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Echocardiographic Dyssynchrony and Health Status Outcomes From Cardiac Resynchronization Therapy

Insights From the PROSPECT Trial

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OBJECTIVES This study sought to assess the prognostic utility of echocardiographic dyssynchrony for health status improvement after cardiac resynchronization therapy (CRT).

BACKGROUND Echocardiographic measures of dyssynchrony have been proposed for patient selection for CRT, but prospective validation studies are lacking.

METHODS A prospective cohort of 324 patients from 53 centers with moderate to severe heart failure, left ventricular dysfunction, QRS ≥130 ms, and available echocardiographic and health status information were identified from the PROSPECT (Predictors of Response to Cardiac Re-Synchronization Therapy) trial, which evaluated the prognostic utility of dyssynchrony measures in CRT recipients. The association of 12 echocardiographic dyssynchrony parameters with 6-month improvement in health status, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), was assessed both as a continuous variable and by responder status (ΔKCCQ ≥+10 points reflecting moderate to large improvement).

RESULTS Of 12 pre-defined dyssynchrony parameters, only 3 were consistently reported: interventricular mechanical delay (IVMD), left ventricular filling time relative to the cardiac cycle (LVFT), and left ventricular pre-ejection interval. After multivariable adjustment, IVMD (+5.18, 95% confidence interval [CI]: +0.76 to +9.60; p = 0.02) and LVFT (+5.19, 95% CI: +0.45 to +0.94; p = 0.03) were independently associated with 6-month improvements in KCCQ. Patients with 6-month improvements in KCCQ had lower subsequent mortality (adjusted hazard ratio [HR] for each 5-point improvement: 0.83; 95% CI: 0.72 to 0.93; p = 0.03). Additionally, IVMD was associated with CRT responder status (for ΔKCCQ ≥+10 points: odds ratio [OR]: 1.85; 95% CI: 1.12 to 3.05; p = 0.03), whereas LVFT was not (OR: 1.63; 95% CI: 0.85 to 3.11; p = 0.14). Patients classified as health status responders had a 76% lower subsequent risk of all-cause mortality (adjusted HR: 0.24; 95% CI: 0.07 to 0.84; p = 0.03).

CONCLUSIONS The presence of pre-implantation IVMD and LVFT was associated with 6-month health status improvement, and IVMD was associated with a significant CRT response. These echocardiographic factors may help clinicians counsel patients regarding their likelihood of symptomatic improvement with CRT. (PROSPECT: Predictors of Response to Cardiac Re-Synchronization Therapy; NCT00253357) (J Am Coll Cardiol Img 2010;3:451–60) © 2010 by the American College of Cardiology Foundation

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The primary goals of heart failure treatment are to prolong survival and to improve patients' health status. Cardiac resynchronization therapy (CRT) has previously been shown to reduce symptoms (1), hospitalizations (2), and mortality (3) in patients with moderate to severe heart failure, left ventricular systolic dysfunction, and electrocardiographic evidence of ventricular dyssynchrony. Although most patients benefit from CRT, there is a gradient of response, with 30% to 40% of CRT recipients receiving little symptomatic improvement (1,4). One possible explanation is that a prolonged QRS duration may not be the optimal marker of mechanical dyssynchrony. Because the presumed physiologic mechanism underlying CRT is to reduce dyssynchrony, more direct assessments of ventricular dyssynchrony could improve patient selection and optimize CRT use. Although a variety of echocardiographic parameters of dyssynchrony have been identified (5–8), multicenter prospective studies evaluating the feasibility of their measurement or their prognostic utility in predicting improvements in health status (symptoms, function, and quality of life) have not been performed.

ABBREVIATIONS AND ACRONYMS

CCS = Clinical Composite Score

CI = confidence interval

CRT = cardiac resynchronization therapy

HR = hazard ratio

IDI = integrated discrimination improvement

IVMD = interventricular mechanical delay

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-os = Kansas City Cardiomyopathy Questionnaire overall score

LVFT = left ventricular filling time relative to the cardiac cycle

LVPEI = left ventricular pre-ejection interval

NYHA = New York Heart Association

OR = odds ratio

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a validated disease-specific measure of patient health status in heart failure (9,10). The KCCQ is easy to administer; offers patient-centered insights into health status not available with traditional risk factors, biomarkers, or noninvasive tests; and can be serially monitored (11). Baseline assessment with the KCCQ has been shown to predict future hospitalization and mortality (9,11), and its prognostic utility over more traditional markers of heart failure severity, including the New York Heart Association (NYHA) functional class and the 6-min walk test, has been previously reported (10). Given that a principal goal of CRT is to improve patients' health status, determining which pre-implantation clinical characteristics and dyssynchrony parameters are associated with improvements in health status would enhance patient selection and empower patients with additional prognostic information for informed decision making.

Accordingly, the PROSPECT (Predictors of Response to Cardiac Re-Synchronization Therapy) trial (12) was used to prospectively evaluate which clinical variables and pre-defined echocardiographic markers of dyssynchrony predict health status improvement with CRT. Our goal was to determine the feasibility of measuring these echocardiographic markers and to develop a parsimonious risk model to evaluate whether these measures were associated with health status improvement after CRT.

METHODS

Study population. The PROSPECT trial is a prospective, international, multicenter, nonrandomized study designed to evaluate whether echocardiographic measures of dyssynchrony predict clinical response to CRT. The study design has been previously described (12,13). Briefly, 467 patients with left ventricular ejection fraction ≤35%, NYHA functional class III or IV heart failure, and optimal medical treatment were enrolled from 53 centers in the U.S., Asia, and Europe from March 2004 to December 2005. Details of study exclusion criteria and CRT programming for A-V optimization and V-V timing have been previously described (13).

For the purposes of the current study, we were interested in only those patients with an approved indication for CRT by electrocardiographic criteria and excluded 41 patients with QRS <130 ms (only 2 of whom had a QRS duration >120 ms) (Fig. 1). We also excluded those patients in whom a change in health status could not be assessed (45 without baseline KCCQ and 26 without 6-month KCCQ). Finally, we excluded 31 patients in whom all dyssynchrony measures on echocardiography were deemed uninterpretable by the core laboratories (see the second paragraph of the Clinical variables section). Importantly, there were no significant differences in demographics, clinical characteristics, baseline health status, or rates of echocardiographic dyssynchrony among patients in the study cohort and those who were excluded for the above reasons

investigators (<$10,000), is a consultant/advisory board member for the Medtronic steering committee (<$10,000), and has received a grant for ECHO core laboratory (≥$10,000). Dr. Gerritse is an employee at Medtronic, Inc., and owns approximately $10,000 worth of Medtronic stock shares. Dr. Spertus has received a research grant from Medtronic (<$10,000), and has developed and owns the copyrights for the Kansas City Cardiomyopathy Questionnaire.

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(Online Appendix A). The final study population comprised 324 patients.

Clinical variables. Baseline data on demographics (age, sex, country of origin), clinical variables (left ventricular ejection fraction as determined by the core laboratories, QRS duration, body mass index), medical comorbidities (diabetes mellitus; hypertension; atrial fibrillation; and prior myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, or implantable cardioverter-defibrillator placement), clinical symptoms (chest pain, dyspnea, orthopnea, pre-syncope, and paroxysmal nocturnal dyspnea), and medication use (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, class I or III antiarrhythmic agents, diuretics, aldosterone blockers, and lipid-lowering therapy) were collected within 30 days before CRT implantation in the PROSPECT trial. Health status assessment was performed at baseline and at the 6-month follow-up.

Initially, the PROSPECT trial had planned to evaluate 12 published and unpublished echocardiographic markers of atrioventricular, interventricular, and intraventricular dyssynchrony. Details for the measurement of each parameter performed by the 3 core laboratories have been previously outlined (13) and are described in greater detail in Online Appendix B. In the event that image quality was determined to be poor by a core laboratory for a given echocardiographic parameter, the value for that parameter was considered missing. We excluded 31 patients in whom all 12 dyssynchrony measures were deemed uninterpretable by the core laboratories. Due to the technical challenges involved in obtaining high-quality images for many of these measures, we also determined a priori to exclude from our analysis those dyssynchrony parameters with >20% missing data because their inclusion would limit the generalizability of study inferences (Table 1). Therefore, our study focused on evaluating the prognostic utility of 3 dyssyn-

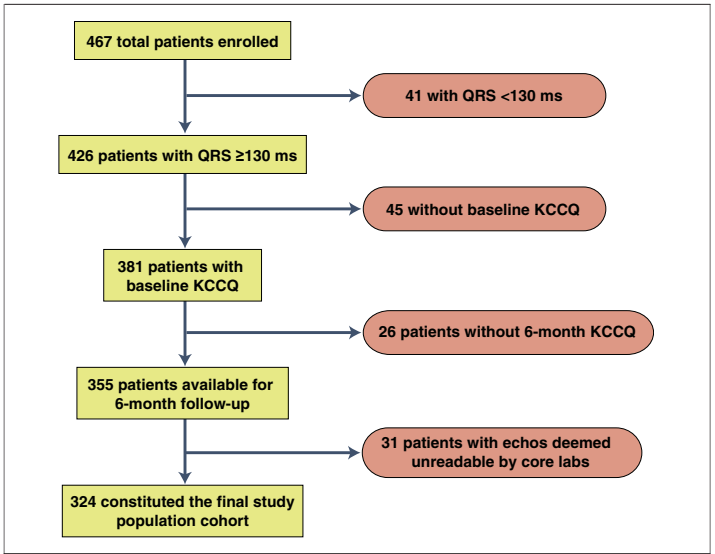

Figure 1. Definition of Study Cohort

KCCQ = Kansas City Cardiomyopathy Questionnaire.

Table 1. Frequency of Missing Data for Dyssynchrony Study Measures

Echocardiographic Method	Echocardiographic Dyssynchrony Measures	Missing Rates Excluding 31 Patients Without Any Echocardiographic Data (n = 324)	Missing Rates Including 31 Patients Without Any Echocardiographic Data (n = 355)
M-mode	Septal-posterior wall motion delay (≥130 ms)	80 (24.7%)	111 (31.3%)
Pulsed Doppler	Interventricular mechanical delay (≥40 ms)	9 (2.8%)	40 (11.3%)
	LV filling time relative to RR (≤40%)	34 (10.5%)	65 (18.3%)
	LV pre-ejection interval (>140 ms)	2 (0.6%)	33 (9.3%)
M-mode + pulsed Doppler	Left lateral wall contraction overlap with LV filling (≥0)	122 (37.7%)	153 (43.1%)
		(n = 310)*	(n = 341)*
Tissue Doppler imaging	Time difference between lateral and septal peak systolic wall velocity (≥60 ms)	126 (40.6%)	157 (46.0%)
	SD of time to peak velocity (≥32 ms)	176 (56.8%)	207 (60.7%)
	Maximum difference of time to peak velocity (≥median)	75 (24.2%)	106 (34.2%)
	Maximum difference of time to onset systolic velocity (≥median)	75 (24.2%)	106 (34.2%)
	Delayed longitudinal contraction (≥2)	77 (24.8%)	108 (31.7%)
	Maximum difference of time to peak velocity outside IVCT (≥110 ms)	77 (24.8%)	77 (31.7%)
	Maximum difference of time to peak displacement (≥median)	222 (71.6%)	253 (74.2%)

Echocardiographic assessments for each of the 12 prospectively evaluated dyssynchrony measures were categorized as missing data if the images were determined by the core laboratories to be of poor quality. *Twenty patients in atrial fibrillation or enrolled at sites not performing tissue Doppler imaging.
IVCT = isovolumic contraction time; LV = left ventricular.

chrony measures (interventricular mechanical delay [IVMD] ≥40 ms, percentage of cardiac cycle length occupied by left ventricular filling time [LVFT] ≤40%, and left ventricular pre-ejection interval [LVPEI] ≥140 ms) that were obtained with reasonable consistency in our study cohort of 324 patients.

Outcome assessment. The primary study outcome was change in patient health status between the baseline and 6-month visit using the KCCQ, which evaluates discrete health status domains for heart failure (physical limitations, symptoms, social function, self-efficacy, and quality of life). The choice of the 6-month follow-up was dictated by the PROSPECT trial design and from prior clinical trials (2,13). An overall score (KCCQ-os), based on contributions from each domain (except self-efficacy and recent change in symptoms), quantifies the multiple domains of the KCCQ into 1 summary health status measure. We chose to examine the KCCQ overall summary score because it has been previously shown to be a robust predictor of future morbidity, mortality, and health care utilization in heart failure patients (11,14). Scores from the KCCQ-os are transformed to a scale from 0 to 100, with higher scores denoting better health status. Therefore, the primary outcome was determined as the difference between the 6-month and baseline KCCQ-os scores (ΔKCCQ-os), with a positive value indicating improvement. The outcome of ΔKCCQ-os was assessed as a continuous variable for the primary outcome. To aid in clinical interpretability, we also assessed the ΔKCCQ-os as a categorical variable (secondary outcome), where ΔKCCQ-os ≥+10 indicated CRT responders with significant health status improvement. The choice of a 10-point improvement in KCCQ-os for CRT responder status was based on our prior work, which showed that a 5-point KCCQ-os threshold would be the minimal clinically significant difference and a change ≥10 points would represent a moderately large difference in patients' health status (11).

To establish the clinical importance of our primary outcome, as a secondary analysis, we examined the importance of a change in health status at 6 months with survival. Vital status was determined at office visits through May 2006, when the last PROSPECT patient had completed the 6-month follow-up visit.

Statistical analysis. Baseline characteristics of the entire study cohort were summarized as means with standard deviations for continuous variables and frequencies for categorical variables. The distributions of continuous covariates were examined and confirmed for normality. The bivariate association between each variable and the 6-month change in KCCQ-os, adjusted for baseline KCCQ-os, was determined with linear regression models. Because a small proportion of clinical and included echocardiographic covariates had missing values, we performed multiple imputation of missing values to allow for incorporation of all patients and to correctly account for uncertainty due to missing values. Analyses were replicated on 10 imputed datasets and pooled to obtain final model estimates.

Multivariable linear regression models were then constructed to assess which clinical and echocardiographic variables were independently associated with a significant health status change (ΔKCCQ-os). Age, sex, and baseline KCCQ-os were included in the model regardless of significance level, as well as covariates with a significant ($p < 0.05$) association with the study outcome. Furthermore, to ensure parsimony and inclusion of only those variables that provided incremental prediction value, we used the approximation of full-model methodology for model reduction (15). The R^2 of the final model was then compared with that of a clinical model without dyssynchrony measures using the log likelihood test to assess whether the echocardiographic measures significantly improved model discrimination. Finally, a scoring algorithm was developed by rounding coefficients from the multivariable linear regression model.

To aid in the interpretability of our findings, we next constructed multivariable logistic regression models and assessed which clinical and echocardiographic variables predicted a moderate-to-large health status improvement with CRT (i.e., CRT response with a ≥10 point increase in KCCQ-os; reference group <10 points). We then examined whether these dyssynchrony measures improved model discrimination to predict CRT response by comparing this model with a clinical model without dyssynchrony parameters using C-statistics and the integrated discrimination improvement (IDI) statistic. The IDI is interpreted as the difference between improvement in average sensitivity and any decrease in average specificity between the compared logistic regression models, which is then tested against the null hypothesis of IDI = 0 (16).

Finally, we examined the importance of our study end point—improvements in 6-month health status—by constructing Kaplan-Meier curves and multivariable Cox models among surviving patients at 6 months (i.e., 6-month KCCQ follow-up was time 0

in these analyses). These additional analyses evaluated improvements in 6-month KCCQ as a continuous variable (divided into quartiles) and by responder status. For all analyses, the null hypothesis was evaluated at a 2-sided significance level of 0.05 with 95% confidence intervals (CIs) calculated. Analyses were conducted with SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina), Imputation and Variance Estimation Software (IVEWARE, Ann Arbor, Michigan), or R version 2.3.1 (Free Software Foundation, Boston, Massachusetts).

RESULTS

The mean age of the study cohort was 68 years, of which 71% were male. The mean QRS duration

Table 2. Bivariate Associations of Study Covariates With 6-Month Health Status Change

Baseline Characteristics	Study Population Frequency (n = 324)	Bivariate Association With 6-Month Change in KCCQ* (95% CI)	p Value
Baseline KCCQ	11.1%	Reference†	
0 to <25			
25 to <50	36.7%	Reference†	
50 to <75	40.7%	Reference†	
75 to 100	11.4%	Reference†	
Echocardiography dyssynchrony			
IVMD (≥40 ms)	52.2%	5.1 (0.8–9.5)	0.02
LVFT (≤40%)	32.7%	6.4 (1.6–11.2)	0.009
LVPEI (≥140 ms)	61.7%	4.6 (0.1–9.1)	0.04
Demographics			
Age	67.9 ± 11.1	0.1 (−0.1–0.2)	0.55
Male sex	71.0%	1.4 (−3.1–6.0)	0.54
Clinical data			
LVEF	29.4 ± 10.0	−0.2 (−0.4–0.0)	0.08
QRS duration ± SD	164.1 ± 22.9	0.1 (−0.0–0.2)	0.10
QRS >160	44.1%	3.4 (−0.8–7.6)	0.11
Body mass index	28.3 ± 5.4	0.0 (−0.4–0.4)	0.84
Prior myocardial infarction	50.0%	−2.3 (−6.5–1.8)	0.27
Diabetes mellitus	32.1%	−2.3 (−6.8–2.2)	0.31
Atrial fibrillation or flutter	20.4%	−0.8 (−6.0–4.4)	0.76
Prior CABG	29.9%	−2.5 (−7.0–2.1)	0.29
Prior PCI/PTCA	24.7%	−4.2 (−9.0–0.7)	0.09
Prior ICD	9.6%	−1.9 (−9.0–5.2)	0.60
Clinical symptoms			
Dyspnea	95.7%	5.8 (−5.0–16.5)	0.29
Orthopnea	23.8%	−3.3 (−8.4–1.7)	0.19
PND	19.1%	1.8 (−3.5–7.2)	0.49
Pre-syncope	31.8%	−5.0 (−9.6–0.5)	0.03
Chest pain	28.7%	−3.2 (−7.8–1.5)	0.18
Medications			
Beta-blockers	86.1%	6.4 (0.1–12.7)	0.05
ACE-I or ARB	91.7%	−0.7 (−8.3–6.9)	0.86
Lipid-lowering agents	57.4%	0.2 (−4.0–4.4)	0.93
Aldosterone blocker	37.0%	−2.0 (−6.3–2.3)	0.34
Diuretics	82.7%	−1.4 (−6.9–4.1)	0.61
Class I antiarrhythmic	1.5%	3.1 (−14.3–20.5)	0.73
Class III antiarrhythmic	19.8%	−6.3 (−11.5–1.0)	0.02

Baseline characteristics of the study cohort and their bivariate associations with 6-month change in KCCQ scores with CRT, adjusted for baseline KCCQ, are presented. *Absolute change in continuous KCCQ, adjusted for baseline KCCQ score. †Not determined, as the bivariate associations are adjusted for baseline KCCQ score.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CI = confidence interval; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; IVMD = interventricular mechanical delay; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVFT = left ventricular filling time relative to cardiac cycle; LVPEI = left ventricular pre-ejection interval; PCI = percutaneous coronary intervention; PND = paroxysmal nocturnal dyspnea; PTCA = percutaneous transluminal coronary angioplasty.

was 164 ± 23 ms (43% with QRS >160 ms), and the mean left ventricular ejection fraction was 29% (Table 2). All patients in the cohort had symptoms of heart failure, including dyspnea (96%), paroxysmal nocturnal dyspnea (19%), orthopnea (24%), or pre-syncope (32%). Half the cohort described a prior history of myocardial infarction, 54% had prior surgical or percutaneous coronary revascularization therapy, and 29% had chest pain at enrollment. Baseline medical therapy included a high use of beta-blockers (86%), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (92%), and antiplatelet therapy (79%). Regarding echocardiographic dyssynchrony, of the 3 pulsed Doppler measures that could be reliably assessed in at least 80% of patients, evidence of dyssynchrony by IVMD was observed in 52%, LVFT in 33%, and LVPEI in 62%.

The mean baseline KCCQ-os was 50.7 ± 19.5, and the mean 6-month KCCQ-os was 70.9 ± 22.2, suggesting a marked average improvement in heart failure health status with CRT overall (mean KCCQ-os increase of 20.1 ± 21.3). When stratified by baseline KCCQ range categories, patients in the lower 2 categories (i.e., with the worst baseline health status) had the largest improvements in 6-month KCCQ-os compared with the upper 2 categories: range 1 (KCCQ-os = 0 to 24): +26; range 2 (KCCQ-os = 25 to 49): +29; range 3 (KCCQ-os = 50 to 74): +15; range 4 (KCCQ-os = 75 to 100): +5; $p < 0.001$ (Fig. 2).

Adjusted for baseline KCCQ score, a number of variables had bivariate associations with 6-month improvements in KCCQ-os after CRT (Table 2).

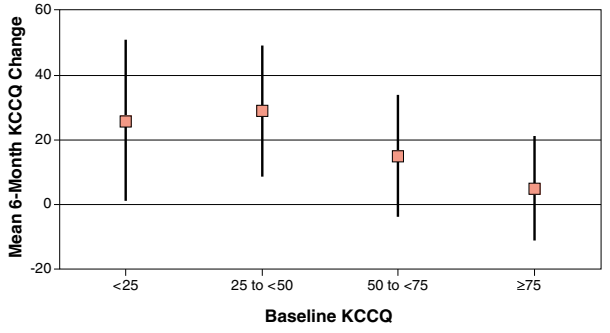

Figure 2. Unadjusted 6-Month Improvements in Health Status Associated With CRT by Baseline KCCQ Range Quartiles

The mean 6-month change in KCCQ ± 1 SD is shown for each baseline KCCQ range quartile. An inverse relationship between improvement in patient-reported symptoms and quality of life (ΔKCCQ) associated with CRT and baseline range quartile of heart failure health status was observed ($p < 0.001$). CRT = chronic resynchronization therapy; KCCQ = Kansas City Cardiomyopathy Questionnaire.

These included wider QRS duration ($p = 0.05$), beta-blocker use ($p = 0.05$), and the 3 echocardiographic parameters: IVMD ($p = 0.02$), LVFT ($p = 0.009$), and LVPEI ($p = 0.04$).

Multivariable model results. After multivariable adjustment, echocardiographic dyssynchrony as measured by IVMD (+5.18 points on the KCCQ-os, 95% CI: +0.76 to +9.60; $p = 0.02$) and LVFT (+5.19 points, 95% CI: +0.45 to +9.94; $p = 0.03$) were independently associated with an improvement in 6-month health status with CRT (Fig. 3A), whereas LVPEI was not. The estimates for IVMD and LVFT were similar when we assigned patients who died before 6 months follow-up KCCQ score of 0. Other clinical variables associated with 6-month improvement in KCCQ-os included male sex, lower baseline KCCQ-os, and beta-blocker use. Table 3 outlines a scoring algorithm based on the estimates from the regression model to predict absolute changes in 6-month KCCQ-os associated with CRT. When compared with a model not including dyssynchrony measures (R^2 of 0.21), the inclusion of IVMD and LVFT was found to improve model discrimination (R^2 of 0.26; $p = 0.005$). Importantly, an $R^2 \geq 0.20$ denotes good model prediction.

Notably, of the 9 echocardiographic parameters that had been excluded because of high rates of missing data, only 1 (maximum difference of time to onset of systolic velocity) showed a bivariate association with 6-month KCCQ change (Online Appendix C). However, this variable was not a significant predictor of 6-month health status improvement when forced into the multivariable model (Online Appendix D).

When considered from the perspective of a moderate large improvement in patient health status (≥10-point increase in KCCQ-os), 65% of patients were identified as CRT responders. The rate of CRT response was 64% (23 of 36) for patients with baseline KCCQ scores of <25, 79% (94 of 119) for baseline KCCQ scores of 25 to 49, 61% (80 of 132) for baseline KCCQ scores of 50 to 74, and 38% (14 of 37) for baseline KCCQ scores of ≥75. After multivariable adjustment, IVMD (odds ratio [OR]: 1.85, 95% CI: 1.12 to 3.05; $p = 0.03$), lower baseline KCCQ-os, and beta-blocker use were associated with CRT response, whereas LVFT (OR: 1.63, 95% CI: 0.85 to 3.11; $p = 0.14$) was not. In contrast, a history of chest pain and use of class III antiarrhythmic medications were associated with not having significant health status improvement with CRT (Fig. 3B). Notably, our model was found

to have good discrimination (C-statistic: 0.73) and calibration (Hosmer-Lemeshow goodness-of-fit test, p = 0.51). When compared with a model without dyssynchrony measures, the model discrimination for CRT response was improved after inclusion of IVMD (C-statistic: 0.709 to 0.732 with p = 0.05; IDI = 0.03 with p < 0.001) (Online Appendix E). Finally, as a sensitivity analysis, we found that all model results were not meaningfully different when analyzed without imputation (Online Appendix F).

Survival by health status improvement. Last, we examined the importance of achieving 6-month gains in patients' health status among recipients of CRT. Patients in the quartile with the smallest gains in health status had the lowest rate of 6-month survival from the 6-month follow-up assessment: 81.1% for patients in the lowest quartile of KCCQ improvement (range: −63 to 6 points), 93.8% in the second quartile (range: 7 to 18 points), 93.8% in the third quartile (range: 19 to 34 points), and 95.2% in the highest quartile of KCCQ improvement (≥35 points) (Fig. 4A). After multivariable adjustment, the 6-month change in KCCQ was a significant predictor of survival (adjusted hazard ratio [HR] for each 5-point improvement in 6-month KCCQ: 0.83; 95% CI: 0.72 to 0.93; p = 0.03). Similarly, patients classified as health status responders had higher crude rates of 6-month survival from the 6-month follow-up than nonresponders (98.4% vs. 89.3%; p = 0.0003) (Fig. 4B), and responder status was associated with a 76% lower risk of all-cause mortality after multivariable adjustment (HR = 0.24; 95% CI: 0.07 to 0.84; p = 0.03).

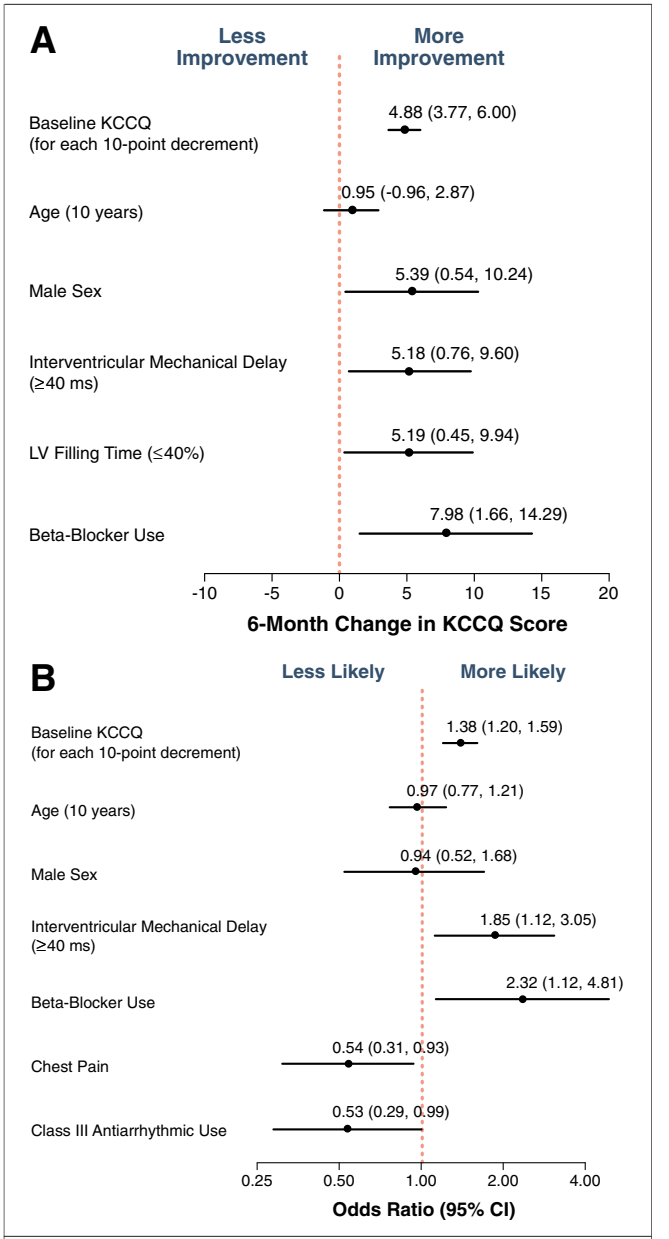

Figure 3. Predictors of 6-Month Changes in Health Status With CRT

Multivariable model predictors of a significant 6-month change in KCCQ associated with CRT are presented as a continuous **(A)** and a binary **(B)** CRT responder outcome. The presence of dyssynchrony, as measured by IVMD and LVFT, was found to independently predict 6-month improvement in health status with CRT. The CRT response was defined as a 6-month increase of ≥10 points in KCCQ scores. CI = confidence interval; CRT = cardiac resynchronization therapy; IVMD = interventricular mechanical delay; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVFT = left ventricular filling time relative to the cardiac cycle ≤40%.

DISCUSSION

The PROSPECT trial is the first large-scale multicenter clinical study to prospectively evaluate the feasibility and performance of multiple echocardiographic measures of mechanical dyssynchrony in predicting health status benefits from CRT. There were significant challenges in obtaining accurate, reliable measurements for the majority of dyssynchrony parameters, and only 3 were obtained with sufficient consistency to warrant further consideration for risk stratification. Despite these challenges, we found that pre-implantation LVFT and IVMD were significantly associated with 6-month improvements in heart failure symptoms and quality of life with CRT, and that IVMD was associated with marked (≥10 point increase in KCCQ scores) improvements in CRT response. In addition, significant heterogeneity in baseline health status in this population of patients with NYHA functional class III or IV heart failure was observed, with patients of poorer health status deriving the

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Table 3. Scoring Algorithm Using Pre-Implantation Variables to Predict 6-Month Change in KCCQ With CRT

Variables	Points*
Model intercept	−8
Baseline KCCQ	
0 to 24	20
25 to 49	23
50 to 74	8
75 to 100	0
Male sex	3
Presence of echocardiographic dyssynchrony	
IVMD ≥40 ms	5
LVFT ≤40%	6
Beta-blocker use	10

*Derived from coefficients of multivariable linear regression model. Abbreviations as in Table 2.

greatest benefit from CRT. Lastly, patients with large improvements in health status at 6-month follow-up were found to have significantly higher survival than patients with minimal health status response after CRT. This suggests that a limited pulsed Doppler echocardiographic study and baseline health status screening may help identify a subgroup of patients most likely to derive health status improvement with CRT, which was found to be associated with higher rates of overall survival.

Prior studies have suggested a wide variety of dyssynchrony measures that may improve patient selection for CRT (5–8). Many of these studies, however, were single-center studies with small sample sizes, evaluated only 1 or 2 dyssynchrony measures at a time, used nonclinical end points, or enrolled patients only when the specific measure of dyssynchrony could be determined. Considering these limitations, a key rationale for the PROSPECT trial was to examine the feasibility in obtaining different measures of mechanical dyssynchrony prospectively across multiple centers and to evaluate the external validity of these parameters. Whereas dyssynchrony measured by pulsed Doppler imaging (IVMD, LVFT, LVPEI) was obtainable for most patients in the PROSPECT trial, dyssynchrony measures assessed with M-mode or tissue Doppler imaging inconsistently yielded adequate image quality for reliable interpretation. Difficulty in obtaining high-quality images for many of these parameters was an unanticipated but important finding. The PROSPECT trial's experience may have differed from that of prior studies because of the technical issues associated with the use of tissue Doppler imaging for timing measurements across multiple sites. This is further compounded by the fact that significant levels of intraobserver and interobserver variability in obtaining these measures have been reported previously (12). Alternatively, potential publication bias, enrollment bias (e.g., excluding patients in whom measures could not be obtained), or selection bias (e.g., operator or reader expertise in tissue Doppler imaging) in prior studies may have overestimated the feasibility of obtaining many measures of dyssynchrony. Regardless, it suggests that the potential generalizability of many reported measures of dyssynchrony in routine clinical practice remains far from ideal. Future studies should routinely report the number of patients screened but in whom the dyssynchrony measures of interest could not be reliably obtained. Meanwhile, newer imaging modalities for dyssynchrony (e.g., real-time 3-dimensional echocardiography, speckle tracking) may potentially overcome some of the problems with the techniques used in the PROSPECT trial.

Despite the limitations of most dyssynchrony measures, 3 different measures for dyssynchrony from the PROSPECT trial were available for assessment: LVFT, IVMD, and LVPEI. We found that LVFT and IVMD were significantly associated with 6-month improvements in heart failure symptoms and quality of life with CRT, and that IVMD was associated with marked (≥10 point increase in KCCQ scores) improvements in CRT response. Although IVMD also was found to predict a better outcome in the CARE-HF (Cardiac Resynchronization in Heart Failure) trial (17,18), the magnitude of health status benefit has not been previously quantified. Although interventricular markers of dyssynchrony, such as IVMD, for CRT patient selection may seem intuitive (19), the finding that shorter left ventricular filling times in relation to the cardiac cycle (LVFT) also identifies patients with improvements in health status suggests that diastolic dysfunction may have significant effects on symptom burden in the CRT-eligible population (7) or that LVFT may simply be a marker of longer times spent in isovolumic contraction (and therefore less time available for left ventricular filling) due to more severe interventricular dyssynchrony.

Our study extends the findings of a prior report from the PROSPECT trial that found that none of the dyssynchrony measures had sufficient sensitivity and specificity for the Clinical Composite Score (CCS) to warrant their use alone to exclude patients for CRT (12). Importantly, as compared with the previously reported outcomes of CCS and reduced left ventricular end-systolic volume, the discrimina-

tion of our model for patient-centered health status outcomes, including the dyssynchrony measures, was significantly greater than that reported previously (C-statistic = 0.73 for improvements in KCCQ-assessed health status as compared with a peak discrimination of 0.60 for CCS and 0.62 for left ventricular end-systolic volume reduction of ≥15%) (12). Nevertheless, it is important to note that given the high rate of CRT responder status, even a hypothetical model with 95% sensitivity and specificity would only yield a modestly acceptable negative predictive value of 90% in the PROSPECT trial population, thus highlighting the challenges in using dyssynchrony measures for patient selection and coverage decisions regarding CRT implantation. We found, however, that dyssynchrony measures do add significant incremental prognostic information regarding health status improvement with CRT and believe that our scoring algorithm (Table 3) can be used by physicians to counsel patients regarding their likelihood of health status improvement with CRT. Given that improvements in symptoms and quality of life are of substantial importance to patients when considering therapy, these data should be useful in describing the potential risks and benefits of therapy to patients considering CRT implantation. For example, a 70-year-old man with a baseline KCCQ score of 45, IVMD on dyssynchrony evaluation, and on beta-blockers, would on average be expected to have a 33-point improvement in his health status at 6-months—a very large improvement in health status. In contrast, a 70-year-old woman with a baseline KCCQ score of 80 and an otherwise similar clinical profile would be expected to have a more modest 7-point improvement.

It is also notable that patients with the greatest symptom burden and worst quality of life (KCCQ-os <50) were the most likely to benefit from CRT, which suggests a gradient of benefit among NYHA functional class III and IV heart failure patients. Because mean health status scores improved in each of the 4 KCCQ-os range ranges at 6 months, this cannot be explained by simple regression to the mean. Instead, there is likely a ceiling effect that limits the extent of health status improvement for patients in the upper quartiles of baseline KCCQ-os. However, it is precisely this limited potential to further improve one's health status in those with the best health status (and highest KCCQ-os scores) that makes the use of health status screening for CRT evaluation attractive. Indeed, the relative contribution of baseline KCCQ and beta-blocker use relative to echocardiographic dyssynchrony measures in our scoring algorithm (Table 3) underscores the importance of weighing both clinical factors and imaging results to identify those patients most likely to have improvements in symptoms and quality of life with CRT.

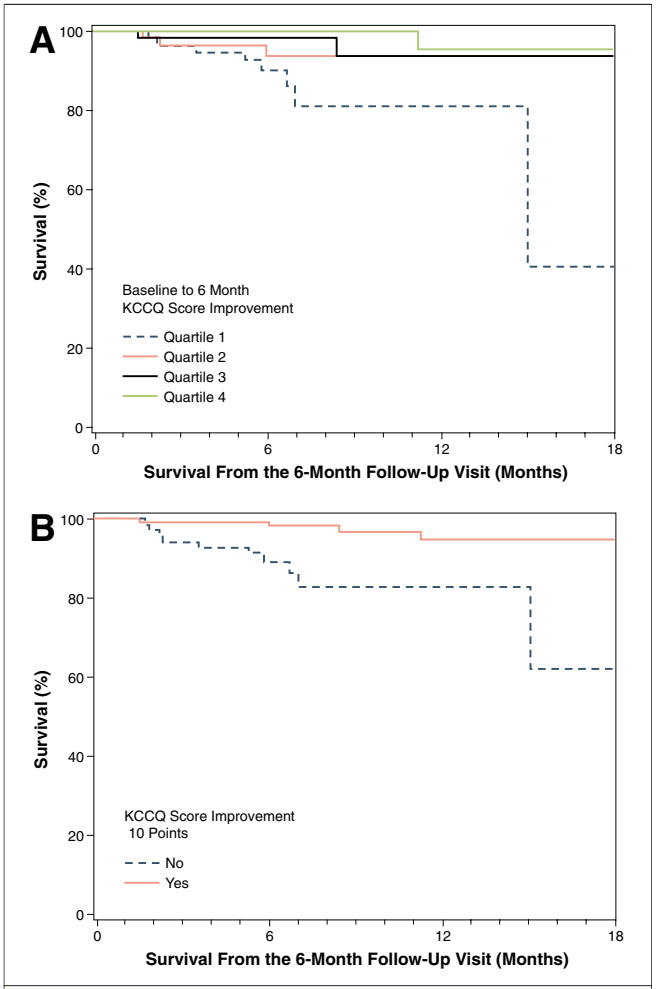

Figure 4. Overall Survival by Achieved Improvement in Patients' Health Status After CRT

Survival from the 6-month health status assessment is depicted, stratified by quartiles of changes in KCCQ scores (**A**) and by responder status (**B**). Abbreviations as in Figure 2.

Our findings should be interpreted with the following limitations. Our findings do not account for the potential survival benefits of CRT and should not be used to deny CRT to eligible patients. Because a number of dyssynchrony measures were eliminated from consideration because of poor image quality, we were unable to fully assess whether these measures, if they had been more reliably obtained, would have had prognostic utility with respect to predicting patients' health status

benefit from CRT. Our preliminary analyses for these excluded parameters in Online Appendixes C and D, however, did not suggest a significant association with 6-month health status change. Our analyses could not account for operator-level variation in successful CRT lead implantation or patient variation in ventricular scar location and size (20), both of which are known to affect CRT response. Finally, the PROSPECT trial was a nonrandomized study. Therefore, our findings require external validation in future studies.

CONCLUSIONS

In this large prospective study that evaluated the prognostic utility of multiple echocardiographic parameters of dyssynchrony in CRT recipients, the vast majority of measures could not be reliably obtained with sufficient image quality. Among the 3 parameters that could be consistently measured, pre-implantation IVMD and LVFT were independent predictors of 6-month health status improvement after CRT. Our scoring algorithm, using these measures in conjunction with other baseline clinical and health status characteristics, may help guide physicians to counsel patients regarding their likelihood of symptomatic improvement with CRT.

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Key Words: dyssynchrony ■ heart failure ■ health status ■ resynchronization therapy.

APPENDIX

For supplementary data and tables, please see the online version of this article.