients in QRSd/LVEDV$_{Q4}$ [CRT-ON=22; CRT-OFF=24] and paucity of events occurring during the time interval assessed may underpower this comparison.) Echocardiographic data were available in 175

Table 5. Characteristics of Patients at Baseline by QRS/LVEDV Grouping, All Subjects

Variable	Q1–Q3, n	Q1–Q3, statistic	Q4, n	Q4, statistic	*P* Value
Age, y	590	56.3 (12.85)	197	63.1 (11.11)	<0.001
Men	590	442 (74.92)	197	123 (62.44)	<0.001
QRS width (site) ms	590	104.8 (12.81)	197	106.3 (12.85)	0.168
QRS width (core) ms	590	105.5 (12.26)	197	107.0 (13.38)	0.146
Walking distance, m	581	328.5 (119.02)	191	313.7 (120.70)	0.137
Quality-of-life score	588	51.6 (24.73)	196	49.8 (23.24)	0.362
NYHA classification					
I	590	4 (0.68)	197	1 (0.51)	*
II	590	16 (2.71)	197	2 (1.02)	
III	590	552 (93.56)	197	188 (95.43)	
IV	590	18 (3.05)	197	6 (3.05)	
BNP, pg/mL	292	240.0 (109.00–569.00)	95	226.0 (72.00–540.00)	0.110
NT-proBNP, pg/mL	276	1167.0 (535.50–2328.5)	94	919.0 (443.00–2356.0)	0.720
Sitting SBP, mm Hg	590	118.2 (19.23)	197	120.3 (19.37)	0.193
Sitting DBP, mm Hg	590	72.9 (12.10)	197	72.4 (11.13)	0.578
BMI, kg/m^2	590	31.7 (13.57)	196	28.2 (6.28)	<0.001
Height cm	590	172.2 (12.78)	196	169.2 (10.35)	0.003
Ischemic cardiomyopathy	589	301 (51.10)	197	121 (61.42)	0.012
Myocardial infarction >3 mo ago	590	231 (39.15)	197	82 (41.62)	0.539
Percutaneous coronary intervention >3 mo ago	590	210 (35.59)	197	75 (38.07)	0.531
CABG >3 mo ago	590	105 (17.80)	197	42 (21.32)	0.272
Hypertension	587	392 (66.78)	193	129 (66.84)	0.988
Prior ischemic stroke or TIA	585	68 (11.62)	196	24 (12.24)	0.815
Diabetes mellitus	588	229 (38.95)	196	82 (41.84)	0.474
Chronic lung disease	585	111 (18.97)	195	35 (17.95)	0.750
Chronic kidney disease	587	75 (12.78)	194	28 (14.43)	0.554
LVEF biplane, %	590	26.1 (5.56)	197	29.8 (4.31)	<0.001
LV end-diastolic diameter, mm	590	68.0 (7.32)	197	61.4 (5.59)	<0.001
LVEDV, mL		208.5 (53.8)		129.9 (23.7)	<0.001
Qualified by TDI and/or radial strain dyssynchrony					
TDI only	590	138 (23.39)	196	56 (28.57)	0.188
Radial strain only	590	142 (24.07)	196	37 (18.88)	
TDI and radial strain	590	310 (52.54)	196	103 (52.55)	
Medication					
ACE inhibitor or ARB	590	563 (95.42)	197	184 (93.40)	0.263
Aldosterone antagonist	590	364 (61.69)	197	108 (54.82)	0.088
β Blocker	590	569 (96.44)	197	192 (97.46)	0.646
Diuretic agent	590	519 (87.97)	197	162 (82.23)	0.041

Categorical variable number (percentage) values are reported. Continuous variable mean (SD) values are reported, except for BNP and NT-proBNP, for which median (interquartile range) values are presented. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LF ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; SBP, systolic blood pressure; TDI, tissue Doppler imaging; and TIA, transient ischemic attack.
**P* value not reported because of small numbers.

Table 6. End Point Results by QRSd/LVEDV Grouping, All Subjects

End Point	Subgroup	CRT-OFF	CRT-OFF, No. (%) With Event	CRT-ON	CRT-ON, No. (%) With Event	Fully Adjusted Hazard Ratio (95% Confidence Interval), *P* Value*	*P* Value for Interaction Between Randomized Treatment and Groupings
Death or HF hospitalization	Q1–Q3	290	72 (24.83)	300	95 (31.67)	1.47 (1.07–2.02), 0.016	0.046
	Q4	106	30 (28.30)	91	19 (20.88)	0.64 (0.34–1.24), 0.188	
Death	Q1–Q3	290	16 (5.52)	300	35 (11.67)	2.53 (1.36–4.72), 0.003	0.038
	Q4	106	10 (9.43)	91	8 (8.79)	0.74 (0.24–2.31), 0.609	
HF hospitalization	Q1–Q3	290	66 (22.76)	300	82 (27.33)	1.40 (1.00–1.95), 0.050	0.104
	Q4	106	24 (22.64)	91	15 (16.48)	0.63 (0.31–1.28), 0.203	
CVD death	Q1–Q3	290	11 (3.79)	300	29 (9.67)	3.13 (1.51–6.47), 0.002	0.079
	Q4	106	6 (5.66)	91	6 (6.59)	1.00 (0.22–4.59), 1.000	

CRT indicates cardiac resynchronization therapy; CVD, cardiovascular disease; HF, heart failure; LVEDV, left ventricular end-diastolic volume; Q, quartile; and QRSd, QRS duration. *Hazard ratio (95% confidence interval) adjusted for country, sex, walking distance, quality of life, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, and diuretic use; *P* value from Wald test.

women (CRT-ON versus CRT-OFF, 82 versus 93) and 446 men (CRT-ON versus CRT-OFF, 229 versus 217). No significant changes were observed in men (Figure 3B). However, CRT elicited significant reverse remodeling in $QRSd/LVEDV_{Q4\ Women}$ (Figure 3C).

Discussion

Among patients with HF with QRSd <130 ms in the EchoCRT trial, those with larger LV dimensions deteriorated with treatment, but in contrast those with larger QRSd and smaller LV size appeared to benefit from CRT. Baseline dyssynchrony did not separate these groups.

The QRSd represents the time taken for the electrical wave of myocardial depolarization to move from the His-Purkinje system through the ventricular myocardium. It is prolonged most obviously by HPS delay (eg, LBBB) but also by increased LV dimension, which increases "path length."[2] LV size itself may increase with cardiomyopathy and larger body size. These correlations have been observed in healthy subjects and in patients with cardiomyopathy and LBBB.[10–14] Among patients with normal QRSd with normal LV function, Stewart et al found that each 10 ms increase in QRSd was associated with a 9.2% increase in LVEDV.[13] Moreover, increase in QRSd was associated with greater height (but not body mass index). We report similar, although modest, correlations in our population with HF with "narrow" QRSd (<130 ms). The correlation of QRSd and LVEDV was 0.32, and the correlation of LVEDV with patient height was 0.30 (thus, reported LVEDV values were normalized for height [mL/m]). No sex differences were observed. However, although a prior study of patients with normal QRSd (but no cardiomyopathy) found no significant sex difference across QRSd when linked to LVEDV and height,[13] here in patients with narrow QRS and HF, we discovered a slight (10%) but significant sex difference in QRSd/LVEDV/height. These interactions are important because any given value of QRSd, the determinant of any individual's candidacy for CRT, represents a composite result of delayed myocardial conduction (ie, the substrate for CRT) but also increased LV size (mass/volume), which may degrade CRT benefit.[5] The ratio of QRSd/LV size was shown recently to be a better predictor of CRT effect than QRSd alone in patients with LBBB, and it differed between sexes and among individuals.[3,6]

Herein, we extended these principles to patients with HF with QRSd <130 ms. First, we tested the impact of LV size, noting that the EchoCRT trial enrolled patients with LV dilatation (assessed by LV diameter). LV volume ranged widely, but QRSd ranged only slightly. We discovered that CRT effect was neutral in those with $LVEDV_{<Median}$, but it was deleterious in patients with $LVEDV_{\geq Median}$ (Figure 1). (This observation is consistent with the negative impact of larger LV size on the success of CRT applied for standard indications.[5]) This may explain our prior result that male patients determined the worse outcomes of CRT-ON for the entire EchoCRT trial cohort[8]: more men were enrolled, and their LV size was larger, but this was not a sex-specific effect, according to our results. Next, we assessed the impact of QRSd/LV size stratified by quartiles. The primary outcome was worsened among patients treated by CRT in those with lower QRSd/LV size, but it was possibly improved in the highest quartile ($QRSd/LVEDV_{Q4}$) (Figure 2) (similar to prior observations in patients with LBBB[3,6]). Effects on overall death and on structural remodeling indexes were consistent, with CRT benefit in $QRSd/LVEDV_{Q4}$.

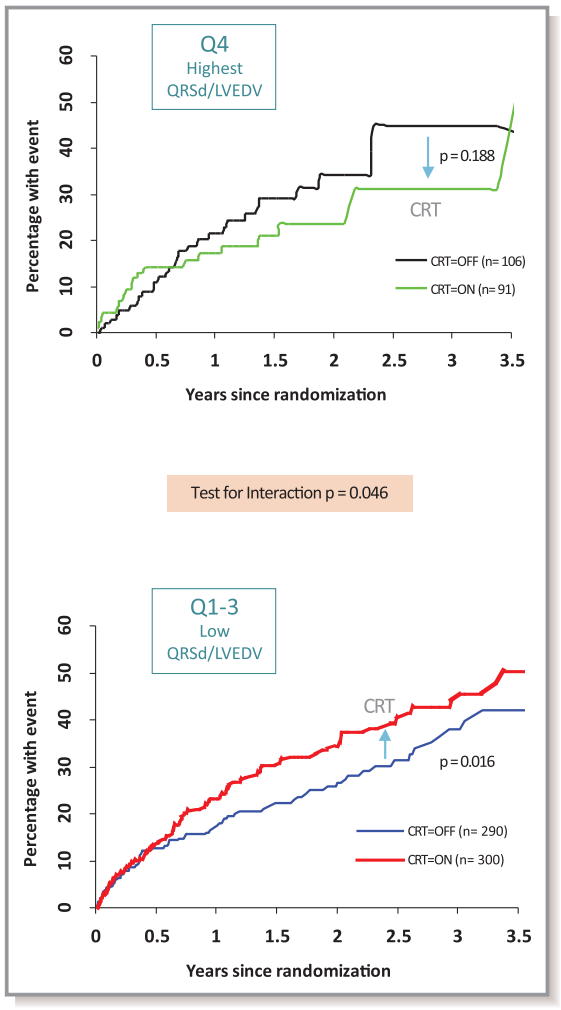

Figure 2. Cardiac resynchronization therapy (CRT) effect by the ratio of QRS duration (QRSd)/left ventricular (LV) size: primary outcomes. Primary end point (death from any cause or hospitalization for worsening heart failure) is contrasted for treatment effects in patients grouped according to quartile (Q) ranges (QRSd/LV end-diastolic volume $[LVEDV]_{Q1–Q3}$ vs $QRSd/LVEDV_{Q4}$). CRT caused deterioration in $QRSd/LVEDV_{Q1–Q3}$ but improvement in $QRSd/LVEDV_{Q4}$ (hazard ratio, 0.64; 95% confidence interval, 0.34–1.24; significant test for interaction P=0.046).

Notably, although CRT elicited opposite effects in these 2 groups (ie $QRSd/LVEDV_{Q1–Q3}$ vs $QRSd/LVEDV_{Q4}$), QRSd and echocardiographic dyssynchrony indexes were similar (ie, these were not differentiators). There was a significant sex difference in QRSd/LVEDV ratio: it was greater in women. Despite this favorable substrate, no sex difference between CRT response in $QRSd/LVEDV_{Q1–Q3}$ and $QRSd/LVEDV_{Q4}$ was found in multivariable analysis for the primary and secondary outcomes. Although there were proportionally more women in $QRSd/LVEDV_{Q4}$, they were still a minority (CRT-ON versus CRT-OFF, 22 versus 24) and experienced few events, underpowering this comparison. Interestingly, improved structural remodeling in $QRSd/LVEDV_{Q4}$ was largely accounted for by CRT effects in women (Figure 3).

The demonstration that some patients with QRS <130 ms may derive benefit from CRT may appear counterintuitive, because CRT aims to reverse delayed LV depolarization, typically LBBB. However, normal QRSd is 85 to 92 ms, and the cut point of 120 ms to select “wide” was arbitrarily defined.[11,15–17] Hence, it is conceivable that some patients with QRSd <130 ms may have significant LV conduction delay that may form the substrate for successful CRT. However, simple QRSd cut points failed to separate subgroups with positive response to CRT in the EchoCRT trial, as reported previously.[18] Outcomes of patients with QRSd 120 to 130 ms did not differ from those with QRSd <120 ms. Elsewhere, it is well appreciated that accepted LBBB criteria may be seen with QRSd <130 ms, usually in women with smaller stature, and CRT may be beneficial, an effect attributed to smaller heart size.[11] Inclusion of height (and presumably its effect on LV size) in an individual patient meta-analysis of randomized CRT trials supported CRT benefit for patients of shorter stature and QRS <130 ms.[4] Conversely, a nonresponse rate of >20% persisted among patients undergoing CRT with class I indications (LBBB and QRS >150 ms), minimal comorbidities, and well-sited LV leads, an effect at least partially attributable to excessive LV dilatation.[3] Collectively, these reports may explain why QRSd alone is an incomplete predictor of CRT response. Although this influence of LV size on QRSd is recognized in electrocardiographic guidelines,[2] it has not been included in the electrocardiographic criteria exercised for CRT selection.

Our results have significant implications. There has been recurring interest in transferring the well-established benefits of CRT in patients with HF with a wide QRSd to those with narrow QRSd (<130 ms), who account for most patients with HF. Despite anecdotal experience and initial promise from small studies selecting narrow QRSd patients on the basis of echocardiographic evidence of dyssynchrony, results from subsequent randomized trials have been disappointing.[19] Indeed, the overall results of the EchoCRT trial pointed to futility of CRT. The current study shows that inclusion of LV dimension and height in conjunction with QRSd separated groups who were harmed versus others who may gain benefit. Because the trial required LV dilation for enrollment, male patients (72%) dominated the cohort and determine overall trial results. Under these conditions, the isolation of a minority sustaining a positive effect is all the more striking. Because this group was characterized by smallest LV size, and the trial excluded patients with LV diastolic diameter <55 mm, it likely underrepresents the fraction of patients with HF with QRS <130 ms but high QRSd/LVEDV ratio in the community.

Strengths and Limitations

Although conducted post hoc, this analysis assessed prespecified end points using prospectively collected data sets, requiring no additional review or imputation. Electrocardiographic and echocardiographic data were adjudicated in core laboratories. Analyses were investigator driven (N.V.) and conducted independently without involvement of the sponsor. However, our conclusions should be interpreted as hypothesis generating, because the trial was prematurely terminated, reducing the statistical power of any subgroup analysis and tests for interactions. QRSd/LVEDV ratio was not a stratification factor at trial entry but LV dilatation was, greatly reducing the number of patients with smaller ventricles and the proportion of female enrollees (ie, our interest groups). We indexed LVEDV to height. Indexing LV volumes to body size has not been consistently followed in CRT studies and may contribute to differing conclusions of efficacy among different studies.[20] Structural remodeling data are restricted to baseline to 6-months postimplantation comparison in 621 patients (ie, 78% of the cohort) and not aligned with outcome measures that were assessed at 19 months. Separating contributions to QRSd into either increased path length (size) or conduction slowing by ratio is an approximate method. HF remodeling is a complex process affecting cardiomyocyte and interstitium. Impulse propagation may be affected by LV dilatation but also at tissue, cellular, and subcellullar levels. Thus fibrosis, scar, and reduced intercellular coupling will affect conduction velocity as well as path length. We can only speculate on mechanisms. LV epicardially paced wave fronts during CRT generally propagate more slowly than normal intrinsic conduction and are negatively inotropic, even in normal myocardium.[21] This action may be exaggerated in dilated LVs without myocardial conduction delay, and risks harm. On the contrary, when myocardial conduction is retarded, the same stimulation in a smaller ventricle may restore electrical synchrony and be clinically beneficial.

Conclusion

In the EchoCRT trial, enrolled patients displayed large heterogeneity in LV size, and the negative effects of CRT were concentrated in men with larger ventricles. Conversely, CRT appeared to be beneficial in a minority with smallest indexed LV volumes. These results add to the growing body of data that QRSd assessment for CRT selection should include attention to the nonelectrical modulating influences of LV size, sex, and stature.[3,4,6] The hypothesis that CRT may be beneficial in patients with HF with narrow QRSd and smaller ventricles merits prospective evaluation.

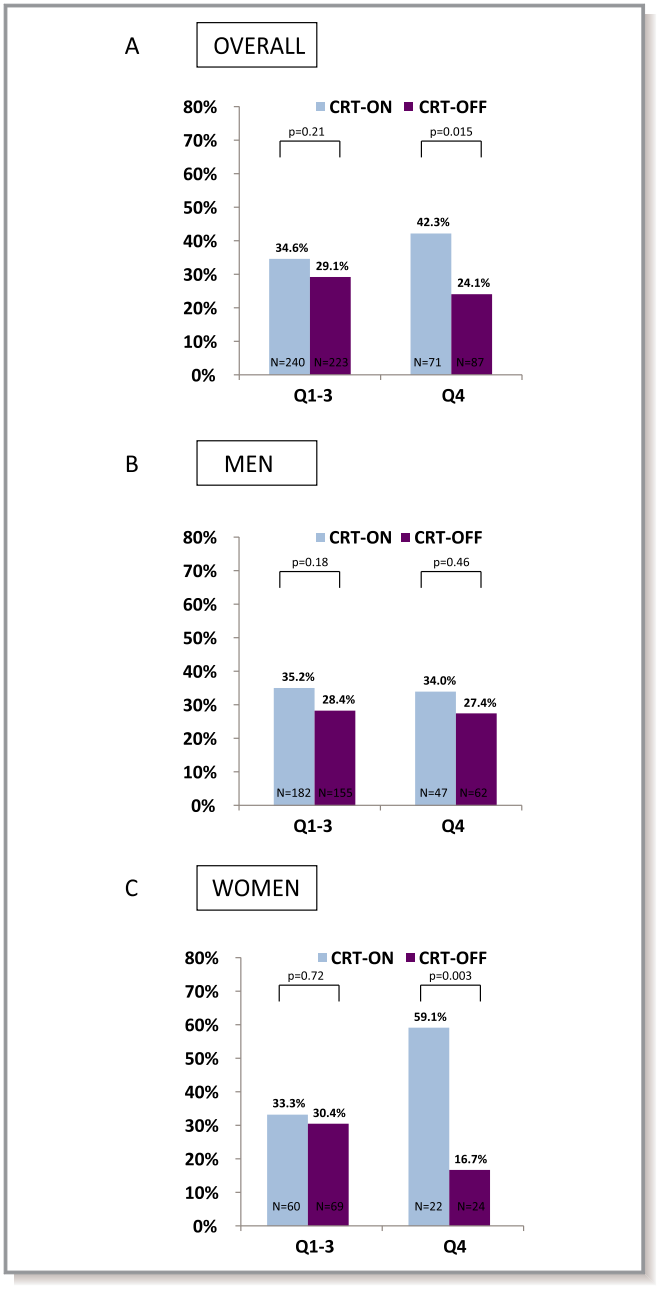

Figure 3. Structural remodeling. Figures depict proportions of patients in each group who demonstrated the combination of left ventricular (LV) ejection fraction increase of ≥5% and LV end-systolic volume decrease of ≥10% (ie, sustained a positive structural remodeling[9]) in response to cardiac resynchronization therapy (CRT) in patients grouped according to quartile (Q) ranges (QRS duration [QRSd]/LV end-diastolic volume [LVEDV]$_{Q1–Q3}$ vs QRSd/LVEDV$_{Q4}$). A, Overall. LV function improved in CRT-ON vs CRT-OFF (42.3% [n=30] vs 24.1% [n=21]) (*P*=0.015) in the Q4 group. In comparison, there was no change in QRSd/LVEDV$_{Q1–Q3}$ (34.6% [n=83] in CRT-ON vs 29.1% [n=65] in CRT-OFF; *P*=0.21; test for interaction *P*=0.17). By sex. Echocardiographic data were available in 175 women (CRT-ON vs CRT-OFF, 82 vs 93) and 446 men (CRT-ON vs CRT-OFF, 229 vs 217). CRT in men (B) produced no effect, but in women (C), a beneficial effect was seen in QRSd/LVEDV$_{Q4Women}$ (test for interaction *P*=0.02).

Table 7. Outcomes According to QRS/LVEDV, Separated by Sex

End Point	Subgroup	CRT-OFF	CRT-OFF, No. (%) With Event	CRT-ON	CRT-ON, No. (%) With Event	Fully Adjusted Hazard Ratio (95% Confidence Interval), *P* Value*	*P* Value for Interaction Between Randomized Treatment and Groupings
Men (n=565)							
Death or HF hospitalization	Q1–Q3	204	45 (22.06)	219	67 (30.59)	1.62 (1.09–2.41), 0.016	0.142
	Q4	78	23 (29.49)	64	17 (26.56)	0.83 (0.40–1.74), 0.628	
Death	Q1–Q3	204	12 (5.88)	219	29 (13.24)	2.49 (1.21–5.15), 0.013	0.218
	Q4	78	9 (11.54)	64	9 (14.06)	1.28 (0.41–3.94), 0.671	
HF hospitalization	Q1–Q3	204	40 (19.61)	219	56 (25.57)	1.52 (1.00– 2.32), 0.052	0.218
	Q4	78	17 (21.79)	64	12 (18.75)	0.82 (0.35–1.93), 0.657	
CVD death	Q1–Q3	204	8 (3.92)	219	23 (10.50)	2.74 (1.16–6.49), 0.022	0.550
	Q4	78	5 (6.41)	64	8 (12.50)	1.74 (0.40–7.49), 0.456	
Women (n=222)							
Death or HF hospitalization	Q1–Q3	85	26 (30.59)	81	24 (29.63)	1.16 (0.62–2.19), 0.646	0.513
	Q4	29	8 (27.59)	27	6 (22.22)	0.63 (0.16–2.54), 0.514	
Death	Q1–Q3	85	3 (3.53)	81	4 (4.94)	1.39 (0.23–8.47), 0.722	0.180
	Q4	29	2 (6.90)	27	1 (3.70)	0.49 (0.03–8.22), 0.619	
HF hospitalization	Q1–Q3	85	26 (30.59)	81	23 (28.40)	1.12 (0.59–2.13), 0.729	0.749
	Q4	29	7 (24.14)	27	6 (22.22)	0.79 (0.18–3.58), 0.763	
CVD death	Q1–Q3	85	3 (3.53)	81	4 (4.94)	1.39 (0.23–8.47), 0.722	. . .
	Q4	29	1 (3.45)	27	0 (0.00)		

Three-way test of interaction of sex with effects of QRS/LVEDV on CRT effect for outcomes: death/HF hospitalization, *P*=0.65; death, *P*=0.79; HF hospitalization, 0.52; and CVD death, *P*=0.98. CRT indicates cardiac resynchronization therapy; Q1-3, QRSd/LVEDVQ1–Q3 ; Q4, QRSd/LVEDVQ4; CVD, cardiovascular disease; HF, heart failure; LVEDV, left ventricular end-diastolic volume; and Q, quartile.

*Hazard ratio (95% confidence interval) adjusted for country, walking distance, quality of life, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, and diuretic use; *P* value from Wald test.

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