kcj

Korean Circulation Journal

Prognostic Estimation of Advanced Heart Failure With Low Left Ventricular Ejection Fraction and Wide QRS Interval

Changmyung Oh, MD[1], Hyuk-Jae Chang, MD[1], Ji Min Sung, PhD[2], Ji Ye Kim, MD[1], Wooin Yang, MD[1], Jiyoung Shim, MD[1], Seok-Min Kang, MD[1], Jongwon Ha, MD[1], Se-Joong Rim, MD[1], and Namsik Chung, MD[1]

[1]Departments of Internal Medicine and [2]Research Affairs, Yonsei University College of Medicine, Seoul, Korea

Background and Objectives: Cardiac resynchronization therapy (CRT) has been known to improve the outcome of advanced heart failure (HF) but is still underutilized in clinical practice. We investigated the prognosis of patients with advanced HF who were suitable for CRT but were treated with conventional strategies. We also developed a risk model to predict mortality to improve the facilitation of CRT.
Subjects and Methods: Patients with symptomatic HF with left ventricular ejection fraction ≤35% and QRS interval >120 ms were consecutively enrolled at cardiovascular hospital. After excluding those patients who had received device therapy, 239 patients (160 males, mean 67±11 years) were eventually recruited.
Results: During a follow-up of 308±236 days, 56 (23%) patients died. Prior stroke, heart rate >90 bpm, serum Na ≤135 mEq/L, and serum creatinine ≥1.5 mg/dL were identified as independent factors using Cox proportional hazards regression. Based on the risk model, points were assigned to each of the risk factors proportional to the regression coefficient, and patients were stratified into three risk groups: low- (0), intermediate- (1-5), and high-risk (>5 points). The 2-year mortality rates of each risk group were 5, 31, and 64 percent, respectively. The C statistic of the risk model was 0.78, and the model was validated in a cohort from a different institution where the C statistic was 0.80.
Conclusion: The mortality of patients with advanced HF who were managed conventionally was effectively stratified using a risk model. It may be useful for clinicians to be more proactive about adopting CRT to improve patient prognosis. **(Korean Circ J 2012;42:659–667)**

KEY WORDS: Heart failure; Prognosis; Cardiac resynchronization therapy.

Introduction

Despite advances in pharmacotherapeutic strategies, congestive heart failure (HF) is a chronic disease and a major public health concern because of its high morbidity and mortality.[1] In advanced HF with severe systolic dysfunction {left ventricular ejection fraction (LVEF) ≤35%} with wide QRS interval (>120 ms), device therapies such as cardiac resynchronization therapy (CRT) have been shown to improve prognosis.[2-4]

Evidence from several studies revealed that CRT significantly reduces mortality and all-cause hospitalizations in patients with advanced HF.[5)6] The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure study demonstrated that use of CRT was associated with a significant 20% decrease in mortality of advanced HF at 6 month follow-up.[5-8] The Cardiac Resynchronization-Heart Failure trial showed a significant 36% decrease in the combined end point of all-cause mortality and HF hospitalizations with CRT.[5)6]

Recent studies revealed that CRT is still underutilized in clinical practice with significant variations despite being recommended.[9] To facilitate the consideration of CRT, we investigated prognostic factors in patients with advanced HF who were suitable candidates for CRT but were treated by conventional strategy. In addition, we developed a risk model to identify the patients who had poor prognosis. The validity of this model was tested in a separate group of

patients.

Subjects and Methods

Study population

Between January 2007 and February 2009, 1345 patients with HF visited the tertiary referral hospital (Severance Cardiovascular Hospital, South Korea). Of these, 239 patients (18%) who had advanced HF {New York Heart Association (NYHA) functional class II-IV and LVEF ≤35%} with a wide QRS interval (>120 ms) were consecutively enrolled. Patients 1) who received device therapy or heart transplantation and 2) who had a malignancy were excluded from this study (Fig. 1). For the validation of a risk model, 66 patients were enrolled from a different affiliated institution (Kangnam Severance Hospital, South Korea) with the same inclusion and exclusion criteria (validation cohort) during the same period.

Echocardiography and electrocardiogram measurements

Echocardiography was performed on all patients at the index visit. A standard echocardiography was performed and the left ventricular end diastolic diameter (LVEDD), left arterial volume index, and early mitral inflow velocity to early diastolic mitral annular velocity (E/E') were measured. LVEF was measured by the Simpson method. All electrocardiograms were recorded at a 25 mm/s sweep speed, and QRS duration was measured by 2 experienced cardiologists from lead V2.

Clinical and biochemical data

Demographic variables, co-morbidities, and medications were collected at the index visit. Biochemical data included the following variables: serum hemoglobin (Hb), hematocrit (Hct), creatinine (SCr), sodium (Na), and total cholesterol. The rhythm and QRS interval on ECG were also obtained and analyzed.

Outcomes

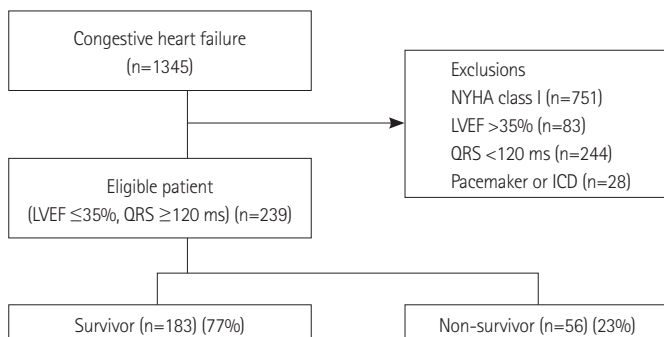In order to identify and evaluate risk factors associated with prog-

Fig. 1. Diagram of study workflow. CHF: congestive heart failure, LVEF: left ventricular ejection fraction, ICD: implantable cardioverter-defibrillator.

nosis in advanced HF, we retrospectively reviewed the clinical course. The primary end point of the study was all-cause death during the follow-up period. We also investigated a composite endpoint of all-cause death and unplanned hospitalization due to major adverse cardiovascular event (MACE; worsening HF, acute coronary syndrome, and fatal arrhythmia).

Statistical analysis

Continuous variables were expressed as the mean and standard deviations. Baseline characteristics were compared by chi-square analysis for dichotomous variables and Student's t-test for continuous variables. Cox proportional hazard regression analysis was performed to evaluate the relationship between risk factors and outcomes. To develop a prognostic model, we assigned the risk factors identified by multivariate analysis weighted points based on β regression coefficient values. Survival curves were constructed according to the Kaplan-Meier method and comparisons of the survival rate between risk groups were compared using the log-rank test. The discriminative ability of our prediction model was evaluated by receiver-operating curve analysis (C statistic). P were all 2-sided and considered to be statistically significant at p<0.05. SAS (version 9.1.3, SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis.

Results

Patient characteristics

The clinical characteristics and the use of various cardiac medications at the time of enrollment are presented in Table 1. Our subject group consisted of 239 patients (160 males) with a mean age of 67±11 years. The mean duration of the follow-up was 308±236 days. From this group, 56 (23%) patients died. The etiology of HF included 131 (55%) ischemic cases and 108 (45%) non-ischemic cases. There were 131 (55%) hypertensive and 94 (39%) diabetic patients, and 141 (59%) were chronic kidney disease (CKD) patients. 77 (32%) patients suffered from atrial fibrillation.

The mean LVEF was 25±7% and the mean QRS interval was 145±20 ms. All patients were being treated with diuretics (68%), aldosterone receptor blockers (39%), angiotensin converting enzyme inhibitors (10%), angiotensin II receptor blockers (32%), and digoxin (27%). Beta-blockers were taken by only 12 (5%) patients.

All-cause death

By the end of the study, all-cause death (primary end point) occurred in 56 (23%) patients. Table 2 presents the univariate analysis that identified risk factors affecting all-cause death. The following demographic, clinical, biochemical, and echocardiography vari-

Table 1. Baseline demographic and clinical characteristics in the derivation cohort

Variables	Non-survivor (n=56)	Survivor (n=183)	p
Age (years)	70±13	66±11	0.046
Male, n (%)	35 (63)	125 (68)	0.419
Etiology of heart failure, n (%)			
Ischemic	32 (57)	99 (54)	0.689
Non-ischemic	24 (43)	84 (46)	
NYHA class, n (%)			<0.001
II	6 (11)	69 (38)	
III	16 (29)	72 (39)	
IV	34 (61)	42 (23)	
Co-morbidity, n (%)			
Hypertension	37 (66)	94 (51)	0.053
Diabetes mellitus	25 (45)	69 (38)	0.352
Chronic kidney disease	40 (71)	101 (55)	0.031
Dyslipidemia	86 (47)	23 (41)	0.436
Body mass index ≥25 (kg/m²)	9 (16)	55 (30)	0.049
Prior stroke	8 (14)	10 (5.5)	0.092
Smoking	13 (23)	57 (31)	0.069
Thyroid disease	6 (11)	14 (7.7)	0.749
Clinical and Laboratory findings at enrollment			
Systolic BP (mm Hg)	115±22	113±14	0.773
Diastolic BP (mm Hg)	96±12	105±10	0.003
Heart rate (bpm)	90±20	78±15	<0.001
Hb (g/dL)	11±2	13±2	<0.001
Creatinine (mg/dL)	2.7±2.4	1.6±1.7	0.003
Total cholesterol (mg/dL)	125±49	155±45	<0.001
NT-proBNP (pg/mL)	23282±51786	9281±10885	0.01
Echocardiographic findings			
LVEF (%)	22±7	26±7	<0.001
LVEDD (mm)	61±12	64±9	0.015
LA volume index (mm³/m²)	50±30	50±31	0.998
E/E'	22±10	24±12	0.509
EKG findings			
Atrial fibrillation, n (%)	20 (36)	57 (31)	0.626
QRS duration (ms)	142±20	146±21	0.147
Medications, n (%)			
Aldosterone antagonists	23 (41)	70 (38)	0.705
ACE inhibitors	22 (39)	70 (38)	0.472
Angiotensin receptor blockers	10 (18)	67 (37)	0.009
Beta blockers	16 (29)	107 (58)	<0.001
Digitalis	13 (23)	51 (28)	0.491
Diuretics	35 (63)	127 (69)	0.334

Data are expressed as n (%) or mean±standard deviation. NYHA: New York Heart Association, BP: blood pressure, Hb: hemoglobin, NT-proBNP: N-terminal pro-B-type natriuretic peptide, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LA: left atrium, EKG: electrocardiography, ACE: angiotensin converting enzyme

ables had significant correlations with all-cause death: NYHA class (III, IV vs. II) {hazard ratio (HR) 4.2; 95% confidence interval (CI): 1.81 to 9.87; p<0.001}, body mass index (≥25 kg/m²) (1.7; 95% CI: 1.01 to 3.04; p=0.05), the presence of hypertension (0.5; 95% CI: 0.23 to 0.98; p=0.04), CKD (2.1; 95% CI: 1.17 to 3.75; p=0.01), prior stroke (2.1; 95% CI: 1.00 to 4.47; p=0.05), LVEF (≤25%) (2.7; 95% CI: 1.55 to 4.68; p<0.001), LVEDD (≥55 mm) (0.4; 95% CI: 0.21 to 0.65; p<0.001), heart rate (>90 bpm) (6.3; 95% CI: 3.7 to 10.6; p<0.001), se-

rum Hb (2.7; 95% CI: 1.30 to 4.14; p<0.001), serum Na (≤135 mEq/L) (2.74; 95% CI: 1.62 to 4.63; p<0.001), and serum creatinine (≥1.5 mg/dL) (3.3; 95% CI: 1.96 to 5.69; p<0.001).

Next, we analyzed significant factors by stepwise multivariate analysis. Prior stroke (HR 2.7; 95% CI: 1.23 to 6.13; p=0.01), heart rate (>90 bpm) (4.6; 95% CI: 2.51 to 8.59; p<0.001), serum Na (≤135 mEq/L) (2.9; 95% CI: 1.61 to 5.37; p<0.001), and serum creatinine (≥1.5 mg/dL) (1.9; 95% CI: 1.02 to 3.64; p=0.04) were defined

Table 2. Univariate Cox regression for all-cause mortality

Variables	Regression coefficient	Hazard ratio	95% CI	p
Age	0.016	1.023	0.998-1.049	0.070
Male	0.082	0.790	0.460-1.357	0.393
IHD	-0.294	1.180	0.695-2.004	0.541
NYHA class III, IV	0.702	4.231	1.814-9.870	<0.001
BMI ≥25 (kg/m²)	-0.235	1.749	1.005-3.044	0.048
HTN	-0.204	0.474	0.230-0.977	0.043
DM	-0.001	1.331	0.785-2.257	0.289
CKD	0.131	2.093	1.169-3.748	0.013
Prior stroke	1.527	2.114	0.999-4.471	0.050
Thyroid disease	-0.001	0.739	0.316-1.727	0.485
Atrial fibrillation	0.065	1.164	0.674-2.012	0.586
QRS duration	-0.005	0.990	0.976-1.004	0.160
Smoking	-0.067	1.743	0.937-3.242	0.080
LVEF ≤25 (%)	0.999	2.693	1.548-4.683	<0.001
LVEDD ≥55 (mm)	-1.285	0.371	0.213-0.646	<0.001
Heart rate >90 (bpm)	1.311	6.269	3.691-10.647	<0.001
Hb ≤12 (g/dL)	0.605	2.316	1.296-4.139	0.005
Na ≤135 (mEq/L)	1.098	2.735	1.615-4.631	<0.001
Scr ≥1.5 (mg/dL)	0.514	3.339	1.959-5.689	<0.001
Aldosterone antagonists	0.064	1.066	0.626-1.816	0.814
ACE inhibitors	-0.287	0.751	0.271-2.076	0.580
Angiotensin receptor blockers	-0.957	0.384	0.194-0.762	0.006
Beta blockers	-1.225	0.294	0.041-2.124	0.225
Digitalis	-0.301	0.740	0.398-1.377	0.342
Diuretics	-0.286	0.751	0.437-1.291	0.301

CI: confidence interval, IHD: ischemic heart disease, NYHA: New York Heart Association, BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, CKD: chronic kidney disease, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, Hb: hemoglobin, Na: sodium, Scr: serum creatinine, ACE: angiotensin converting enzyme

Table 3. Multivariate Cox regression analysis for all-cause death and risk score

	Regression coefficient	Hazard ratio	95% CI	p	Points*
Prior stroke	1.01	2.746	1.231-6.126	0.014	3
Heart rate >90 (bpm)	1.54	4.646	2.512-8.591	<0.001	5
Na ≤135 (mEq/L)	1.08	2.941	1.612-5.365	<0.001	3
Scr ≥1.5 (mg/dL)	0.65	1.924	1.016-3.643	0.045	2

*Assignment of points was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 0.65 (the lowest β value), multiplied by a constant (2), and rounded to the nearest integer.[10] CI: confidence interval, Scr: serum creatinine

as significant predictors (Table 3).

All-cause death or unplanned hospitalization for a major cardiovascular event

The secondary end point (all-cause death or unplanned hospitalization due to MACE) occurred in 92 (38%) patients (Fig. 2). In multivariate analysis, NYHA class (III, IV vs. II) (2.0; 95% CI: 1.05 to 3.71; p=0.04), heart rate (>90 bpm) (2.16; 95% CI: 1.29 to 3.62; p=0.01), serum Na (<135 mEq/L) (2.53; 95% CI: 1.59 to 4.03; p<0.001), and serum creatinine (≥1.5 mg/dL) (2.1; 95% CI: 1.20 to 3.58; p=0.01) were identified as significant risk factors.

Prognostic modeling and risk stratification

We assigned scores to risk factors based on a linear transformation of the corresponding β regression coefficients, as previously
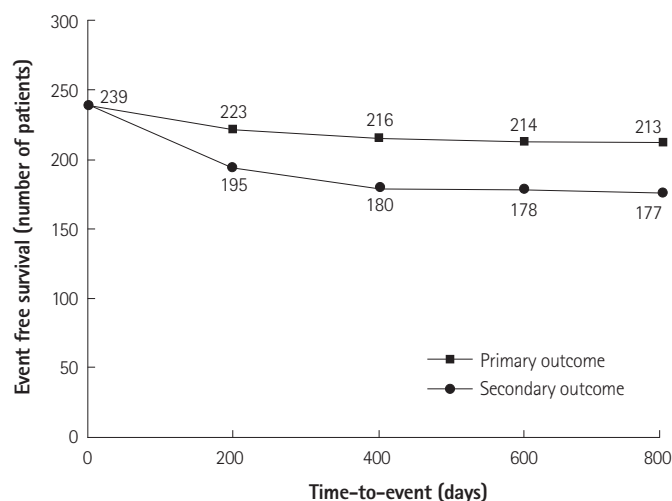
described in Anis Rassi's article.[10] The coefficient of each variable was divided by the lowest β value, then multiplied by a constant (2), and rounded to the nearest integer (Table 3).

The risk model calculated a score by adding together the points corresponding to patient's risk factors: {Risk score=3×prior stroke+5×heart rate (>90 bpm)+3×serum Na (≤135 mEq/L)+2×serum creatinine (≥1.5 mg/dL)}.

All patients were stratified into three groups based on risk score. The cut-points were obtained by maximizing the c-index: low- (0 point), intermediate- (1-5 points), and high-risk group (>5 points). There were 119 (50%) patients identified as low, 81 (34%) patients as intermediate and 39 patients identified (16%) as high-risk group.

The 2-year mortality rates of each group were 5% (6/119), 31% (25/81), and 64% (25/39), respectively. Compared with the low-risk group, the HR of the high-risk group was 20.9 (95% CI: 8.6 to 51.3; p<0.001) and intermediate-risk group was 6.7 (95% CI: 2.7 to 16.3; p<0.001). The C statistic for the risk model for prediction of mortality was 0.78 (Fig. 3A, Table 4).

Atrial fibrillation and mortality

Although CRT in advanced HF with atrial fibrillation was not a class I indication,[2] many studies have reported the benefits of CRT to advanced HF with atrial fibrillation.[11] In our study, 77 patients had atrial fibrillation and 20 (26%) patients had died. We re-classified patients based on the risk score. In these patients, the high-risk group with atrial fibrillation showed higher mortality risk than the low-risk group (HR 32.1; 95% CI: 4.1-251.4; p=0.001).

Validation of the prediction model

A total of 66 patients from a different hospital were selected as the validation cohort (Table 1 and 5). During a mean follow-up of 686± 367 days, 13 patients (20%) died. Classification of the validation co-
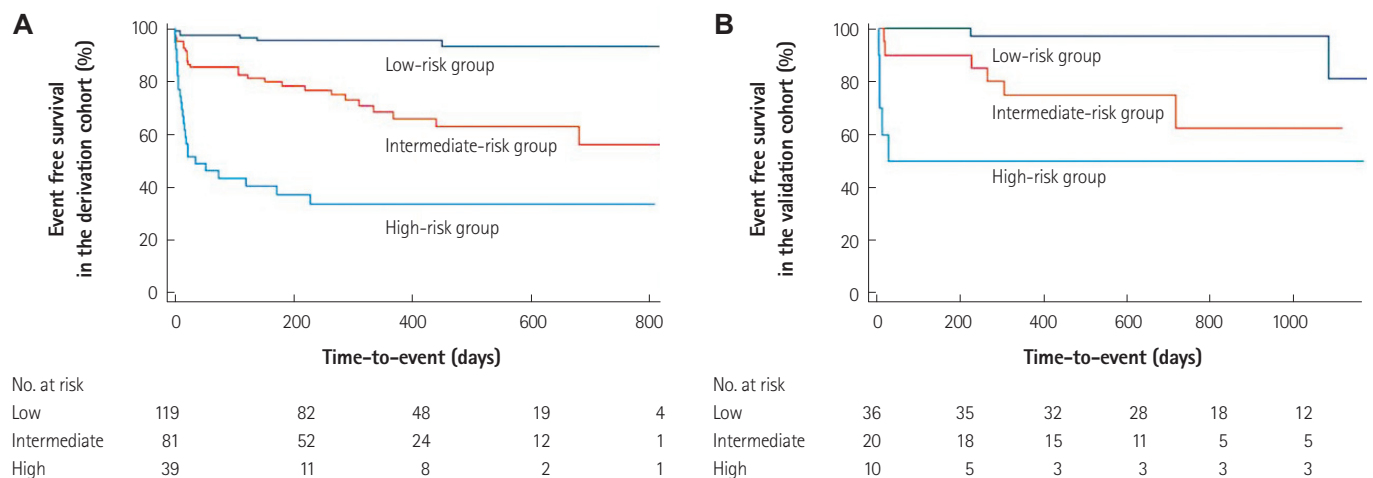

Fig. 2. Primary outcome: all-cause death. Secondary outcome: the composite of all-cause death or unplanned hospitalization due to major adverse cardiovascular event.

No. at risk					
Low	119	82	48	19	4
Intermediate	81	52	24	12	1
High	39	11	8	2	1

No. at risk						
Low	36	35	32	28	18	12
Intermediate	20	18	15	11	5	5
High	10	5	3	3	3	3

Fig. 3. Kaplan-Meier survival curves for the derivation cohort (A) and the validation cohort (B).

Table 4. 2-year mortality

Risk category	No. (%)	Derivation cohort (n=239)	No. (%)	Validation cohort (n=66)
		Death at 2 years (%)		Death at 2 years (%)
Low	119 (49.8)	6 (5.0)	36 (54.5)	1 (2.8)
Intermediate	81 (33.9)	25 (30.8)	20 (30.3)	6 (30.0)
High	39 (16.3)	25 (64.1)	10 (15.2)	5 (50.0)
Difference in probability of death*		0.59		0.47
C-statistic		0.78		0.80

The risk category was classified by the mortality prediction model. The prognostic index was categorized into three groups: low-risk (0 point), intermediate-risk (1 to 5 points), and high-risk (6 to 13 points). *The difference in probability of death was calculated by the formula $(P_{high}-P_{low})/100$

hort according to their risk score resulted in the assignment of 36 patients (55%) to the low-, 20 patients (30%) to the intermediate- and 10 patients (15%) to the high-risk groups. The 2-year mortality rates for these three groups were 3% (1/36), 30% (6/20), and 50% (5/10), respectively. The C statistic was 0.80. Compared with the low-risk group, the HR of the high-risk group was 12.9 (95% CI: 2.5 to 67.4; p=0.002) and intermediate-risk group was 6.2 (95% CI: 1.2 to 30.6; p=0.026) (Fig. 3B, Table 5).

Discussion

Our study demonstrated that patients with advanced HF who were suitable for CRT but treated with a conventional strategy exhibited high mortality (56 deaths, 23%) by the time of the follow-up examinations. The risk of death in advanced HF is predicted by the presence of 4 independent risk factors, which are prior stroke, heart rate (>90 bpm), serum Na (≤135 mEq/L), and serum creatinine (>1.5 mg/dL). We developed a risk model using these factors and stratified patients into the low-, intermediate-, and high-risk groups according to their risk score. The high-risk group demonstrated a 21-fold higher mortality risk compared to the low-risk group. This risk model was also validated in terms of risk stratification and mortality prediction.

Cardiac resynchronization therapy is a well-proven invasive device therapy in patients with advanced HF. It has been reported to improve ventricular conduction delay and ventricular function, reduce the magnitude of mitral regurgitation, and increase pulse pressure, cardiac index, as well as reverse remodeling of the ventricle.[12] However, recent studies revealed that CRT is underutilized in clinical practice with significant variations associated with age, insurance, QRS interval, and geographic location of practices.[9,13] An analysis from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting found that only 38.8% of patients who fit the guidelines for receiving CRT were implanted with a CRT device from May 2007 through June 2009 in the United States.[13] Based on the European Medical Device Trade Organization registry, the number of CRT implantations markedly increased from 46/

million in 2004 to 99/million in 2008. However, this rate (99/million) still indicated only 7% of all eligible HF patients received a CRT device.[14]

To facilitate the use of CRT in eligible HF patients, effective risk stratification of advanced HF is crucial. Using our model, the high-risk group showed a markedly grave prognosis compared with the low-risk group (2-year mortality 64% vs. 5%, HR 20.9; 95% CI: 8.6 to 51.3; p<0.001).

Our prediction model is comprised of 4 independent risk variables. Stroke was proposed as an independent risk factor associated with poor prognosis in HF. This is because stroke is an indicator of severe LV dysfunction[15] and shares common risk factors as well as pathophysiological mechanisms with coronary artery disease, which is the most common cause of HF.[16,17] In the Enhanced Feedback for Effective Cardiac Treatment study, a stroke increased 30-day mortality (odds ratio 1.43; 95% CI: 1.22 to 2.27; p=0.03) among patients hospitalized for HF.[8]

Tachycardia may be a sign of HF and play a role in the deterioration of cardiac pump function. Several types of tachycardia have been related to the development of HF, including atrial fibrillation/flutter, atrial tachycardia, atrioventricular nodal reentry tachycardia, and ventricular tachycardia.[18]

Hyponatremia may also play a role in poor outcomes. This problem is largely related to the associated fall in cardiac output and systemic blood pressure. Patients with hyponatremia showed significantly increased mortality compared with normonatremic patients.[19]

Many studies have reported that renal insufficiency is associated with adverse cardiovascular outcomes.[20,21] McAlister et al.[20] have shown that HF patients with renal insufficiency exhibited a 1% increase in mortality for each 1 mL/min decrease in creatinine clearance.[20]

In our study, prolongation of the QRS interval and enlarged LVEDD were not independent predictors for mortality. There was no significant difference in QRS interval between the survivor and non-survivor groups. This finding is in disagreement with previous studies concerning the prognosis of HF, in which the prolongation of the QRS interval was generally associated with poor prognosis in HF.[22]

Table 5. Baseline demographic and clinical characteristics in the derivation cohort and validation cohort

Variables	Derivation cohort (n=239)	Validation cohort (n=66)	p
Age (years)	67±12	66±11	0.553
Male, n (%)	160 (67)	46 (70)	0.673
NYHA class			0.155
II	75 (31)	29 (44)	
III	88 (37)	21 (32)	
IV	76 (32)	16 (24)	
Co-morbidity, n (%)			
Hypertension	131 (55)	37 (56)	0.857
Diabetes mellitus	94 (39)	21 (32)	0.265
Chronic kidney disease	141 (59)	13 (20)	<0.001
Body mass index ≥25 (kg/m²)	64 (29)	24 (37)	0.256
Prior stroke	18 (8)	8 (12)	0.237
Smoking	70 (29)	26 (39)	0.341
Thyroid disease	20 (8)	0 (0)	0.015
Clinical and Laboratory findings at enrollment			
Systolic BP (mm Hg)	116±17	115±17	0.694
Diastolic BP (mm Hg)	71±11	70±11	0.623
Heart rate (bpm)	81±18	80±20	0.570
Hb (g/dL)	12.1±2.6	13.0±2.3	0.011
Creatinine (mg/dL)	1.9±1.9	1.4±1.1	0.037
Total cholesterol (mg/dL)	147±46	155±45	0.020
Echocardiographic findings			
LVEF (%)	25±7	26±8	0.612
LVEDD (mm)	63±10	60±9	0.005
LA volume index (mm³/m²)	50±30	42±20	0.061
EKG findings			
Atrial fibrillation, n (%)	77 (33)	17 (26)	0.260
QRS duration (ms)	145±21	136±23	<0.001
Medications, n (%)			
Aldosterone antagonists	93 (39)	36 (55)	0.023
ACE inhibitors	92 (38)	39 (59)	0.003
Angiotensin receptor blockers	77 (32)	23 (35)	0.687
Beta blockers	123 (51)	42 (64)	0.079
Digitalis	64 (27)	36 (55)	0.004
Diuretics	156 (65)	49 (70)	0.226

Data are expressed as n (%) or mean±standard deviation. NYHA: New York Heart Association, BP: blood pressure, Hb: hemoglobin, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LA: left atrium, EKG: electrocardiography, ACE: angiotensin converting enzyme

This discrepancy is possibly due to the prolonged QRS interval (>120 ms) in all enrolled patients.

Left ventricular end diastolic diameter is a known risk factor in the prognosis of patients with systolic dysfunction and HF.[23] In our study, LVEDD was associated with lower odds of all-cause mortality based on univariate analysis. This disagreement with previous studies may be attributed to the enlarged (>55 mm) status of LVEDD in most of the enrolled patients. Even though mean LVEDD of survivor was slightly larger than the non-survivor, the proportion of patients with severe LV dilatation (LVEDD ≥75 mm) was higher in the non-survivor group (16.1% vs. 13.1%).

Regarding survival in severe HF, we already have several models for evaluation. The Seattle Heart Failure model suggests a 3-year survival rate in HF and the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness risk model predicts 6 month mortality for acute decompensated HF pa-

tients.[24][25]

These two prediction models are more accurate predictors of survival of advanced HF patients than our prediction model. However, these scoring models require more than 10 variables and invasive procedures like pulmonary catheterization for accurate prediction. In contrast, our prediction model consists of only four risk factors and does not require any invasive procedure.

Our study has several limitations. First, we did not exclude atrial fibrillation patients. Even though advanced HF with atrial fibrillation is not a class I indication for CRT, many studies reported that these patients also benefit from CRT. In a meta-analysis of prospective cohort studies,[11] patients in atrial fibrillation had similar improvement in LVEF with no significant mortality difference compared to patients with a normal sinus rhythm. In our study, patients with atrial fibrillation were effectively stratified into risk groups using a risk model. The high-risk group demonstrated a 32-fold higher mortality than the low-risk group.

Second, as it was a retrospective design study, our results are dependent on the accuracy of medical records. Therefore the accuracy of our decision about optimal cardiac medication is lacking. Additionally, we enrolled patients from tertiary referral hospitals and had a relatively small validation cohort, which may not fully represent the entire spectrum of advanced HF.

In conclusion, the prognosis of patients suffering from advanced HF with low LVEF and a wide QRS interval who were treated with a conventional strategy is primarily dependent on prior stroke, heart rate, serum Na, and serum creatinine. We developed a risk model based on these four factors that predict mortality risk and stratified patients into three levels of risk (low, intermediate, and high) effectively. This model may be useful to clinicians for predicting the patient's prognosis, and CRT should be actively considered in high-risk patients.

Acknowledgments

References

1. Mosterd A, Cost B, Hoes AW, et al. The prognosis of heart failure in the general population: the Rotterdam Study. *Eur Heart J* 2001;22:1318-27.
2. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:1977-2016.
3. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.
4. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1-62.
5. Cleland JG, Daubert JC, Erdmann E, et al. The CARE-HF Study (CArdiac REsynchronisation in Heart Failure Study): rationale, design and endpoints. *Eur J Heart Fail* 2001;3:481-9.
6. Feldman AM, de Lissovoy G, Bristow MR, et al. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *J Am Coll Cardiol* 2005;46:2311-21.
7. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
8. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;290:2581-7.
9. Fonarow GC, Yancy CW, Albert NM, et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. *Circ Heart Fail* 2008;1:98-106.
10. Rassi A Jr, Rassi A, Little WC, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. *N Engl J Med* 2006;355:799-808.
11. Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2008;52:1239-46.
12. Jarcho JA. Biventricular pacing. *N Engl J Med* 2006;355:288.
13. Curtis AB, Yancy CW, Albert NM, et al. Cardiac resynchronization therapy utilization for heart failure: findings from IMPROVE HF. *Am Heart J* 2009;158:956-64.
14. Van Veldhuisen DJ, Maass AH, Priori SG, et al. Implementation of device therapy (cardiac resynchronization therapy and implantable cardioverter defibrillator) for patients with heart failure in Europe: changes from 2004 to 2008. *Eur J Heart Fail* 2009;11:1143-51.
15. Hays AG, Sacco RL, Rundek T, et al. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. *Stroke* 2006;37:1715-9.
16. Adams RJ, Chimowitz MI, Alpert JS, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Circulation* 2003;108:1278-90.
17. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic at-

tack and ischemic stroke: a systematic review and meta-analysis. *Stroke* 2005;36:2748-55.

18. Patel JJ, Whittaker CT. Tachycardia-induced heart failure. *Perm J* 2007; 11:50-2.

19. Oren RM. Hyponatremia in congestive heart failure. *Am J Cardiol* 2005; 95(9A):B2-7.

20. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;109:1004-9.

21. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;108:2154-69.

22. Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN; Department of Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. QRS duration and mortality in patients with congestive heart failure. *Am Heart J* 2002;143:1085-91.

23. Thohan V. Prognostic implications of echocardiography in advanced heart failure. *Curr Opin Cardiol* 2004;19:238-49.

24. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;113:1424-33.

25. O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol* 2010;55; 872-8.