Usefulness of the CRT-SCORE for Shared Decision Making in Cardiac Resynchronization Therapy in Patients With a Left Ventricular Ejection Fraction of <= 35%

Hoke, U.; Mertens, B.; Khidir, M.J.H.; Schalij, M.J.; Bax, J.J.; Delgado, V.; Marsan, N.A.

Usefulness of the CRT-SCORE for Shared Decision Making in Cardiac Resynchronization Therapy in Patients With a Left Ventricular Ejection Fraction of ≤35%

Ulas Höke, MD[a,b], Bart Mertens, PhD[c], Mand J.H. Khidir, MD[a], Martin J. Schalij, MD, PhD[a], Jeroen J. Bax, MD, PhD[a], Victoria Delgado, MD, PhD[a], and Nina Ajmone Marsan, MD, PhD[a,*]

Individualized estimation of prognosis after cardiac resynchronization therapy (CRT) remains challenging. Our aim was to develop a multiparametric prognostic risk score (CRT-SCORE) that could be used for patient-specific clinical shared decision making about CRT implantation. The CRT-SCORE was derived from an ongoing CRT registry, including 1,053 consecutive patients (age 67 ± 10 years, 76% male). Using preimplantation variables, 100 multiple imputed datasets were generated for model calibration. Based on multivariate Cox regression models, cross-validated linear prognostic scores were calculated, as well as survival fractions at 1 and 5 years. Specifically, the CRT-SCORE was calculated using atrioventricular junction ablation, age, gender, etiology, New York Heart Association class, diabetes, hemoglobin level, renal function, left bundle branch block, QRS duration, atrial fibrillation, left ventricular systolic and diastolic functions, and mitral regurgitation, and showed a good discriminative ability (areas under the curve 0.773 at 1 year and 0.748 at 5 years). During the long-term follow-up (median 60 months, interquartile range 31 to 85), all-cause mortality was observed in 494 (47%) patients. Based on the distribution of the CRT-SCORE, lower- and higher-risk patient groups were identified. Estimated mean survival rates of 98% at 1 year and 92% at 5 years were observed in the lowest 5% risk group (L5 CRT-SCORE: −4.42 to −1.60), whereas the highest 5% risk group (H5 CRT-SCORE: 1.44 to 2.89) showed poor survival rates: 78% at 1 year and 22% at 5 years. In conclusion, the CRT-SCORE allows accurate prediction of 1- and 5-year survival rates after CRT using readily available and CRT-specific clinical, electrocardiographic, and echocardiographic parameters. The model may assist clinicians in counseling patients and in decision making. **(Am J Cardiol 2017;120:2008–2016)**

Despite the knowledge that beneficial effect of cardiac resynchronization therapy (CRT) is influenced by multiple factors, a comprehensive and customized approach to estimate prognosis after CRT is lacking, although it would be of crucial importance in clinical decision making for high-risk patients with heart failure and for this relatively invasive and costly procedure. Ideally, short-term and long-term survival rates should be accurately estimated and with a patient-specific approach to appropriately tailor CRT implantation. Our objective was therefore to develop an individualized CRT multiparametric prognostic risk score using readily available heart failure and CRT-specific variables in a large registry of unselected patients who underwent CRT. This score may facilitate shared decision making between patients with heart failure and their physicians.

Methods

All patients consecutively included in the ongoing CRT registry from the Department of Cardiology of the Leiden University Medical Centre (Leiden, The Netherlands) from August 1999 to July 2013 were considered for this analysis.[1] Among these patients, only those who underwent CRT device implantation according to the presence of a left ventricular ejection fraction (LVEF) of ≤35%, a QRS duration of ≥120 ms, and a New York Heart Association (NYHA) functional class II-ambulatory IV, despite optimal heart failure medical treatment, were included.[2] Furthermore, patients with a decompensated heart failure before the implantation or a recent myocardial infarction (<3 months) were excluded. All patients underwent extensive clinical evaluation and transthoracic 2-dimensional echocardiography before the CRT implantation. All patients were scheduled for regular visits at the outpatient clinic of

[a]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [b]Interuniversity Cardiology Institute of the Netherlands (ICIN), Utrecht, The Netherlands; and [c]Medical Statistics Department, Leiden University Medical Center, Leiden, The Netherlands. Manuscript received May 2, 2017; revised manuscript received and accepted August 1, 2017.

See page 2015 for disclosure information.

*Corresponding author: Tel: +31(0)71-5262020; fax: +31(0)71-5266809.
E-mail address: N.Ajmone@lumc.nl (N. Ajmone Marsan).

https://doi.org/10.1016/j.amjcard.2017.08.019

our center and/or at the referral hospital on the long-term follow-up. Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and were subsequently analyzed. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without previous approval from an institutional review board, provided that the data are acquired for routine patient care. All data used for this study were acquired for clinical purposes and were handled anonymously.

Before CRT implantation, extensive clinical evaluation was performed and included NYHA functional class, quality-of-life score according to the Minnesota Living with Heart Failure Questionnaire (higher scores indicate poorer quality of life), blood pressure, and exercise capacity by the 6-minute walk test.[3,4] Hemoglobin levels and serum creatinine were also routinely assessed before implantation. Assessment of renal function evaluation was based on the glomerular filtration rate (GFR) estimation in milliliter per minute.[5] The etiology of heart failure was considered ischemic in the presence of a significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization. The number of patients with atrial fibrillation (AF) at baseline, either chronic or paroxysmal, was noted. The atrioventricular junction (AVJ) ablation for AF before CRT implantation was recorded. The presence of left bundle branch block (LBBB) on a 12-lead electrocardiogram was defined by the presence of a QRS duration of ≥120 ms with typical features of LBBB described by the current guidelines.[6]

Echocardiographic studies were performed with patients in the left lateral decubitus position using a commercially available ultrasound system (Vivid 7 and e9; General Electric Vingmed Ultrasound, Horten, Norway) equipped with 3.5 MHz and M5S transducers. Images were digitally stored for offline analysis in cine-loop format (EchoPac 112.0.1; GE-Vingmed, Horten, Norway). Left ventricular (LV) end-diastolic volume and end-systolic volume and LVEF were calculated using the Simpson biplane rule.[7] Mitral regurgitation severity was evaluated using a semiquantitative multiparametric approach from color Doppler and Doppler acquisitions and was graded according to the recommendations of the European Association of Cardiovascular Imaging as mild (grade 1), moderate (grade 2), and severe (grades 3 to 4).[8] LV diastolic function was evaluated according to current recommendations using the multiparametric approach, including transmitral flow Doppler velocities and tissue Doppler imaging-derived mitral annular velocities.[9] LV diastolic dysfunction was therefore graded (grades 1, 2, and 3) and restrictive function was considered in case of an LV diastolic dysfunction grade 3.[9]

Survival data were obtained by a review of medical records and by a retrieval of survival status through the municipal civil registries. The end point was all-cause mortality. Cardiovascular death was defined as death due to progression of heart failure, sudden cardiac death, myocardial infarction, ventricular arrhythmias, other cardiac cause, and stroke according to a modified Hinkle-Thaler system.[10] Furthermore, patients who underwent heart transplantation or LV assist device implantation were classified as cardiac death on the day of their procedure.

Variables were presented as mean values ± standard deviation, median and interquartile range, or frequencies and percentages in the case of categorical variables. To account for missing observations, 100 multiple imputed datasets were generated (using the package MICE, R; TNO, Leiden, the Netherlands), based on the following variables: age, gender, etiology, AF, QRS duration, LBBB, NYHA functional class, diabetes mellitus, GFR, hemoglobin level, mitral regurgitation, LVEF, and LV diastolic dysfunction, as well as the survival time and censoring indicator.[11] For each multiple imputed dataset, the predictive performance of estimated survival outcomes using Cox regression was estimated from a 10-fold cross-validatory approach.[12] Estimation was carried out on a fixed set of clinical predictors, which were chosen as well-known prognostic parameters of long-term outcome after CRT based on the relevant published CRT literature.[1,2,13,14] Considering the multiple imputation, an additional or unnecessary statistical complexity was therefore prevented using predefined parameters at the univariate and multivariate Cox regression analyses.[12] The estimation of each individual Cox regression model was carried out as follows. First, a Cox model was generated, which adjusts for age, gender, and AVJ ablation. The linear predictor derived in this model was entered as an offset in a new Cox regression model with the abovementioned prognostic relevant variables. For each left-out partition of the data within the cross-validatory procedure and for each multiple imputation, the resulting model was then applied to the left-out data and their cross-validated linear prognostic scores were calculated, as well as the cross-validated (per-patient) survival fractions at 1 and 5 years. For each multiple imputed dataset, the (cross-validated) receiver operating characteristic (ROC) curve was calculated to examine the discriminatory value of the joint set of variables for the prediction of the survival end point. The area under the curve (AUC) calculation was adjusted for censoring (package timeROC, R; University of Copenhagen, Copenhagen, Denmark) and based on the cross-validated prognostic scores at 1 and 5 years.[15] The CRT-SCORE was simplified by reducing the number of parameters required for the calculation of the score by rounding without loss of discriminatory capacity. To calculate the CRT-SCORE on a new patient, each variable in the multivariate model was multiplied by its pooled rounded regression coefficient and the products were summed. For clinical decision making, life tables were generated using averaged cross-validated prognostic scores across all imputations into a single combined mean score. Likewise, the cross-validated per-patient survival fractions at 1 and 5 years were averaged across all imputations to generate a single mean consensus survival fraction. Evaluation of the 1-year survival rate was performed considering the currently recommended life expectancy of 1 year for CRT implantation.[2] Analysis of the 5-year survival rate was performed to give an estimation of the long-term outcome in this high-risk patient population. Using these aggregated multiple imputation cross-validation results, the 0%, 5%, 10%, 20%, 40%, 60%, 80%, 90%, 95%, and 100% percentiles of the cross-validated prognostic score range were identified. To improve the readability, the groups based on the prognostic score were renamed based on the corresponding range, that is, the highest 5% score (the

range 95% to 100%) was named as H5. The range 40% to 60% was named M, and the lowest percentage, that is, the range 0% to 5%, was named L5. The groups were named H5, H10, H20, H40, M, L40, L20, L10, and L5, respectively. For each interval between subsequent percentiles of the cross-validated predictor, the 0%, 25%, 50%, 75%, and 100% percentiles of 1- and 5-year survival fractions were calculated within that corresponding prognostic range as well as the corresponding Kaplan-Meier estimates (for 1 and 5 years). Kaplan-Meier estimates were also generated for the 0 to 20, 20 to 40, 40 to 60, 60 to 80, and 80 to 100 percentile ranges of the average cross-validated prognostic score. The separate Cox model estimates were pooled across the 100 multiple imputed datasets, and standard errors and p values were adjusted for multiple imputations (package MICE, R) using the Rubin rules.[11,16] The calculated univariate and multivariate Cox regression tests were 2-sided and a p value of <0.05 was considered statistically significant. Windows IBM SPSS Statistics software (SPSS version 20.0; IBM SPSS statistics, Chicago, Illinois) and R version 3.0.1 (R Development Core Team, Vienna, Austria) were used for data analyses.

Results

A total of 1,053 CRT patients were included in the analysis. The clinical characteristics are listed in Table 1. During the long-term follow-up (median 60 [interquartile range 31 to 84] months), all-cause mortality was observed in 494 (47%) patients, 438 (87%) of which were considered as cardiovascular death. The datasets were nearly complete (>99%) with the exception of LV diastolic function. This variable was missing in 49.8% of the patients. The missing datasets were imputed using 100 multiple imputation and repeated after 10-fold cross-validatory approach for each imputed dataset. The univariate Cox regression analysis is listed in Table 2. The predefined and the additional parameters that were significant at the univariate analysis were entered in a multivariate model; besides age, gender, and AVJ ablation (predefined for adjustment), only ischemic etiology, diabetes, QRS duration of ≥150 ms, NYHA functional class, renal function, LVEF, mitral regurgitation grade ≥3, and restrictive LV diastolic function were independently associated with mortality after CRT implantation after rounding (Table 3). Furthermore, the LBBB, AF, and the hemoglobin level were also included in the calculation of

Table 1
Baseline characteristics

Characteristics	Value
Age, (years)	67 ± 10
Men, n (%)	805(76)
New York Heart Association functional class II	250(24%)
New York Heart Association functional class III	713(68%)
New York Heart Association functional class IV	90(9%)
Six-minute walk distance, (meters)	306 ± 125
Minnesota quality of life score, (point)	35 ± 19
Systolic blood pressure, (mmHg)	124 ± 21
Diastolic blood pressure, (mmHg)	73 ± 12
Glomerular filtration rate, (ml/min)	70 ± 32
Hemoglobin, (mmol/L)	8.3 ± 1.0
Ischemic etiology	587(56%)
Diabetes mellitus	221(21%)
Atrial fibrillation	177(17%)
Atrio-ventricular junction ablation	42(4%)
QRS duration, (ms)	166 ± 26
Left bundle branch block	692(66%)
Diuretics	880(84%)
β-blockers	741(70%)
Angiotensin-converting enzyme inhibitor/ Angiotensin II receptor blocker	928(88%)
Amiodarone,	204(19%)
Left ventricular end-diastolic volume, (ml)	218 ± 80
Left ventricular end-systolic volume, (ml)	165 ± 71
Left ventricular ejection fraction, (%)	26 ± 8
Mitral regurgitation grade ≥3	182(18%)
Restrictive left ventricular diastolic function	175(33%)

Table 2
Univariate Cox-regression analysis for all-cause mortality after cardiac resynchronization therapy

Variable	β	SE	p-Value
Age, (per year)	0.038	0.005	**<0.001**
Men	0.397	0.116	**0.001**
Atrio-ventricular junction ablation	-0.069	0.234	0.768
New York Heart Association functional class III	0.653	0.133	**<0.001**
New York Heart Association functional class IV	1.293	0.179	**<0.001**
Glomerular filtration rate, per ml/min	–0.023	0.002	**<0.001**
Hemoglobin, (per mmol/L)	–0.279	0.047	**<0.001**
Ischemic etiology	0.579	0.095	**<0.001**
Diabetes mellitus	0.522	0.103	**<0.001**
Left bundle branch block	–0.315	0.093	**0.001**
QRS duration ≥150 ms	–0.170	0.098	0.084
Atrial fibrillation	0.413	0.106	**<0.001**
Left ventricular ejection fraction, (per %)	–0.028	0.006	**<0.001**
Mitral regurgitation grade ≥3	0.507	0.105	**<0.001**
Restrictive left ventricular diastolic dysfunction	0.432	0.124	**0.001**

Table 3
Refitted multivariate Cox-regression for all-cause mortality after cardiac resynchronization therapy after rounding (simplified CRT-SCORE)

Variable	HR	B	SE	p-Value
Age, (per year)	1.038	0.037	0.005	**<0.001**
Men	1.443	0.367	0.116	**0.001**
Atrio-ventricular junction ablation	0.845	–0.169	0.234	0.469
New York Heart Association functional class III	1.483	0.394	0.137	**0.004**
New York Heart Association functional class IV	2.284	0.826	0.189	**<0.001**
Glomerular filtration rate, per ml/min	0.987	–0.013	0.002	**<0.001**
Hemoglobin, (per mmol/L)	0.919	–0.084	0.049	0.084
Ischemic etiology	1.247	0.221	0.099	**0.026**
Diabetes mellitus	1.675	0.516	0.107	**<0.001**
Left bundle branch block	0.841	–0.173	0.096	0.072
QRS duration ≥150 ms	0.856	–0.156	0.103	0.130
Atrial fibrillation	1.049	0.048	0.122	0.691
Left ventricular ejection fraction, (per %)	0.974	–0.026	0.006	**<0.001**
Mitral regurgitation grade ≥3	1.296	0.259	0.109	**0.018**
Restrictive left ventricular diastolic dysfunction	1.384	0.325	0.137	**0.018**

the CRT-SCORE, considering that their clinical value and/or a p value <0.1. ROC curves at 1- and 5-year survival rates based on the 10-fold cross-validation within each multiple imputation were generated (supplemental file, Supplementary Figures S1 and S2). The discriminative ability of the model was good with an area under the ROC curve of 0.773 (minimum 0.733 and maximum 0.753) at 1 year and 0.748 (minimum 0.728 and maximum 0.734) at 5 years.

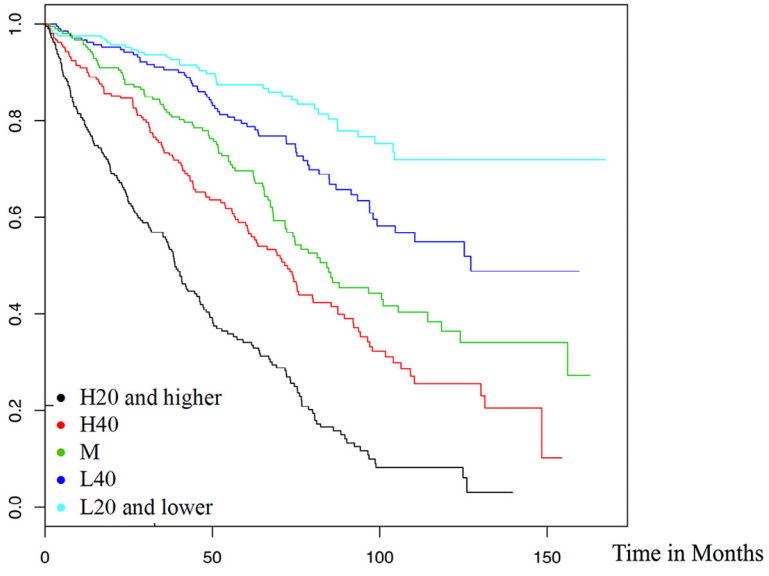
Predicting a patient's risk in daily clinical practice requires adding up the β-coefficients of the predictors from Table 3 to calculate the mortality risk score. The CRT-SCORE was therefore calculated as follows:

$$\begin{aligned}\text{CRT-SCORE} = {} & (-0.169 \times \textbf{AVJ ablation}) + (0.037 \times \textbf{Age}) \\ & + (0.367 \times \textbf{Male gender}) + (0.221 \times \textbf{Ischemic etiology}) \\ & + (0.048 \times \textbf{AF}) + (0.516 \times \textbf{Diabetes Mellitus}) \\ & - (0.173 \times \textbf{LBBB}) + (0.394 \times \textbf{NYHA class III}) \\ & + (0.826 \times \textbf{NYHA class IV}) \\ & - (0.156 \times \textbf{QRS duration} \geq \textbf{150 ms}) \\ & - (0.013 \times \textbf{GFR} - (0.084 \times \textbf{Hemoglobin level}) \\ & - (0.026 \times \textbf{LVEF}) + (0.259 \times \textbf{Mitral regurgitation} \geq \textbf{3}) \\ & + (0.325 \times \textbf{Restrictive LV diastolic function}).\end{aligned}$$

Kaplan-Meier curves were generated per 20% of the study population during the entire follow-up (Figure 1). The CRT score was used as a risk score to estimate individual survival rates. Using Cox regression analysis, the survival curves were generated for 1- and 5-year survival rates stratified per 20% prognostic index (Figure 2). For clinical decision making, the individual risk scores were displayed in more detail, per 5% of the prognostic index in the high and low ends of the CRT score ranging from L5 to H5 (Table 4A and B). In the lowest-risk group (L5; CRT score −4.42 to −1.60), the estimated mean survival rate was 98% at 1 year and 92% at 5 years. More interestingly, in the highest-risk group (H5; CRT score 1.44 to 2.89), the survival rate was 78% at 1 year and 22% at 5 years (Table 4A and B). The groups between the 2 ends with their corresponding CRT-SCORE are listed in Table 4A for the 1-year survival fractions and in Table 4B for the 5-year survival fractions. Also, a graphical presentation of these data is shown for the 1-year survival fractions and for the 5-year survival fractions in Figure 3. Although the CRT-SCORE was estimated for all-cause mortality, the cause-specific incidence of mortality was evaluated among the CRT-SCORE percentiles. As shown in Figure 4, the increase in risk groups was associated with more likelihood of cardiovascular mortality, suggesting therefore that the CRT-SCORE is able to risk-stratify also cardiovascular mortality.

Discussion

Using preimplantation clinical, electrocardiographic, and echocardiographic data from a large cohort of unselected patients treated with CRT, we derived a risk stratification score (CRT-SCORE), which was able to predict mortality at 1 and 5 years after implantation. Importantly, the CRT-SCORE identified the highest-risk group (H5) characterized by a very poor



Patients at risk				
H20 and higher	211	73	12	2
H40	210	112	30	2
M	211	135	41	16
L40	210	139	46	16
L20 and lower	211	154	53	44

Figure 1. Kaplan-Meier curve of the overall survival rate after CRT implantation. The survival rate indexed per 20% of the CRT-SCORE, that is, the top 20% (H20 and higher) in black and the bottom 20% (L20 and lower) in light blue. (Color version available online.)

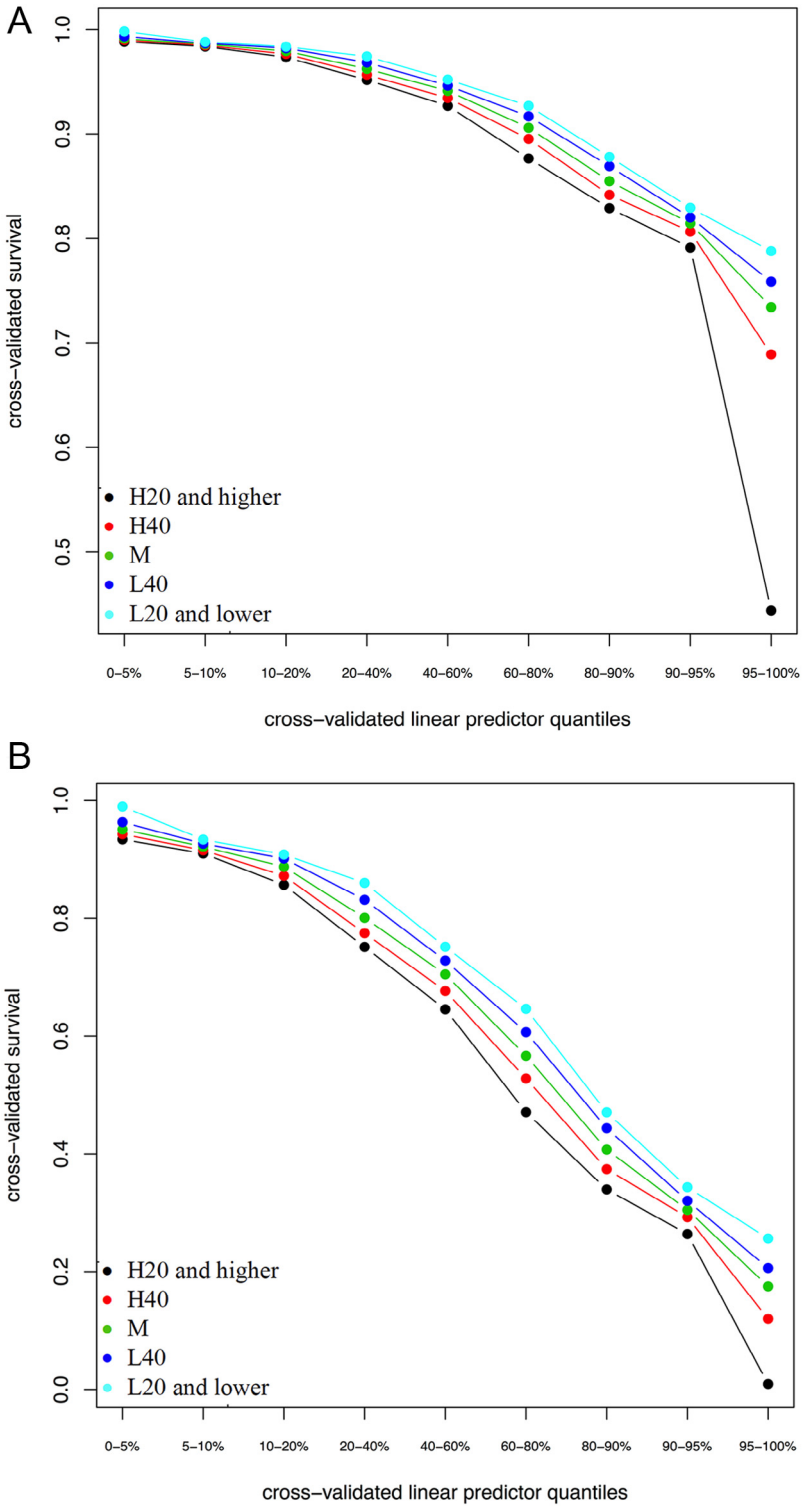


Figure 2. *(A)* Cross-validated survival estimation per 20% prognostic index at 1 year after CRT implantation. *(B)* Cross-validated survival estimation per 20% prognostic index at 5 years after CRT implantation.

prognosis both at the short- and long-term follow-ups, suggesting the very limited beneficial effect of CRT in these patients. For a potential implementation in clinical practice and widespread use, the CRT-SCORE calculator is possible for smartphone applications and/or online using the CRT-SCORE website (see Appendix).

In addition to the criteria currently recommended by the guidelines, which include the NYHA class, the LVEF, the QRS morphology, and the duration, several clinical, electrocardiographic, and echocardiographic parameters have been suggested to further modulate the spectrum of CRT response and, more importantly, to predict prognosis after

Table 4A
Quantiles of cross-validated survival fractions free from all-cause mortality (columns) versus range of cross-validated linear predictor (rows) at 1 year

			Cross-validated survival fractions at 1 year				
Group name	Proportion of patients	CRT-SCORE	0%	25%	50%	75%	100%
L5	0–5%	[−4.42—−1.60]	0.99	0.99	0.99	0.99	1.00
L10	5–10%	[−1.60—−1.31]	0.98	0.99	0.99	0.99	0.99
L20	10–20%	[−1.31—−0.82]	0.97	0.98	0.98	0.98	0.98
L40	20–40%	[−0.82—−0.16]	0.95	0.96	0.96	0.97	0.97
M	40–60%	[−0.16–0.28]	0.93	0.93	0.94	0.95	0.95
H40	60–80%	[0.28–0.79]	0.88	0.89	0.91	0.92	0.93
H20	80–90%	[0.79–1.18]	0.83	0.84	0.86	0.87	0.88
H10	90–95%	[1.18–1.44]	0.78	0.80	0.81	0.82	0.83
H5	95–100%	[1.44–2.89]	0.36	0.68	0.73	0.76	0.78

Table 4B
Quantiles of cross-validated survival fractions (columns) free from all-cause mortality versus range of cross-validated linear predictor (rows) at 5 years

			Cross-validated survival fractions at 5 years				
Group name	Proportion of patients	CRT-SCORE	0%	25%	50%	75%	100%
L5	0–5%	[−4.42—−1.60]	0.93	0.94	0.95	0.96	0.99
L10	5–10%	[−1.60—−1.31]	0.91	0.92	0.92	0.93	0.93
L20	10–20%	[−1.31—−0.82]	0.86	0.87	0.89	0.90	0.91
L40	20–40%	[−0.82—−0.16]	0.75	0.78	0.80	0.83	0.86
M	40–60%	[−0.16–0.28]	0.64	0.68	0.70	0.73	0.75
H40	60–80%	[0.28–0.79]	0.48	0.53	0.57	0.61	0.64
H20	80–90%	[0.79–1.18]	0.34	0.38	0.41	0.45	0.48
H10	90–95%	[1.18–1.44]	0.25	0.28	0.31	0.33	0.34
H5	95–100%	[1.44–2.89]	0.00	0.11	0.17	0.21	0.25

implantation.[1,2,13,14,17–20] In the present study, most of these preimplantation parameters confirmed their significant association with survival rate through the univariate and multivariate Cox regression analyses or were a priori included in the CRT-SCORE: gender, NYHA class, etiology of heart failure, diabetes, renal function, hemoglobin level, AF, LBBB morphology, severely prolonged QRS duration, severe mitral regurgitation, and restrictive LV diastolic function. Estimation of short- and long-term prognoses in patients with heart failure is a challenge for clinicians and can be either over- or underestimated. Considering the costs and the potential complications of the procedure, a life expectancy of at least 1 year is currently advised when referring patients for CRT, although no specific criteria for this assessment are suggested.[2] Development of a patient-specific and CRT-specific multiparametric prognostic risk score would be therefore of great clinical value in decision making. Involvement of patients in this process, the so-called shared decision making, would also require a reliable estimation of the long-term beneficial effect of CRT using readily available and easily understandable parameters. With this aim, several studies already proposed different prognostic models.[21–24] The Seattle Heart Failure Model is an accepted prognostic score of 25 parameters for predicting the survival rate in patients with heart failure, although it has been shown to systematically underestimate mortality risk, particularly in patients with implanted devices.[22] CRT studies using the Seattle Heart Failure Model show a relatively high survival rate for the highest-risk category of patients compared with the cumulative incidence (91% vs 93% at 1 year and 66% vs 75% at 5 years), suggesting a suboptimal prognostic performance at the short-term follow-up,[23] and the relatively low discriminative ability (AUC = 0.64) at the long-term follow-up.[22] Other CRT risk stratification scores incorporating baseline clinical parameters such as the presence of advanced chronic kidney disease, age, NYHA class, LVEF impairment, and AF included patients with a narrow QRS complex, in whom CRT implantation is currently discouraged,[2] and surprisingly showed that patients with higher-risk scores and less CRT benefit had a wider QRS duration.[24] The most comprehensive CRT prediction score, so far, was proposed by Gasparini et al, who included patients from multiple European centers.[21] Gasparini et al's study showed an acceptable discriminatory capacity of a model comprising 8 clinical and echocardiographic parameters (AUC = 0.70). However, in 89% of the validation population, an LBBB morphology was present, and moreover, essential prognostic parameters such as renal function and mitral regurgitation were not included in their final model. Furthermore, missing data were at random and not completely at random, which could have introduced bias[25,26] and probably explain the discrepancy between the predicted and the observed survival rates at the 6-year follow-up (better for the predicted survival rate in the lowest-risk group). The CRT-SCORE was shown to have a higher discriminative value (by a higher AUC) than other risk stratification models and was used to identify different patient risk groups. As clearly shown by the distribution in Figure 1, patients in the

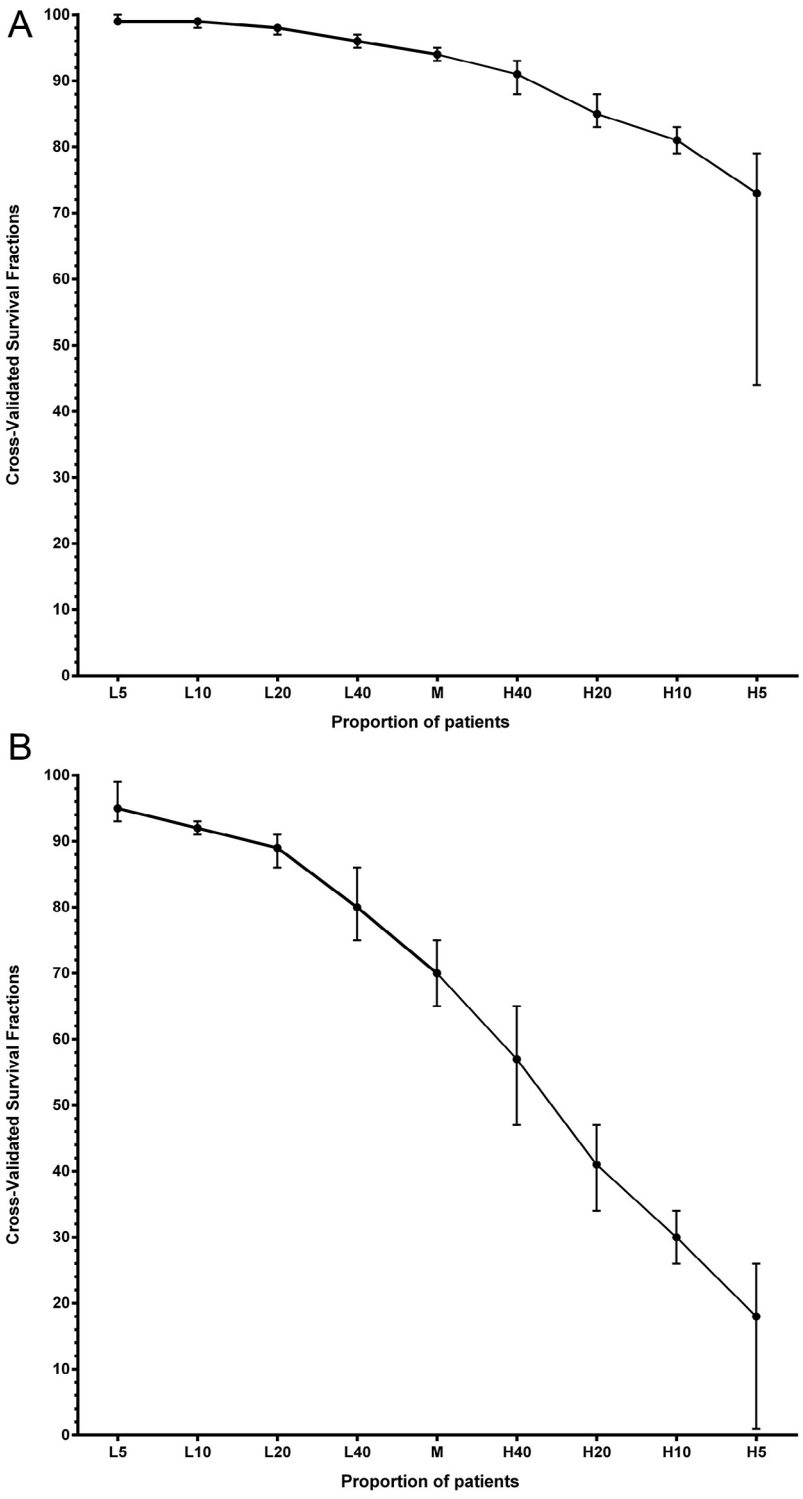


Figure 3. *(A)* Cross-validated survival fractions at 1 year in 9 CRT-SCORE segments ranging from the highest 5% (H5) to the lowest 5% (L5). *(B)* Cross-validated survival fractions at 5 years in 9 CRT-SCORE risk groups ranging from the highest 5% (H5) to the lowest 5% (L5).

highest 5% (H5) risk group demonstrated a remarkable decrease in the survival rate at 1 year (36% to 78% survival rates), suggesting that a more weighted and tailored decision should be taken in these patients when referring for CRT because, in most of these patients, life expectancy is under the time range currently suggested (1 year). On the other hand, identification of low-risk patients might be relevant to determine follow-up checkups and for a potential early discharge from the outpatient clinic of tertiary hospitals. Compared with previously proposed scores, the present

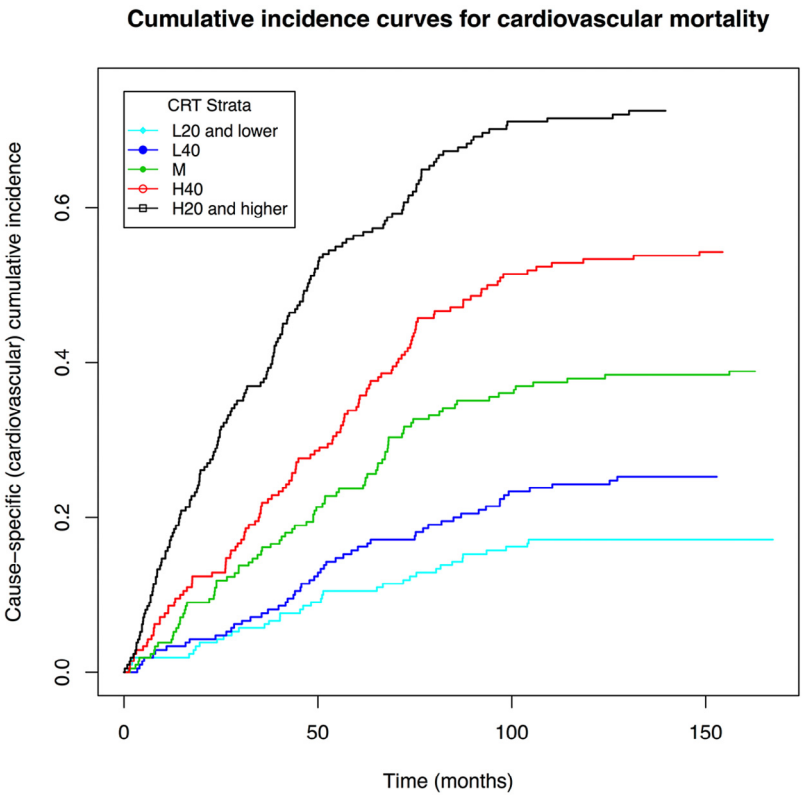


Figure 4. Cumulative incidence curves for cardiovascular mortality in CRT-SCORE quantiles.

study also used an appropriate approach for missing data. Although no estimation method is fail-safe, the multiple imputation method is considered the optimal approach regarding missing values. Several limitations should also be mentioned. Several parameters were not included in the model: (1) medical therapy considering the already optimized pharmacologic treatment in all patients; (2) biochemical data (e.g., N-terminal probrain natriuretic peptide) were not systemically available; (3) echocardiographic measurements of LV mechanical dyssynchrony due to vendor dependency and variability[27]; and (4) CRT response, considered a postimplantation assessment. Furthermore, CRT devices without defibrillator backup were not evaluated separately, considering the small number (61 patients, 5.8%) and because the CRT-SCORE was based on the overall mortality (the specific cause of death would not affect the score). Finally, both external validation and comparison with previous risk stratifications scores could not be performed. We have performed an internal validation and encourage future studies to perform further validation of our findings and comparison of the CRT-SCORE with previous scores in larger cohorts.

In conclusion, the CRT-SCORE allows prediction of the survival rate in CRT using readily available and CRT-specific clinical, electrocardiographic, and echocardiographic characteristics. The model provides estimates of 1- and 5-year mortalities that may assist clinicians in counseling patients and families and guide clinical shared decision making. Furthermore, by estimation of the prognosis, the CRT-SCORE may facilitate an optimized and tailored outpatient follow-up.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

The CRT-SCORE can be calculated in individual patients using the free of charge CRT-SCORE applications available at Apple AppStore and Google Play Store or online at *http://www.crt-score.com*.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2017.08.019.

1. Hoke U, Thijssen J, van Bommel RJ, van Erven L, van der Velde ET, Holman ER, Schalij MJ, Bax JJ, Delgado V, Marsan NA. Influence of diabetes on left ventricular systolic and diastolic function and on long-term outcome after cardiac resynchronization therapy. *Diabetes Care* 2013;36:985–991.
2. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Guidelines ESCCfP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the Euro-

pean Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;34:2281–2329.
3. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *CMAJ* 1985;132:919–923.
4. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol* 1993;71:1106–1107.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
6. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H, American Heart Association E, Arrhythmias Committee CoCC, American College of Cardiology F, Heart Rhythm S. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 2009;119:e235–e240.
7. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463.
8. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL. Scientific Document Committee of the European Association of Cardiovascular I. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J cardiovascular Imaging* 2013;14:611–644.
9. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165–193.
10. Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. *Circulation* 1982;65:457–464.
11. Buuren SV, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011;45.
12. Verweij PJ, Van Houwelingen HC. Cross-validation in survival analysis. *Stat Med* 1993;12:2305–2314.
13. van Bommel RJ, Borleffs CJ, Ypenburg C, Marsan NA, Delgado V, Bertini M, van der Wall EE, Schalij MJ, Bax JJ. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome. *Eur Heart J* 2010;31:2783–2790.
14. Lin G, Gersh BJ, Greene EL, Redfield MM, Hayes DL, Brady PA. Renal function and mortality following cardiac resynchronization therapy. *Eur Heart J* 2011;32:184–190.
15. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013;32:5381–5397.
16. Carpenter JR, Kenward MG. Multiple Imputation and Its Application. New York, NY: Wiley; 2013.
17. Van Bommel RJ, Mollema SA, Borleffs CJ, Bertini M, Ypenburg C, Marsan NA, Delgado V, Van Der Wall EE, Schalij MJ, Bax JJ. Impaired renal function is associated with echocardiographic nonresponse and poor prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2011;57:549–555.
18. Garg N, Thomas G, Jackson G, Rickard J, Nally JV Jr, Tang WH, Navaneethan SD. Cardiac resynchronization therapy in CKD: a systematic review. *Clin J Am Soc Nephrol* 2013;8:1293–1303.
19. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol* 2008;52:818–827.
20. Shanks M, Antoni ML, Hoke U, Bertini M, Ng AC, Auger D, Marsan NA, van Erven L, Holman ER, Schalij MJ, Bax JJ, Delgado V. The effect of cardiac resynchronization therapy on left ventricular diastolic function assessed with speckle-tracking echocardiography. *Eur J Heart Fail* 2011;13:1133–1139.
21. Gasparini M, Klersy C, Leclercq C, Lunati M, Landolina M, Auricchio A, Santini M, Boriani G, Proclemer A, Leyva F. Validation of a simple risk stratification tool for patients implanted with cardiac resynchronization therapy: the VALID-CRT risk score. *Eur J Heart Fail* 2015;17:717–724.
22. Regoli F, Scopigni F, Leyva F, Landolina M, Ghio S, Tritto M, Calo L, Klersy C, Auricchio A, Collaborative Study Group. Validation of Seattle Heart Failure Model for mortality risk prediction in patients treated with cardiac resynchronization therapy. *Eur J Heart Fail* 2013;15:211–220.
23. Smith T, Levy WC, Schaer BA, Balk AH, Sticherling C, Jordaens L, Theuns DA. Performance of the Seattle Heart Failure Model in implantable defibrillator patients treated with cardiac resynchronization therapy. *Am J Cardiol* 2012;110:398–402.
24. Khatib M, Tolosana JM, Trucco E, Borras R, Castel A, Berruezo A, Doltra A, Sitges M, Arbelo E, Matas M, Brugada J, Mont L. EAARN score, a predictive score for mortality in patients receiving cardiac resynchronization therapy based on pre-implantation risk factors. *Eur J Heart Fail* 2014;16:802–809.
25. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006;59:1087–1091.
26. Little RJA, Rubin DB. Statistical Analysis with Missing Data. Hoboken, NJ: John Wiley and Sons; 2002.
27. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608–2616.