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Predicting Early Mortality Among Implantable Defibrillator Patients Treated With Cardiac Resynchronization Therapy

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ABSTRACT

Background: The beneficial effects of a cardiac resynchronization defibrillator (CRT-D) in patients with heart failure, low left ventricular ejection fraction (LVEF), and wide QRS have clearly been established. Nevertheless, mortality remains high in some patients. The aim of this study was to develop and validate a risk score to identify patients at high risk for early mortality who are implanted with a CRT-D.

Methods and Results: For predictive modelling, 1282 consecutive patients from 5 centers (74% male; median age 66 years; median LVEF 25%; New York Heart Association class III−IV 60%; median QRS-width 160 ms) were randomly divided into a derivation and validation cohort. The primary endpoint is mortality at 3 years. Model development was performed using multivariate logistic regression by checking log likelihood, Akaike information criterion, and Bayesian information criterion. Model performance was validated using C statistics and calibration plots. The risk score included 7 independent mortality predictors, including myocardial infarction, LVEF, QRS duration, chronic obstructive pulmonary disease, chronic kidney disease, hyponatremia, and anemia. Calibration-in-the-large was suboptimal, reflected by a lower observed mortality (44%) than predicted (50%). The validated C statistic was 0.71 indicating modest performance.

Conclusion: A risk score based on routine, readily available clinical variables can assist in identifying patients at high risk for early mortality within 3 years after CRT-D implantation. (*J Cardiac Fail 2019;00:1−7*)

Key Words: Heart failure, mortality, risk modeling, cardiac resynchronization therapy, implantable cardioverter-defibrillator.

Heart failure (HF) is a progressive disease associated with high morbidity and mortality. The prevalence of HF is increasing and the associated costs are rising.[1,2] Data from randomized and observational studies have shown the beneficial effect of cardiac resynchronization therapy (CRT) in selected patients with drug refractory HF, reduced left ventricular ejection fraction (LVEF), and electrical dyssynchrony: it improves clinical symptoms, reduces hospitalizations, and lowers mortality in a considerable proportion of patients.[3−6] In addition, HF patients with low LVEF are at increased risk for arrhythmic death. Prophylactic implantable cardioverter-defibrillator (ICD) implantation is indicated for patients with ischemic or non-ischemic cardiomyopathy and LVEF ≤35%.[7−9] Theoretically, all patients with HF and left ventricular dysfunction who meet the indication criteria for CRT also qualify to have an ICD for primary prevention of sudden cardiac death. Consequently, ICDs combined with CRT (CRT-D) are part of the standard management of HF patients with reduced LVEF.[10,11] However, given the heterogeneity in mortality risk among HF patients and the fact that only a minority of patients will experience ventricular arrhythmias, appropriate risk prediction is of paramount importance in maximizing the survival benefit conferred by the CRT-D.[12] Several models have been developed to predict mortality risk in HF patients such as the Seattle Heart Failure Model (SHFM) and the Heart Failure Survival Score.[13,14] Despite the fact that the SHFM takes the eventual use of device therapy, such as an ICD or CRT, into account, the model was not designed for HF patients who already had a device implanted. Recently, a clinical risk score was developed to predict CRT response, which also appeared to have reasonable discriminative power to predict survival.[15] However, risk estimation models to predict early mortality in HF patients following CRT-D implantation are scarce. Therefore, the purpose of

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See page XXX for disclosure information.

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this study was to develop a risk estimation model to predict early mortality in primary prevention CRT-D patients.

Methods

Study Population

We used data from prospective ICD registries of the cardiology departments of Erasmus MC (Rotterdam, the Netherlands), the University Hospital of Basel (Basel, Switzerland), Ziekenhuis Oost-Limburg (Genk, Belgium), Noordwest Ziekenhuisgroep (Alkmaar, the Netherlands), and Medisch Spect Twente (Enschede, the Netherlands). From these registries, all patients (n = 1282) who received a first implantation of a CRT-D device for the primary prevention of sudden cardiac death between January 1, 2000 and October 31, 2013 were identified.

This retrospective study was not subjected to the Dutch Medical Research Involving Human Subjects Act and the need for written informed consent was waived. The study was carried out according to the ethical principles for medical research involving human subjects established by the Declaration of Helsinki. The privacy of all patients and the confidentiality of their personal information were protected.

Data Collection, Variable Definitions, and Clinical Endpoint

Potential candidate variables associated with mortality in HF were identified based on review of the literature, clinical relevance, and their routine availability. They included demographic characteristics, clinical presentation, laboratory data, and preexisting comorbid conditions.

Demographics, clinical data, and medical therapy prior to CRT-D implantation were obtained for all patients by searching the health records of the hospital. If multiple laboratory data were available, values from the date closest to the date of implantation were used; all laboratory values obtained up to 7 days prior to CRT-D implantation were accepted.

Diabetes mellitus was defined as HbA_{1c} >6.5% or the use of oral hypoglycemic agents or use of parenteral insulin; anemia as a serum hemoglobin concentration of <12 g/dL (female) or <13 g/dL (male). The glomerular filtration rate (GFR) was estimated with the formula of Modified Diet in Renal Disease.[16] Renal function was stratified according to the KDIGO/KDOQ stages for chronic kidney disease (CKD): stage 1, ie, ≥90 mL/min/1.73 m^2; stage 2, ie, 60−89 mL/min/1.73 m^2; stage 3, ie, <60 mL/min/1.73 m^2 and stage 4, ie, <30 mL/min/1.73 m^2.[17] Presence of CKD was defined as GFR <60 mL/min/1.73 m^2. Hyponatremia was defined as serum sodium level <136 mmol/L.

The clinical endpoint for this study was all-cause mortality; patients who underwent cardiac transplantation were censored at the day of transplantation.

Statistical Analysis

For the purpose of this study, one-half of the patients were randomly selected by use of random integer assignment to form the derivation cohort, and the remainder formed the validation cohort. Summary baseline data are presented as median with 25th and 75th percentiles, and categorical data are presented as percentages and counts. Data were compared by the Kruskal−Wallis H test and chi-square test as appropriate. Although most patients had a relatively complete dataset, variables with >5% of missing data were excluded from analysis (body mass index, diastolic and systolic blood pressure, and baseline heart rate). The method of multiple imputation was used to include variables with <5% of missing data in model selection and regression analysis.

Candidate variables in the derivation cohort that were associated with mortality on univariate analysis ($P \leq .1$) were included as covariates in a series of multivariate binary logistic regression models for further analysis. The goodness of fit was evaluated by calculating the likelihood ratio (LR), Akaike information criterion (AIC), and Bayesian information criterion (BIC). A higher LR and lower AIC and BIC suggest better goodness of fit.

Discrimination of the final prediction model was assessed by the use of the Harrell C statistic. Model discrimination was deemed poor if the C statistic was between 0.50 and 0.70, modest between 0.70 and 0.80, and good if >0.80. To assess the prognostic value of the risk score, the population was stratified into quintiles of the continuous risk score. Model calibration was visualized by plotting the predicted risks against the observed risks in a calibration plot, and further described by the calibration slope (ideally equal to 1) and intercept (ideally equal to 0).[18] As a measure of accuracy, the Brier score was calculated, which is the averaged squared difference between predicted and observed values. The Brier score ranges from 0 to 1; lower scores being better, a 0 indicates a perfect model. Usually, a model is considered useful if the Brier score is <0.25.

Cumulative mortality rates were calculated according to the Kaplan−Meier method and differences between groups compared with the log rank test. Statistical analysis was performed using STATA v11 SE for Windows (StataCorp, College Station, TX) and R statistical software, v3.5.3. Statistical significance was defined as $P < .05$ (two-tailed).

Results

Description of the Derivation and Validation Cohorts

The study included 1282 patients with a median follow-up of 3.4 years (1.8−5.4 years). After random assignment, the derivation cohort consisted of 639 patients and the validation cohort of 643 patients (N = 1282 patients). The median follow-up was not different between the derivation and validation cohort ($P = .99$). Demographics and clinical characteristics of both cohorts are presented in Table 1. The derivation and validation cohort were similar with respect to age, gender, etiology of heart failure, comorbid conditions, laboratory values, and medical treatment. The majority of CRT-D recipients were men (76%) with a median age of 66 years. Ischemic etiology of heart failure was present in 50% of the patients.

Table 1. Clinical Characteristics of the Derivation and Validation Cohorts

	Derivation Cohort (n = 639)	Validation Cohort (n = 643)	*P* Value
Demographics			
Age, y	67 (58−73)	66 (59−72)	.95
Male gender	483 (76%)	469 (73%)	.31
Clinical characteristics			
NYHA class III−IV	372 (58%)	374 (58%)	.91
Ejection fraction, %	24 (20−30)	25 (20−30)	.40
Ischemic etiology	313 (49%)	326 (51%)	.64
QRS duration, ms	160 (140−180)	160 (140−177)	.07
Comorbid condition			
Atrial fibrillation	128 (20%)	139 (22%)	.54
Diabetes mellitus	163 (26%)	169 (26%)	.75
Cerebrovascular disease	54 (8%)	72 (11%)	.11
Chronic obstructive pulmonary disease	93 (15%)	83 (13%)	.42
Renal failure	254 (40%)	254 (40%)	.91
Laboratory values			
Hemoglobin, g/dL	13.7 (12.4−14.7)	13.9 (12.7−14.9)	.05
Serum sodium, mmol/L	140 (137−142)	140 (137−142)	.79
Serum BUN, mg/dL	8.3 (6.4−11.7)	8.1 (6.1−10.9)	.16
Serum creatinine, mg/dL	1.1 (0.9−1.4)	1.1 (0.9−1.4)	.23
Medications			
ACE inhibitor	481 (75%)	476 (74%)	.65
Angiotensin receptor blocker	152 (24%)	160 (25%)	.65
Amiodarone	82 (13%)	81 (13%)	.93
Beta-blocker	521 (82%)	528 (82%)	.83
Digoxin	104 (16%)	127 (20%)	.11
Diuretic	513 (80%)	513 (80%)	.82
Aldosterone antagonist	309 (48%)	284 (44%)	.15
Allopurinol	48 (8%)	55 (9%)	.54
Statin	350 (55%)	390 (61%)	.04

Continuous data are presented as median (interquartile range). Categorical data are presented as n(%).
ACE, angiotensin converting enzyme; BUN, blood urea nitrogen; NYHA, New York Heart Association.

The mortality rate in the overall cohort was 5.7% and 16.5%, at 1 and 3 years, respectively. In the derivation cohort (n = 639), 1- and 3-year mortality was 5.0% and 15.9%. In the validation cohort (n = 643), 1- and 3-year mortality was 6.4% and 17.0%. The mortality rates were not different between the derivation and the validation cohort ($P = .64$).

Predictors of Mortality

Univariate logistic regression analysis was performed to identify variables associated with mortality (Table 2). We found that age, the presence of myocardial infarction (MI), diabetes mellitus, LVEF, New York Heart Association (NYHA) III-IV, chronic obstructive pulmonary disease (COPD), CKD, hyponatremia, and anemia were all associated with a higher risk of mortality at 3 years follow-up. In addition, QRS ≥150 ms was associated with a lower risk of mortality. In Table 3, the β-coefficients for the variables and AIC, BIC, and C statistic for successive models are presented. Model 1 included age (per decade) as continuous variable and LVEF ≤25%, MI, COPD, CKD, hyponatremia, anemia, and QRS duration ≥150 ms as dichotomous variables. Model 1 performed fairly well in goodness of fit and discrimination. In Model 2, LVEF as dichotomous variable was replaced by LVEF as a continuous variable, which improved goodness of fit and discrimination. When using GFR as continuous variable, model performance did not improve. Comparing Models 2 and 5, the AIC and C statistic did not improve, whereas BIC was lower in Model 5.

Table 2. Univariate Logistic Regression Analysis

Variable	OR (95% CI)	*P* Value
Age (10 years)	1.26 (1.00−1.57)	.051
Male gender	1.30 (0.75−2.26)	.35
AF	1.11 (0.64−1.93)	.70
MI	2.12 (1.35−3.34)	.001
LVEF ≤25%	1.79 (1.08−2.94)	.023
LVEF (5% decrease)*	1.31 (1.10−1.55)	.002
NYHA 34	2.06 (1.24−3.40)	.005
QRS ≥150 ms	0.58 (0.37−0.93)	.022
DM	1.83 (1.14−2.95)	.013
COPD	1.93 (1.10−3.36)	.021
CVA	1.28 (0.60−2.72)	.52
Hyponatremia†	3.47 (1.99−6.05)	<.001
GFR (per 15 mL/min)‡	1.84 (1.40−2.41)	<.001
CKD‖	3.12 (1.95−4.98)	<.001
Anemia¶	2.17 (1.37−3.43)	.001

AF, atrial fibrillation; CVA, cerebrovascular accident incl. transient ischemic attack; DM, diabetes mellitus.
*LVEF per 5% decrease in patients with LVEF ≤35%.
†Hyponatremia defined as serum sodium <136 mmol/L.
‡GFR per 15 mL/min decrease in patients with GFR <60 mL/min/1.73 m^2.
‖CKD defined as GFR <60 mL/min/1.73 m^2.
¶Anemia defined as serum hemoglobin < 12 g/dL (female) or < 13 g/dL (male).

Risk scores were derived for each individual patient using the obtained the β-coefficients from final chosen Model 5.

Table 3. Model Construction to Predict Mortality

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age (per 10 years)	0.120	.356	0.138	.294	0.183	.160	—	—	—	—
LVEF ≤25%	0.746	.007	—	—	—	—	—	—	—	—
LVEF (per 5%)*	—	—	0.336	.001	0.334	.001	0.316	.001	0.323	.001
MI	0.595	.017	0.608	.015	0.603	.016	0.670	.007	0.656	.008
COPD	0.589	.053	0.605	.049	0.545	.076	0.595	.051	0.641	.035
CKD	0.903	.001	0.929	<.001	—	—	—	—	0.992	<.001
GFR (per 15 mL/min)†	—	—	—	—	0.437	.005	0.474	.002	—	—
Hyponatremia	1.018	.001	0.976	.002	1.005	.001	0.964	.002	0.941	.002
Anemia	0.456	.078	0.419	.104	0.460	.075	0.472	.067	0.427	.097
QRS ≥150 ms	−0.672	.008	−0.689	.007	−0.649	.011	−0.600	.018	−0.660	.010
Parameter										
Goodness of fit										
Log LR chi-square	64.04		68.63		63.58		61.53		67.50	
AIC	466		462		467		467		461	
BIC	506		502		507		502		496	
Discrimination										
C statistic	0.749		0.754		0.737		0.736		0.756	

*The β-coefficient represents the effect of LVEF associated with −5% change in patients with LVEF ≤35%. In patients with LVEF >35%, the score associated with LVEF is 0.

†The β-coefficient represents the effect of GFR associated with 15 mL/min change in patients with GFR <60 mL/min/1.73 m^2.

$$\textit{Risk score} = 0.656 \times (MI) + 0.323 \times (LVEF) + 0.641 \times (COPD) + 0.992 \times (CKD) + 0.941 \times (hyponatremia) + 0.427 \times (anemia) - 0.660 \times (QRS150),$$

where:

LVEF = per 5% decrease of LVEF in patients with LVEF ≤35%. In patients with LVEF >35%, the score associated with LVEF is 0;
CKD = estimated GFR <60 mL/min/1.73 m^2, 1 if present, otherwise 0;
Hyponatremia = serum level of sodium <136 mmol/L, 1 if present, otherwise 0;
Anemia = serum level of hemoglobin <12 g/dL, 1 if present, otherwise 0;
QRS150 = QRS duration ≥150 ms, 1 if present, otherwise 0;
MI, COPD = 1 if present, otherwise 0.

Subsequently, the derivation cohort was stratified by ascending quintiles of the derived risk score (Suppl Table). Mortality rates by quintiles of risk are presented in Fig. 1. Mortality ranged from 2.8% (lowest quintile of risk score) to 31.9% (highest quintile of risk score). Model discrimination as assessed by the C statistic was 0.76 (95% CI, 0.71−0.81).

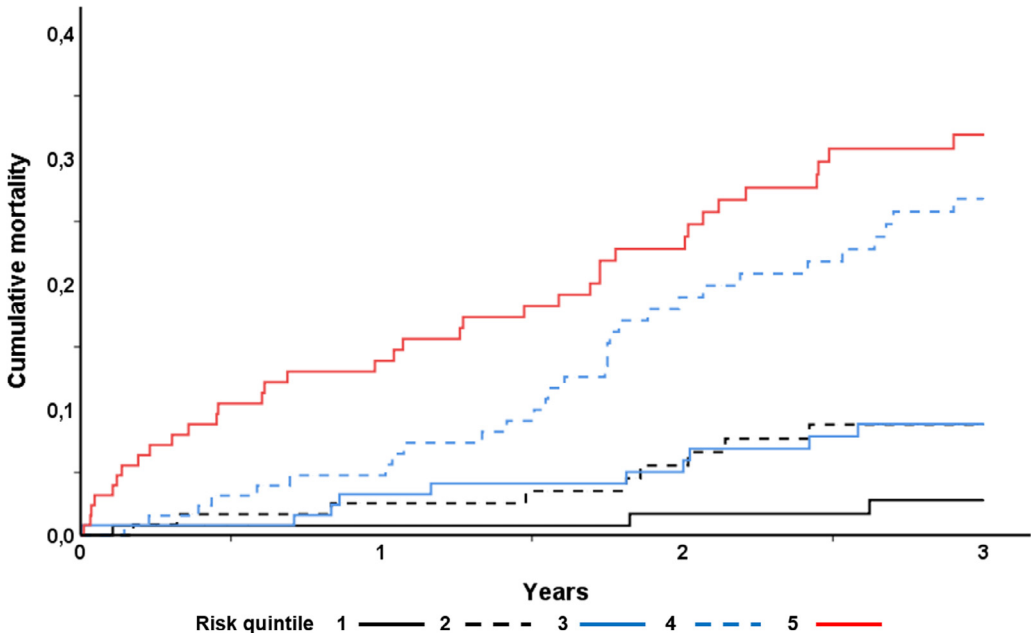

Fig. 1. Mortality rates in the derivation cohort stratified by quintiles of predicted risk.

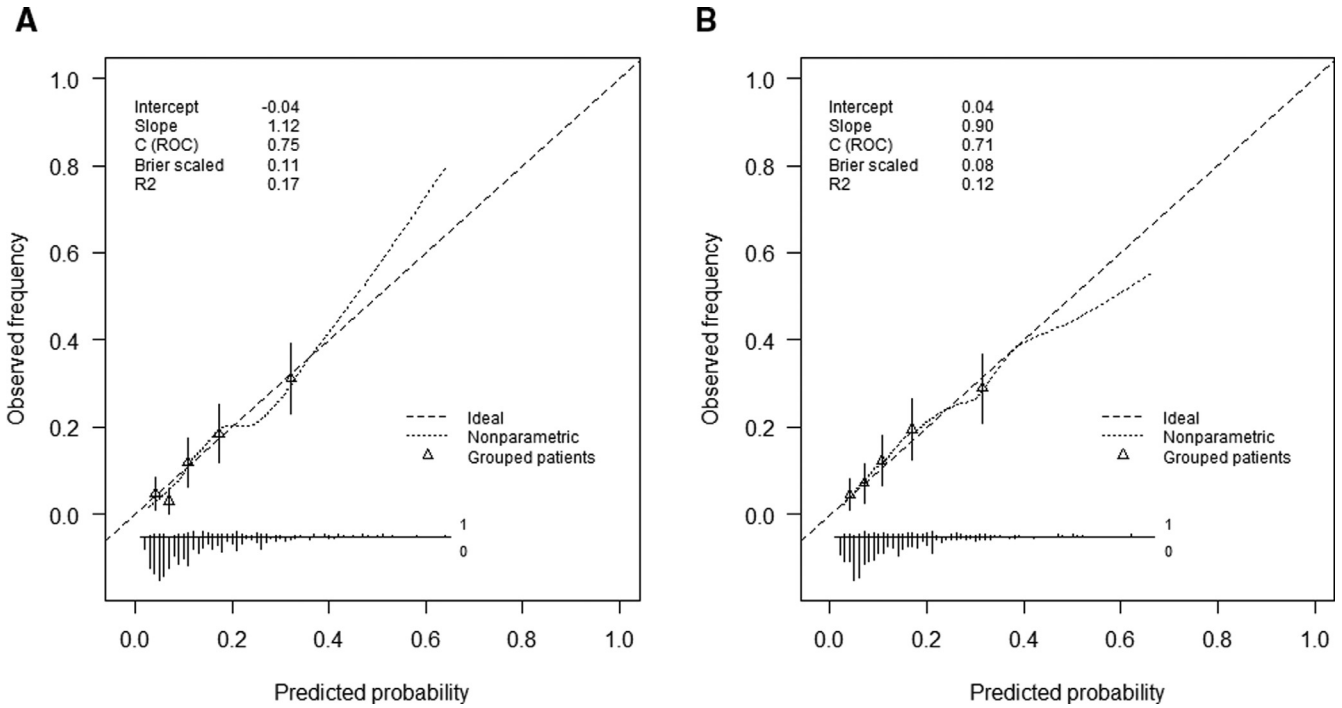

Fig. 2. Calibration plot for derivation cohort (**A**) and validation cohort (**B**). Triangles represent quintiles of subjects grouped by similar predicted risk. The distribution of subjects is indicated with spikes at the bottom of the graph, stratified by endpoint (death above the *x*-axis, survivors below the *x*-axis).

Model Validation

When the 3-year model was applied in the validation cohort (N = 643 patients), the C statistic was 0.71 (95% CI, 0.65−0.76). In Fig. 2, calibration plots of the model are presented. The calibration-in-the-large was suboptimal, the prediction model underestimated the risk in the derivation cohort (A), whereas in the validation cohort (B) risk was overestimated, which is reflected by a lower observed mortality (44%) than predicted (50%). In the validation cohort, the calibration slope was 0.90, which is acceptable indicating that the predicted risks were not too extreme or too close to the baseline risk. Based on the Brier score values, the model can be considered as accurate as they fall below the 0.25 threshold.

Discussion

The present international, multicenter, retrospective cohort study of 1282 HF patients demonstrates the feasibility of using a risk score to predict early mortality in a real-world population of CRT-D recipients. The risk score incorporates MI, LVEF, QRS duration, COPD, CKD, hyponatremia, and anemia. These variables are readily available and individually associated with a poor outcome.

In HF patients with reduced LVEF, NYHA class ≥II, and prolonged QRS duration, CRT improves clinical symptoms, reduces hospitalizations, and lowers mortality in a considerable proportion of patients.[5,19] Patients eligible for CRT also qualify for defibrillator therapy as primary prevention of sudden cardiac death. Consequently, implantation of a CRT-D is part of the standard management of HF patients with reduced LVEF and wide QRS. However, the benefit of defibrillator therapy is not uniform and it remains to be determined which patients benefit and whether patients do not benefit from defibrillator therapy.

Better identification of patients who get the highest benefit of the additional defibrillator therapy is desirable to reduce unnecessary implantations and possible complications. Several previous studies have developed risk scores to estimate mortality in ICD recipients.[20−24] A systematic review and meta-analysis determined older age, poor baseline renal function, history of COPD, diabetes mellitus, peripheral vascular disease, decreased LVEF, and ICD shocks during follow-up as strong predictors of mortality in ICD patients.[25] This meta-analysis provided the basis of a novel prediction model, the HF Meta-score.[26] The HF Meta-score has been validated in the Ontario ICD database, which included a mixed population of patients with primary and secondary prevention indication treated with ICDs or CRT-Ds and showed modest discrimination (C statistic 0.74). Some of the predictors in the HF Meta-score were also identified in our study, eg, ischemic heart disease, poor baseline renal function, COPD, and decreased LVEF. In the current study, we did not compare the performance of our risk estimation model with the HF Meta-score.

In a sub-analysis of the MADIT-II Trial, a risk score consisting of 5 clinical risk factors (NYHA class >II, atrial fibrillation, QRS duration >120 ms, age >70 years, and urea >26 mg/dL) was developed to differentiate between patients who would benefit from the ICD versus those who would not.[21] The MADIT-II risk score has recently been

evaluated in cohorts of CRT patients showing poor to modest discrimination (C statistic of 0.61 and 0.72).[27,28] Of the 5 risk factors in the MADIT-II score, only poor baseline renal function was a factor in our risk score. Risk factors as QRS width >120 ms and NYHA >II mostly indicate CRT use.

The results of the present study are in line with those of several previous studies, indicating that renal dysfunction poses a strong and independent risk factor for overall mortality despite CRT-D implantation and optimized medical treatment of congestive heart failure. Besides renal dysfunction, we identified other clinical risk factors such as hyponatremia and anemia. Hyponatremia is a strong determinant of long-term mortality in HF patients, irrespective of LVEF.[29] Sharma et al[30] investigated the prognostic implication of hyponatremia in HF patients receiving CRT. Low baseline serum levels of sodium were associated with poor prognosis. The results of our study confirm the association between low serum levels of sodium and a higher mortality risk even in a multivariate analysis.

The impact of baseline anemia on all-cause mortality in HF patients with reduced LVEF has been evaluated in the HF-ACTION trial.[31] Over a median follow-up of 30 months, anemia was associated with increased rates of death, hospitalizations, and HF exacerbation. Venkateswaran et al[32] examined the prognostic implication of anemia in CRT patients. Baseline anemia and early post-implantation decline of hemoglobin were associated with a worse 2-year prognosis. In our study, baseline anemia was independently associated with higher mortality.

Taken together, our results confirm that medically complex HF patients, those with low LVEF, anemia, hyponatremia, and comorbidities as COPD and CKD, have an increased risk of mortality. This finding may be explained by an increase in HF and non-arrhythmic mortality as the presence of these clinical variables suggests a more advanced HF status. The decision whether to add ICD therapy must be considered carefully in a shared decision-making process with the patient taking into account risk−benefit tradeoffs and life expectancy. In this context, Levy et al[12] provided compelling evidence of the heterogeneity of risk among primary prevention ICD patients by applying the SHFM to the SCD-HeFT study cohort. The highest risk group had an increased mortality with no benefit of ICD therapy despite the greatest incidence of appropriate ICD shocks.

Limitations

The current study has several limitations and these should be viewed in its methodological context. First, the risk score was not used to decide on implantation of a CRT-D. The aim of study of the study was to calculate and validate a risk score. Second, baseline heart rate, which is a known predictor of mortality, had an excess of missing data and was excluded from analysis. Unfortunately, the impact of baseline heart rate in risk prediction within this model remains unknown. Third, the study cohort included patients over a 13-year period, during which guidelines for the implantation of defibrillators and treatment of HF changed. In the same period, the programming of devices with respect to detection and treatment of ventricular arrhythmias changed.

Conclusion

A risk score based on routine, readily available clinical variables can assist in identifying patients at high risk for early mortality within 3 years after CRT-D implantation.

Disclosures

Dr Theuns has received research grants from Biotronik and Boston Scientific and consulting fees from Boston Scientific. Dr Schaer is listed on the speaker's bureau for Medtronic and Microport CRM. Dr Sticherling has received speaker fees from Boston Scientific, Biotronik and Microport CRM and consulting fees from Biotronik, Boston Scientific, and Medtronic. The other authors have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.08.018.

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