Precision Medicine for Cardiac Resynchronization

Predicting Quality of Life Benefits for Individual Patients—An Analysis From 5 Clinical Trials

BACKGROUND: Clinical trials have established the average benefit of cardiac resynchronization therapy (CRT), but estimating benefit for individual patients remains difficult because of the heterogeneity in treatment response. Accordingly, we created a multivariable model to predict changes in quality of life (QoL) with and without CRT.

METHODS AND RESULTS: Patient-level data from 5 randomized trials comparing CRT with no CRT were used to create a prediction model of change in QoL at 3 months using a partial proportional odds model for no change, small, moderate, and large improvement, or deterioration of any magnitude. The C statistics for not worsening or obtaining at least a small, moderate, and large improvement were calculated. Among the 3614 patients, regardless of assigned treatment, 33.3% had a deterioration in QoL, 9.2% had no change, 9.2% had a small improvement, 13.5% had a moderate improvement, and the remaining 34.9% had a large improvement. Patients undergoing CRT were less likely to have a decrement in their QoL (28.2% versus 38.9%; $P<0.001$) and more likely to have a large QoL improvement (38.7% versus 30.6%; $P<0.001$). A partial proportional odds model identified baseline QoL, age, and an interaction of CRT with QRS duration as predictors of QoL benefits 3 months after randomization. C statistics of 0.65 for not worsening, 0.68 for at least a small improvement, 0.69 for at least a moderate improvement, and 0.73 for predicting a large improvement were observed.

CONCLUSIONS: There is marked heterogeneity of treatment benefit of CRT that can be predicted based on baseline QoL, age, and QRS duration.

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WHAT IS NEW?

- The results of clinical trials average the benefit of treatment across a population, but the expected benefits for individual patients can vary substantially.
- While cardiac resynchronization therapy has a small average benefit on patients' health status (their symptoms, function, and quality of life), some patients benefit a lot and others do not.
- Using 5 randomized clinical trials, we built a model to predict the health status benefits of cardiac resynchronization therapy for individual patients using only 3 variables: age, QRS width, and baseline health status.

WHAT ARE THE CLINICAL IMPLICATIONS?

- By using this new model, clinicians can calculate whether patients are likely to have a large, moderate, or small health status benefit from cardiac resynchronization therapy or whether they are unlikely to feel worse 3 or 12 months after treatment.
- The results of this model can not only inform clinicians but can also be shared with patients as a foundation for shared medical decision making.
- Future studies to define the benefit of this tool in patient engagement, clinical outcomes, and as a component of disease management should be tested.

For patients with advanced systolic heart failure and a widened QRS, guidelines recommend several therapies, including cardiac resynchronization therapy (CRT), to improve survival and quality of life (QoL).[1,2] It is inherently difficult, however, to apply guidelines to individual patients whose benefits from treatment may differ substantially from the average benefit described in clinical trials. This issue is of particular concern for CRT, which requires a relatively complex, expensive, invasive procedure compared with a pharmacological therapy that can easily be given for a trial period and easily withdrawn if it causes problems. Also, the response to CRT is heterogeneous, some patients improve, whereas others worsen. In general, patients are 8% to 10% more likely to experience a favorable improvement in disease-specific QoL with versus without CRT.[3–6]

Previous efforts to create risk models to personalize the estimated benefits of CRT have focused on survival.[7] Importantly, such models do not inform patients and their providers of the likely benefits of CRT on the patient's QoL.[3] Given the importance of QoL to patients,[8] formally modeling the heterogeneity of treatment benefit for QoL outcomes can assist physicians in patient selection, enable more accurate discussions of the risks and benefits of treatment, and support shared medical decision making.[9–11] To address the need for a tool to individualize treatment based on anticipated QoL benefits for individual patients, we used patient-level data from 5 randomized trials of CRT to develop a multivariable risk prediction model of QoL benefit after CRT.

METHODS

Data Source

Patient-level data were pooled from 5 randomized controlled trials of CRT therapy and included 4317 patients. Details of the CARE-HF (cardiac resynchronization-heart failure), MIRACLE (Multicenter InSync Randomized Clinical Evaluation), MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation), REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction), and RAFT studies (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) have been described previously.[3,4,12–14] Each trial was approved by an institutional review board, and informed consent was obtained. The pooled data set was completely deidentified and considered nonhuman subjects research. Although there were differences among the trials, all included adult patients with a diagnosis of chronic heart failure, left ventricular dysfunction, and a wide QRS complex. All trials had at least 6 months of follow-up and collected disease-specific health status data at baseline and follow-up. Given the paucity of data on patients with New York Heart Association (NYHA) class I, we restricted the analyses to those with NYHA II to IV.

Health Status Measures

Disease-specific health status was assessed in the trials using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Kansas City Cardiomyopathy Questionnaire (KCCQ).[15,16] The MLHFQ was collected in all 5 trials, whereas the KCCQs were collected only in REVERSE. The MLHFQ contains 21 questions and has a range in overall scores of 0 to 105 points, with lower scores indicating better QoL. The KCCQ is a 12- or 23-item instrument that ranges in overall scores from 0 to 100 points, where higher scores indicate better health status.[17] Both instruments have been shown to be reliable, responsive, and valid measures of patients' heart failure symptoms, functional status, and disease-specific QoL. However, the data for interpreting what constitutes clinically important changes in overall score has been more clearly defined for the KCCQ,[18] where a 5-, 10-, and 20-point change in the KCCQ overall summary score corresponds to a small, moderate, and large clinical change in patients' health status.[8,18,19]

Selecting the Time for Modeling Health Status Benefits

Given the variability in the timing of QoL collection among the trials, we needed to define a suitable time for modeling follow-up health status. The most QoL data were available at 3 months (Table I in the Data Supplement). However, to ensure that 3 months was a sufficient length of time for the QoL benefits of CRT to be attained, we evaluated the change in QoL from baseline to 3, 6, and 12 months. For the MLHFQ, across all patients, there was a mean improvement

of −12.4 from baseline to 3 months. At 6 months, the mean MLHFQ change from baseline was −12.7, with no significant difference between the changes from baseline at month 3 and month 6, (*P*=0.10); Figure I in the Data Supplement). We, therefore, selected the 3-month health status assessment to model the heterogeneity of treatment benefit from CRT. To evaluate the models' performance on longer-term outcomes, a sensitivity analysis evaluating calibration and discrimination was conducted on patients with 12-month QoL data available.

Defining Clinically Important Changes in QoL

To improve the clinical interpretability of the models and support their use in patient selection and shared decision making, we sought to model clinically important categories of change, rather than modeling the MLHFQ as a continuous score. Given that there are much clearer thresholds to interpret the magnitude of change that is clinically important with the KCCQ, we modeled the improvement in the MLHFQ associated with small, moderate, or large improvements in KCCQ scores.[18,19] To perform this analysis, we used data from REVERSE, which simultaneously collected both the MLHFQ and KCCQ. Changes in KCCQ from baseline to 3 months suggested that a small clinical improvement in the MLHFQ questionnaire was −6.67 points; a moderate improvement was −10.41 points; and a large clinical improvement was −17.90 points (Data Supplement).

Statistical Analyses

As particular patients may find different levels of change in QoL clinically relevant, we used a cumulative logit model to estimate the heterogeneity of treatment benefit with CRT. This cumulative logit model can be thought of as an extension of the logistic regression model that applies to dichotomous dependent variables, allowing for >2 (ordered) response categories. It uses cumulative probability up to a possible threshold, thereby making the whole range of ordinal categories binary at that particular threshold. In this study, we used 4 cutoff points for MLHFQ change from baseline at 3 months (>−2.92 reflecting deterioration, <−6.67 for a small QoL improvement, <−10.41 for a moderate QoL improvement, and <−17.9 for a large QoL improvement). The cumulative logit model thus enables the estimation of the probabilities that a patient will be worse (>−2.92 points), unchanged (−2.92 to −6.67 points), slightly (−6.67 to −10.4 points), moderately (−10.4 to −17.9 points), or substantially better (<−17.9 points) at 3 months.

Candidate variables were selected a priori on the basis of published literature and clinical experience and included age, sex, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, left ventricular ejection fraction, left ventricular end diastolic dimension, diabetes mellitus, QRS duration, left bundle branch block, MLHFQ at baseline, CRT, atrial rhythm, and ischemic cardiomyopathy. Spironolactone use and NYHA class at baseline were both highly collinear with baseline QoL and thus omitted as candidate variables. Interactions between CRT and other variables were examined and retained if statistically significant. We used stepwise variable selection to select the final variables for the model. The assumption of linearity was assessed for each continuous variable with the use of restricted cubic splines. The proportional odds assumptions were tested for all variables included in the final model and assumptions held for all variables except baseline QoL, requiring separate intercepts for each category of 3-month QoL change. To take into clustering of patients by study, study was included a random effect.

Discrimination (C statistic) was calculated for each binary cumulative outcome at each threshold of clinical change. In sensitivity analysis, calibration plots were created by comparing observed versus predicted probability by decile of no change, small improvement, moderate improvement, and large improvements in QoL. Statistical analyses were conducted with SAS, version 9.3 (SAS Institute, Cary, NC), and R version 2.7.2.

RESULTS

Study Population

Of the 4317 patients from the 5 trials, 98 patients were excluded because they died before the 3-month QoL assessment (censored at end of randomization period). Patients not surviving to 3 months were older, with a worse QoL, and generally sicker at baseline (Table II in the Data Supplement). We also excluded patients without baseline (n=117) or 3-month QoL data (n=388) and excluded the patients with NYHA class 1 (n=100), leaving 3614 patients for this analysis, of whom 1890 were assigned to CRT. Patients excluded for missing QoL data had better baseline QoL and were more likely to be on a β-blocker, however, other baseline characteristics were similar to the analytic cohort (Table III in the Data Supplement). Mean age of the cohort was 65±10 years, 78% were men, 30% had diabetes mellitus, and 58% had an ischemic cardiomyopathy. Mean left ventricular ejection fraction was 24±6%, mean QRS duration was 162±24 ms, and 76% had a left bundle branch block. Mean MLHFQ at baseline was 42.4±23.4. Baseline characteristics between CRT and controls were generally well balanced with the exception of more patients in the CRT cohort being NYHA II (52.2% versus 48.3%; *P*=0.017) and on β-blockers (80.3% versus 76.7%; *P*=0.008; Table IV in the Data Supplement).

Change in QoL and CRT Effect

Among the 3614 patients, regardless of assigned treatment, 33.3% had deterioration in QoL, 9.2% had no change, 9.2% had a small improvement, 13.5% had a moderate improvement, and the remaining 34.9% had a large improvement. The baseline characteristics of patients, stratified by change in QoL, are presented in Table. From baseline to 3 months, the MLHFQ score improved, on average, by −14.0±20.6 with CRT versus −10.3±20.8 with optimal medical therapy for a mean

Table. Baseline Characteristics by Change in Quality of Life at 3 Months

	Deterioration (n=1203)	No Change (n=332)	Small Improvement (n=331)	Moderate Improvement (n=488)	Large Improvement (n=1260)	*P* Value
Age, y	65.5±10.3	66.6±9.8	65.6±10.2	64.1±10.8	64.7±10.1	0.004
Male	977 (81.2%)	273 (82.2%)	262 (79.2%)	378 (77.5%)	937 (74.4%)	<0.001
QRS width, ms	161±24	161±23	163±24	164±24	163±24	0.061
Left bundle branch block	73.7%	76.1%	78.2%	76.5%	76.6%	0.349
Cardiac resynchronization therapy	44.3%	53.6%	54.4%	54.7%	58.1%	<0.001
Implantable defibrillator	65.1%	67.5%	66.2%	64.1%	65.9%	0.878
NYHA class						
II	620 (51.5%)	201 (60.5%)	186 (56.2%)	251 (51.4%)	561 (44.5%)	<0.001
III	554 (46.1%)	125 (37.7%)	137 (41.4%)	222 (45.5%)	647 (51.3%)	
IV	29 (2.4%)	6 (1.8%)	8 (2.4%)	15 (3.1%)	52 (4.1%)	
Left ventricular ejection fraction, %	24.2±6.1	24.5±6.3	24.2±6.6	24.1±6.1	23.6±6.1	0.024
Systolic blood pressure, mm Hg	118.4±18.1	119.3±18.5	119.5±17.5	117.8±17.6	117.1±17.7	0.083
Ischemic cardiomyopathy	703 (58.4%)	204 (61.4%)	187 (56.5%)	257 (52.7%)	749 (59.4%)	0.066
Diabetes mellitus	30.8%	30.0%	28.6%	28.4%	30.1%	0.901
MLHFQ at baseline	31.6±21.1	31.8±22.6	37.5±22.1	42.6±21.7	56.6±18.7	<0.001
ACE-I/ARB	1152 (95.8%)	317 (95.5%)	316 (95.5%)	467 (95.7%)	1193 (94.7%)	0.760
β-Blocker	935 (77.7%)	285 (85.8%)	261 (78.9%)	384 (78.7%)	976 (77.5%)	0.018
Spironolactone	43.9%	40.6%	38.7%	48.3%	43.9%	0.080

Values are shown as absolute numbers (percentages), mean±SD. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MLHFQ, Minnesota Living with Heart Failure Questionnaire; and NYHA, New York Heart Association.

difference of 3.7 points (*P*<0.001), which is less than the estimated minimally important difference of –6.67 points. However, there was considerable heterogeneity in response (Figure 1). For patients in NYHA III or IV at baseline (n=1795), the mean difference between CRT and optimal medical therapy was –6.3 (*P*<0.0001) points, but for those in NYHA II (n=1819), it was only –1.5 points (*P*=0.10). In a responder analysis, which categorizes patients' changes in QoL into worse (>–2.92 points), unchanged (–2.92 to 6.67 points), slightly (–6.67 to –10.4 points), moderately (–10.4 to –17.9 points), or substantially better (<–17.9 points) patients undergoing CRT were less likely to have a decrement in their QoL (28.2% versus 38.9%; *P*<0.001) and more likely to have a large QoL improvement (38.7% versus 30.6%; *P*<0.001; Table V in the Data Supplement). These differences were more marked in patients who were in NYHA III or IV at baseline compared with those in NYHA II, respectively (Figure 2A and 2B).

Predictors of QoL Improvement

The partial proportional odds model identified baseline QoL, age, and an interaction of CRT with QRS duration as significant predictors of improvement in QoL at 3 months. (Figure 3). Patients with wider QRS duration had the greatest benefit from CRT. Worse baseline QoL and older age were associated with more improvement at 3 months, regardless of treatment. Baseline QoL had different risks for different magnitudes of clinical change, but overall, the lower the baseline health status, the greater the likelihood of a large improvement in QoL during 3-month follow-up, regardless of CRT. The discrimination (C statistics) of the partial proportional odds model for not worse, at least small improvement, at least moderate improvement, and large improvement were 0.65, 0.68, 0.69, and 0.73, respectively. A sensitivity analysis of the models' performance among subjects with 12-month QoL data available was conducted. At 12 months, the model had better discrimination with C statistics of 0.71, 0.74, 0.76, and 0.79 for not worse, at least small improvement, at least moderate improvement, and large improvement, respectively, and demonstrated excellent calibration (Figures II through V in the Data Supplement).

Figure 4 demonstrates a potentially actionable output format for these models when used at the bedside for clinical decision making. In this example, a 72-year-old with a baseline MLHFQ of 52 and QRS duration of 175 ms would have a 54% probability of a large QoL improvement with CRT as compared with 33% without CRT (number needed to treat=5). Conversely a 35-year-old with a baseline MLHFQ of 40 and QRS duration of 130 would have only a 36% probability of a large improvement with CRT versus 31% without CRT (number needed to treat=20).

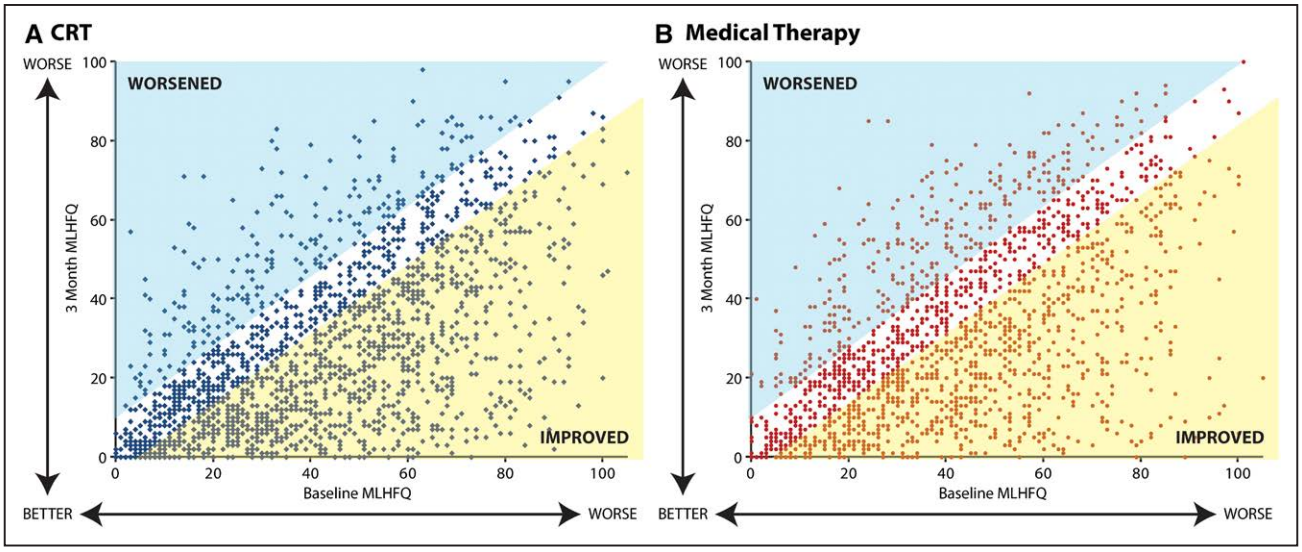

Figure 1. Individual patient's baseline (*x* axis) and 3-mo (*y* axis) Minnesota Living with Heart Failure Questionnaire overall score after being assigned to receive cardiac resynchronization therapy (A) and medical therapy (B). Yellow shaded area represents patients with significant improvement in quality of life. Blue shaded area represents patients with significant worsening in quality of life. MLHFQ indicates Minnesota Living with Heart Failure Questionnaire.

DISCUSSION

Despite the undoubted benefits of CRT, there are concerns that it has been underused in clinical practice, with only about a third of eligible patients being treated.[20,21] More appropriate use of CRT has been estimated to potentially save >8000 lives per year in the United States alone.[21] A potential reason for the underuse of CRT is the difficulty in weighing the risks and benefits of the procedure for a specific patient. Although a substantial amount of work has been done to try to understand which patients will respond to CRT, benefit has been measured in terms of echocardiographic response or a reduction in morbid or fatal events, despite the fact that patients may care more about the quality of their lives than its quantity.[22] To extend prior reports of the average QoL benefits of CRT in a study population, we developed a method for personalizing the estimated likelihood of QoL improvement with CRT. Such a model could support more evidence-based, patient-centered care by helping patients and their providers understand the benefits that they might expect from CRT, especially when coupled with a model estimating the CRT benefits on survival.[7]

Our findings extend prior investigations of the QoL benefits of CRT, which have shown increasing survival with longer QRS duration and in those with more severe heart failure but have not been able to clearly define patient characteristics associated with improved QoL.[4,7,23,24] Our analysis found that after adjusting for QRS duration, QRS morphology does not predict the response to CRT, consistent with 2 prior patient-level analyses[14,25] but not another.[26] It is notable that the majority of patients (76%) in our analysis had left bundle branch block, and it is possible that those with wide right bundle branch block had some underlying left sided dyssynchrony, so extrapolation to those with pure right bundle branch block may be limited. Also contrary to some previous analyses,[27,28] sex was not predictive of QoL improvement in the final multivariable model, despite women deriving more benefit in unadjusted analyses. We hypothesize that this is because of the worse QoL scores in women at the time of treatment

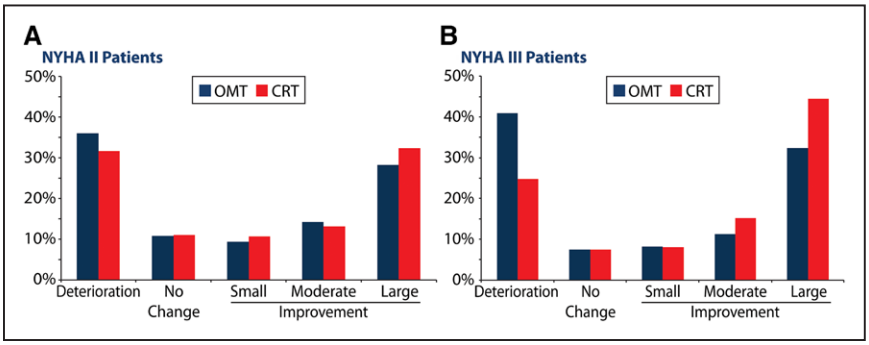

Figure 2. Responder analysis of quality of life change from baseline to 3 mo by New York Heart Association (NYHA) II patients (A) and NYHA III/IV patients (B). CRT indicates cardiac resynchronization therapy; and OMT, optimal medical therapy.

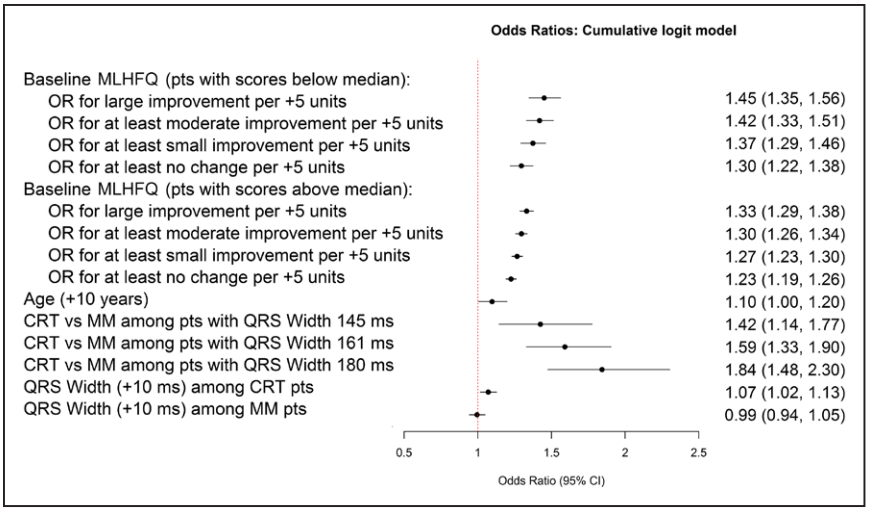

Figure 3. Forest plot of odds ratios (ORs) from partial proportion odds model (higher scores in Minnesota Living with Heart Failure Questionnaire [MLHFQ] indicate a worse quality of life).
CI indicates confidence interval; CRT, cardiac resynchronization therapy; and MM, medical therapy.

and that once baseline QoL was accounted for sex was no longer independently associated with CRT benefit. Moreover, we found that baseline QoL was very important, where worse baseline health status was associated with a greater likelihood of improvement. Older patients obtained greater benefit in QoL, despite prior studies showing less use of CRT in older patients.[29] Using a coarser assessment of QoL than the MLHFQ questionnaire, the NYHA classification, we found more benefit in those with NYHA III/IV as compared with those with NYHA II.

Clinical Implications

Our data provide an opportunity to estimate the QoL benefits for an individual patient and to use this information, coupled with mortality and periprocedural risks, to engage patients in shared decision making about CRT.[7,30] Although, our tool only assesses the initial benefits of CRT, it is reassuring that the model continued to perform well at 12 months post-implant. Further work will be needed to define strategies for optimizing CRT to maximize QoL improvement and to define the longer-term QoL benefits of treatment.

Potential Limitations

Our decision to include a patient-reported outcome into the model as opposed to more commonly available NYHA class may hinder implementation. Our rationale to include MLHFQ (or patient-reported outcomes in general) as opposed to NYHA class is that the later is a crude measurement and subject to gaming. There have been several articles explicitly demonstrating low inter-rater reliability of the NYHA with a concordance between 2 different cardiologists' assessments of the same patient of ≈0.54.[31–33] In contrast, the intraclass correlation of health status questionnaires, such as the KCCQ, are high with an estimate of ≈0.92 in stable patients.[17] Further underscoring the value of collecting patient-reported outcome data is the accuracy of the model when a more detailed, reproducible assessment of health status is used. For these reasons, we think that the improved accuracy of the models is greater and justifies the added burden of collecting patients' health status with a questionnaire.

Our findings should be considered in the context of several potential limitations. QoL change from baseline to 3 months was used as our end point because the largest amount of follow-up QoL data were available at 3 months, and most of the QoL benefit occurred within this

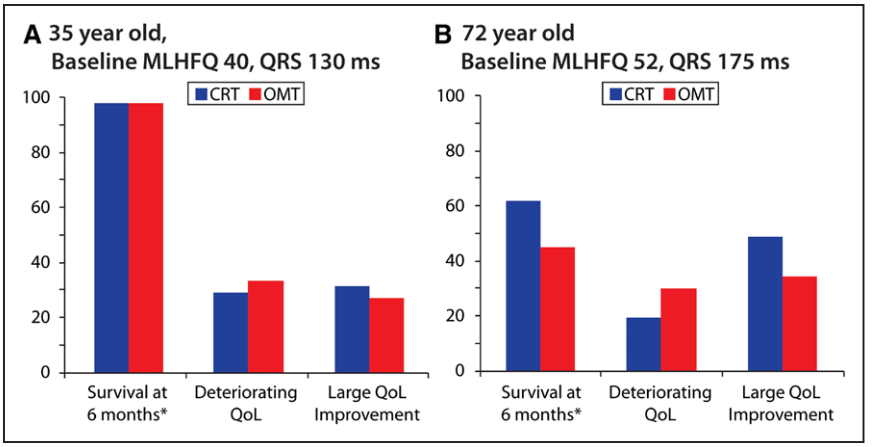

Figure 4. Example model output for patient-shared decision making.
Predicted risk estimates are depicted with bars; lines represent 95% confidence intervals. Estimates of mortality taken from Cleland et al.[7] CRT indicates cardiac resynchronization therapy; MLHFQ, Minnesota Living with Heart Failure Questionnaire; OMT, optimal medical therapy; and QoL, quality of life.

timeframe. In sensitivity analysis, the model performed well at 12 months; however, there was not an opportunity to explore longer-term outcomes that may have been associated with greater QoL benefits, which might be particularly relevant in patients with NYHA II. This will require future research with longer-term outcomes, which may be important given the evidence of continuing positive remodeling of the left ventricle ≤18 months after CRT implantation.[34,35] Second, because there are not well-developed thresholds of clinical change for the MLHFQ, we had to model these thresholds based on the clinically important thresholds of change defined by the KCCQ. We used linear regression from patients with simultaneous MLHFQ and KCCQ in REVERSE to estimate clinical meaningful thresholds in MLFHQ because much more work has been conducted to define clinically important thresholds of change in the KCCQ than the MLHFQ. Although we conducted sensitivity analyses and found consistent results, this methodology has not been validated in other datasets, and REVERSE included healthier patients than many CRT trials. Future efforts to better map the MHLFQ to the KCCQ could validate our estimates and might change, presumably modestly, the results of our model by using a different threshold of clinically significant change. Third, we used older CRT studies, which could impact generalizability of our findings to current practice, because our model may underestimate the benefits of CRT with newer, more advanced devices (quadripolar leads, multipoint pacing, adaptive CRT, etc). Although these evolutions in technology may underestimate the benefits of CRT, it is also possible that evolving medical therapies may have improved the health status of patients not treated with CRT. Thus, these models should be considered an initial step in an evolving effort to validate and improve patient-specific outcome estimates. Fourth, the controls groups of the pooled data were not identical, whereas MIRACLE, MIRACLE-ICD, REVERSE, and RAFT had devices implanted but turned off. CARE had only medical therapy. It is thus possible that the greater QoL benefit in CARE may have reflected a placebo effect, further underscoring the value of including all trials in our analyses. Fifth, although independent patient data were available, certain laboratory values and information about peripheral artery disease, lung disease, and ICD shocks (appropriate and inappropriate) were not available to be included in the model. Finally, our model has not been validated in other randomized controlled trials or in registries, and external validation of these models should be pursued.

Conclusions

We identified substantial variability in the benefits of CRT on QoL, which could be modeled using only 3 variables: age, baseline health status, and QRS duration. This model may contribute to the infrastructure for personalizing the benefits of CRT for those being considered for this intervention. Future studies should examine whether the prospective use of this and models that predict procedural risks and long-term morbidity and mortality can improve patients' participation in shared decision making, target the use of CRT to patients most likely to benefit, and whether this approach to precision medicine can enhance the ability of this important technology to improve the outcomes of patients with heart failure.

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DISCLOSURES

Dr Cleland receives other research support (modest) from Biotronik and is a consultant/advisory board (modest) for Biotronik and St. Jude Medical. Dr Abraham is a consultant/advisory board (significant) for Biotronik and Medtronic St. Jude Medical. Dr Linde receives research grants (modest) and other research support (modest) from Medtronic, honoraria (modest) from Biotronik and St. Jude Medical, and is a consultant/advisory board (modest) at St. Jude Medical. Dr Gold receives research grants (significant) from Medtronic and St. Jude Medical, is a member of the speakers bureau (modest) for Biotronik, and is a consultant/advisory board (modest) for Sorin and (significant) for Boston Scientific, Medtronic, and St. Jude Medical. Dr Young is a consultant/advisory board (modest) at Medtronic. Dr Daubert receives research grants (modest) from Medtronic and is a consultant/advisory board (modest) for Medtronic and St. Jude Medical. Dr Sherfesee is an employee (significant) at Medtronic. Dr Schaber is an employee (significant) at Medtronic. Dr A.S.L. Tang receives research grants (significant) from St. Jude Medical and is a consultant/advisory board (significant) at Medtronic.

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FOOTNOTES

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Circulation
Heart Failure

Precision Medicine for Cardiac Resynchronization: Predicting Quality of Life Benefits for Individual Patients ––An Analysis From 5 Clinical Trials

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SUPPLEMENTAL MATERIAL

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Appendix S1.

Equilibrating the KCCQ and MLWHF to define a responder definition for the MLWHF

While there are well established thresholds for what is a clinically meaningful changes in the KCCQ scores, evidence as to what is meaningful in the MLWHF is more sparse. Bennet et al did report -4.8 +/- 17.43 point change as associated with a minimal clinical change but this was in a small sample (n=165) and given the very high standard deviation was felt to be unreliable.[3] For this reason we attempted to estimate what a 5, 10, and 15 point change in KCCQ at 3 months would be for the MLWHF.

A regression analysis yielded the equation:

MLWHF change at 3 months =KCCQ change at 3 months * (-0.74902) – 2.92430

Using this equation the following assumptions were created:

0 point change in KCCQ = -2.92430 point change in MLWHF

5 point change in KCCQ = -6.6694 point change in MLWHF

10 point change in KCCQ = -10.4145 point change in MLWHF

20 point change in KCCQ = -17.9047 point change in MLWHF

Table S1. Quality of Life Measurements and Time points of Colletction by Trial.

	CARE-HF n = 813	MIRACLE n = 541	MIRACLE-ICD n = 555	RAFT n = 1798	REVERSE n = 610	Total n = 4317
KCCQ at 3 months	0	0	0	0	514	514
KCCQ at 6 months	0	0	0	0	512	512
KCCQ at 9 months	0	0	0	0	0	0
KCCQ at 12 months	0	0	0	0	507	507
KCCQ at 15 months	0	0	0	0	0	0
KCCQ at 18 months	0	0	0	0	162	162
MLWHF at 3 months	658	507	525	1450	576	3716
MLWHF at 6 months	0	480	509	1574	574	3137
MLWHF at 9 months	0	0	260	895	0	1155
MLWHF at 12 months	0	363	423	1528	567	2881
MLWHF at 15 months	0	0	0	729	0	729
MLWHF at 18 months	546	144	238	1334	222	2484

Values are shown as absolute numbers. MLWHF = Minnesota Living with Heart Failure; KCCQ = Kansas City cardiomyopathy questionairre

Table S2. Characteristics of patients deceased prior to 3 months versus those in analytic cohort.

	Died prior to 3 months n=98	Study Cohort n=3614	p-value
Age (y)	67.6 ± 10.3	65.2 ± 10.3	0.020
Male	80 (81.6%)	2827 (78.2%)	0.419
QRS width (ms)	160.4 ± 23.2	162.2 ± 24.2	0.454
Left bundle branch block	74 (77.1%)	2722 (75.8%)	0.764
CRT	47 (48.0%)	1890 (52.3%)	0.396
Implantable defibrillator	48 (49%)	1890 (52.3%)	<0.001
NYHA Class			
II	21 (21.4%)	1819 (50.3%)	<0.001
III	60 (61.2%)	1685 (46.6%)	
IV	17 (17.3%)	110 (3.0%)	
Left ventricular EF	22 ± 7	24 ± 6	0.004
Ischemic cardiomyopathy	72 (73.5%)	2100 (58.1%)	0.002
Diabetes mellitus	33 (42.1%)	888 (30.0%)	0.022
MLWHF at baseline	57.5 ± 23.5	42.5 ± 23.5	<0.001
ACE-I/ARB	81 (84.4%)	3445 (95.3%)	<0.001
Beta blocker	54 (55.1%)	2841 (78.6%)	<0.001

Table S3. Characteristics of patients with missing QoL data versus those in the analytic cohort.

	Missing QoL Data n=505	Study Cohort n=3614	p-value
Age (y)	65.4 ± 9.9	65.2 ± 10.3	0.597
Male	404 (80.0%)	2827 (78.2%)	0.363
QRS width (ms)	160.7 ± 24.7	162.2 ± 24.2	0.200
LBBB	381 (77.6%)	2722 (75.8%)	0.371
CRT	254 (50.3%)	1890 (52.3%)	0.399
ICD	364 (72.1%)	1890 (52.3%)	0.003
NYHA Class			
II	287 (56.8%)	1819 (50.3%)	<0.001
III	192 (38.0%)	1685 (46.6%)	
IV	19 (3.8%)	110 (3.0%)	
Left ventricular EF	24 ± 6	24 ± 6	0.107
Ischemic cardiomyopathy	293 (58.0%)	2100 (58.1%)	0.970
Diabetes mellitus	150 (33.2%)	888 (30.0%)	0.164
MLWHF at baseline	40.0 ± 25.0	42.5 ± 23.5	0.05
ACE-I/ARB	472 (95.4%)	3445 (95.3%)	0.976
Beta blocker	420 (83.2%)	2841 (78.6%)	0.018

Table S4. Baseline characteristics of Cardiac Resynchronization Therapy vs. control

	CRT N = 1890	Control N = 1724	p-value
Male	1486 (78.6%)	1341 (77.8%)	0.541
Age	65.0 ± 10.3	65.3 ± 10.3	0.413
QRS width (ms)	161.6 ± 24.2	162.9 ± 24.2	0.129
LBBB	1441 (76.6%)	1281 (74.9%)	0.235
MLWLHF	42.2 ± 23.5	42.5 ± 23.2	0.741
Systolic Blood Pressure	118.3 ± 18.1	117.8 ± 17.7	0.443
Medical history			
ICD	1246 (65.9%)	1123 (65.1%)	0.619
NYHA II	987 (52.2%)	832 (48.3%)	0.017
NYHA IV	61 (3.2%)	49 (2.9%)	0.500
Ejection fraction	24.0 ± 6.3	24.0 ± 6.1	0.795
Ischemic CM	1112 (58.8%)	988 (57.3%)	0.352
Diabetes	456 (29.0%)	432 (31.0%)	0.229
Baseline Medications			
ACE/ARB Usage	1805 (95.5%)	1640 (95.1%)	0.593
Beta blockers	1518 (80.3%)	1323 (76.7%)	0.008
Spironolactone	752 (42.3%)	725 (45.2%)	0.091

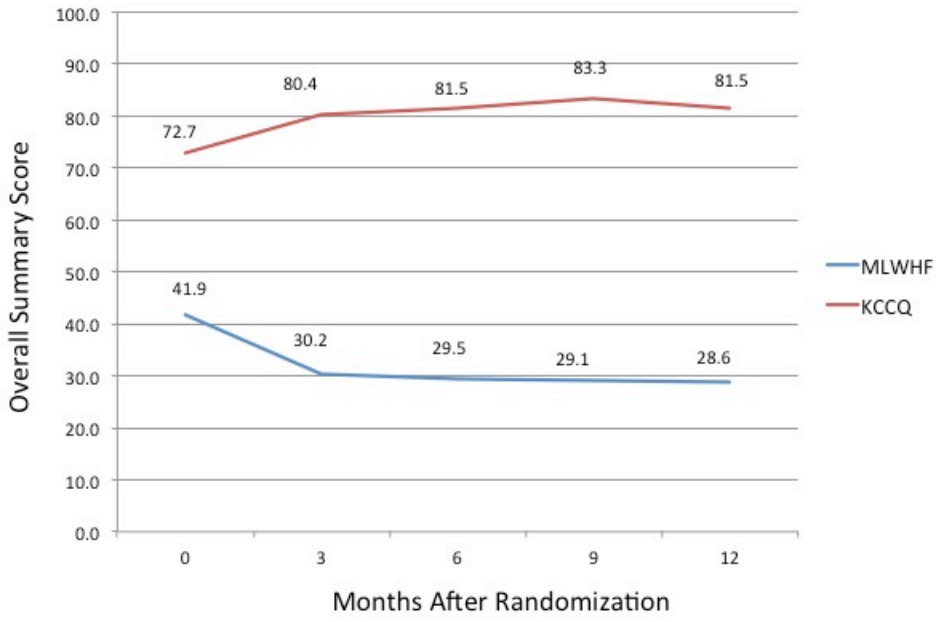
Values are shown as absolute numbers (percentages), mean ± SD. NYHA, New York Heart Association; MLWHF, Minnesota Living with Heart Failure; ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin II receptor blocker

Table S5. Clinically meaningful changes in quality of life of CRT versus control

QOL Change Category	CRT n=1890	Control n=1724	p-value
Large deterioration	7.6	10.0	<0.001
Moderate deterioration	6.5	11.3	
Small deterioration	7.0	7.3	
No change	16.5	19.2	
Small improvement	9.5	8.8	
Moderate improvement	14.1	12.9	
Large improvement	38.7	30.6	

Values are shown as percentages. CRT, cardiac resynchronization therapy

Figure S1. Quality of Life Over time measure by Minnesota Living With Heart Failure and Kansas City Cardiomyopathy Questionnaire



Values shown as mean overall scores. MLWHF = Minnesota living with heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire.
*The KCCQ overall summary scored is 0-100 with higher numbers reflecting better quality of life. The MLWHF is scored 0-105 with lower scores representing better quality of life.

Figure S2. Observed versus predicted probability of no change in quality of life at 12 months

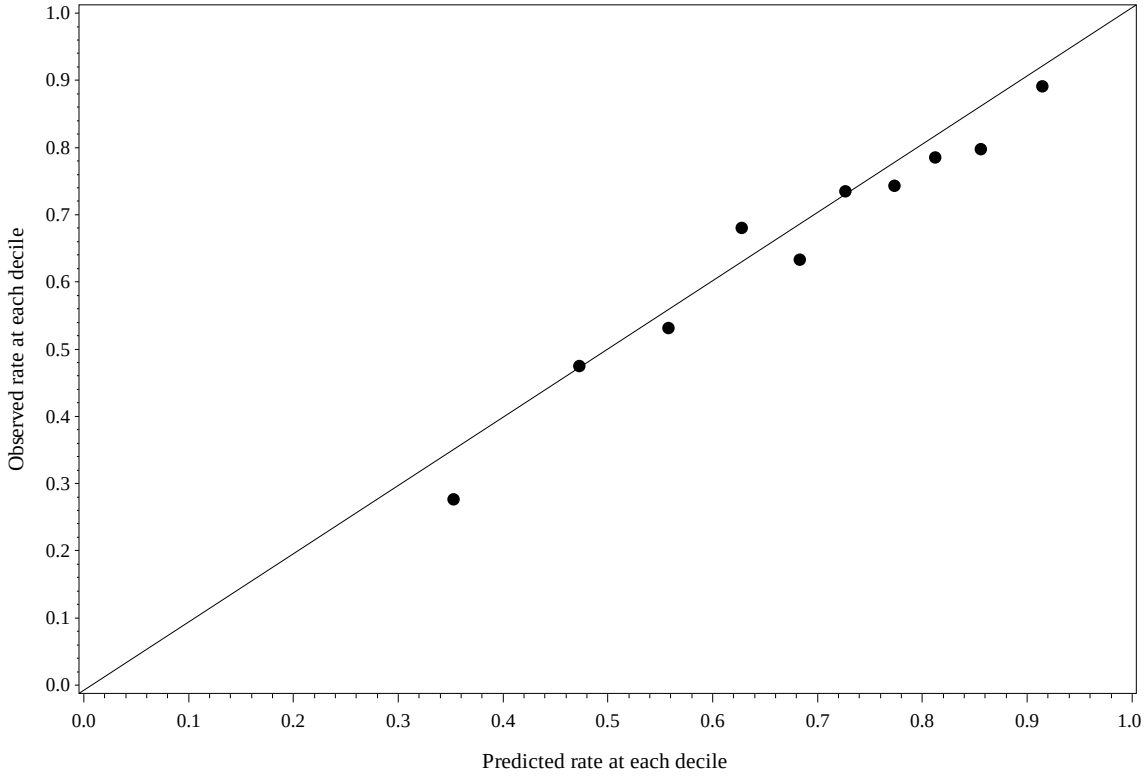


Figure S3. Observed versus predicted probability of a small improvement in quality of life at 12 months

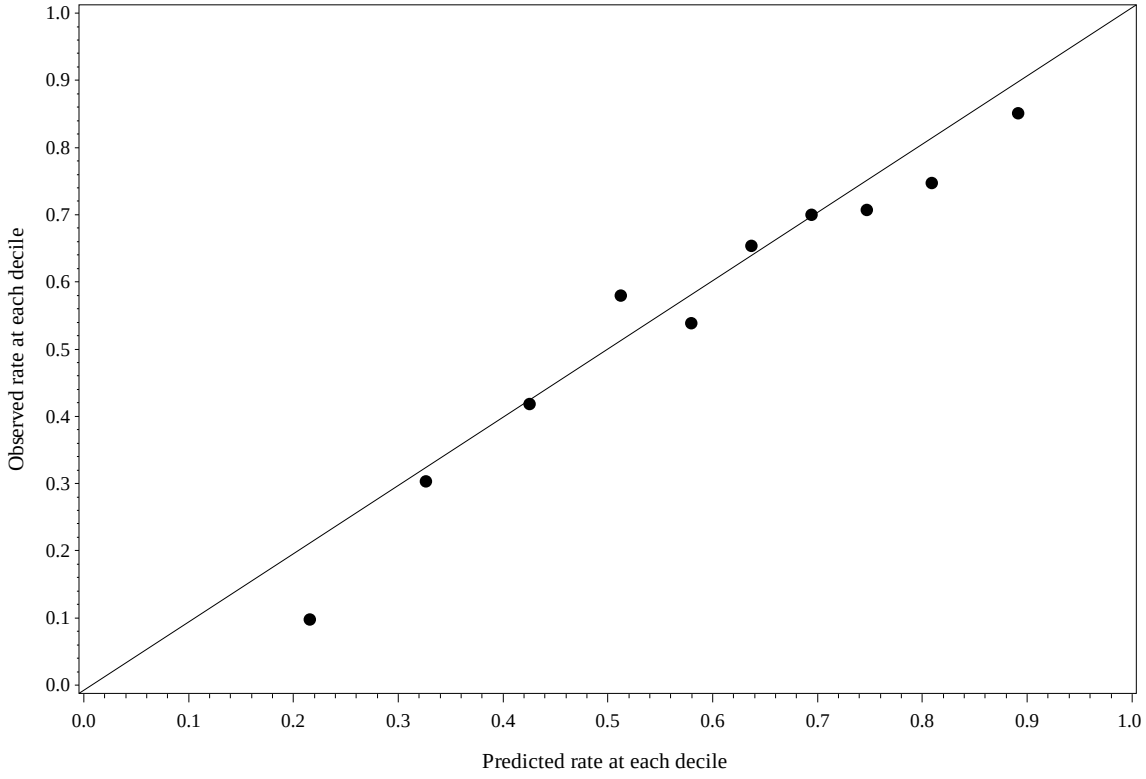


Figure S4. Observed versus predicted probability of a moderate improvement in quality of life at 12 months

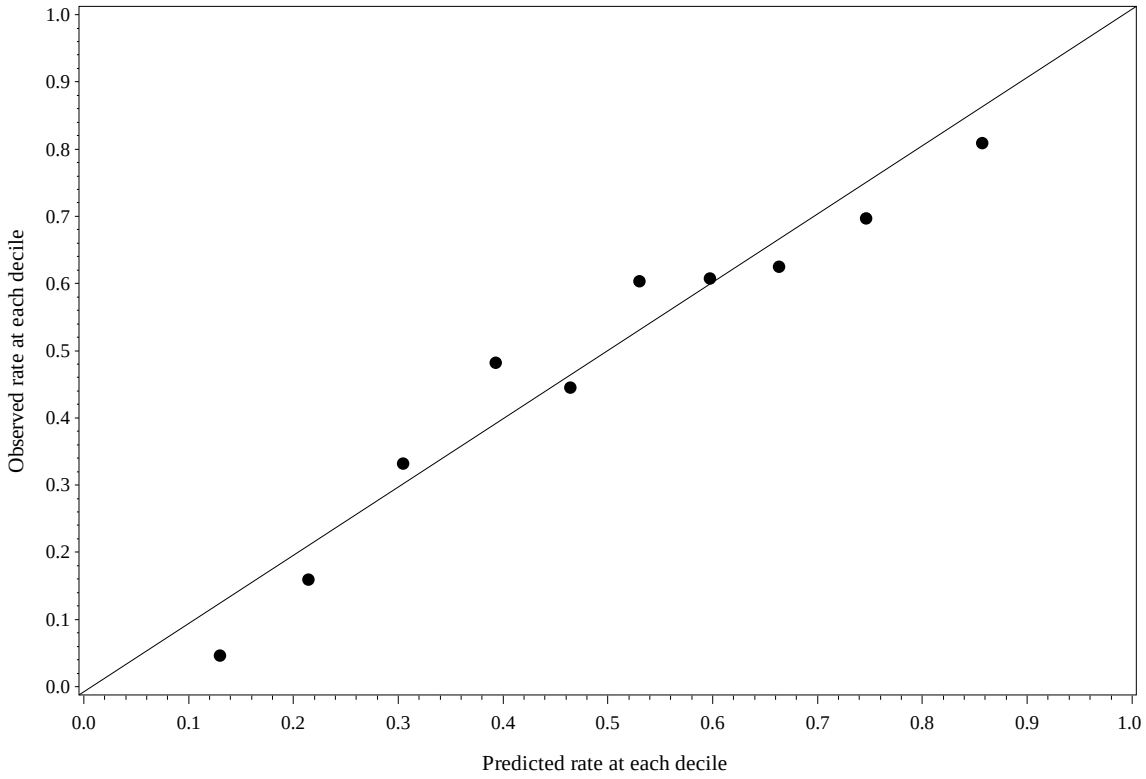


Figure S5. Observed versus predicted probability of a large improvement in quality of life at 12 months