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

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

Directed by Professor Hyuk-Jae Chang

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ABSRACT

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

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Background: 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 strategy. And we developed a risk model to predict mortality to improve the facilitation of CRT.

Method and Results: Patients with symptomatic HF with LVEF≤35 % and QRS interval >120ms were consecutively enrolled at Severance Cardiovascular Hospital. After those patients who had received device therapy were excluded, 239 patients (160 males, mean 67 ± 11 years) were eventually recruited.

During a follow-up of 308 ± 236 days, 56 (23%) patients died. Prior stroke, heart rate >90bpm, and serum Na ≤135mEq/L and serum creatinine ≥1.5mg/dL

were identified as independent factors using Cox proportional hazards regression. Based on the risk model, assigned points to each of the risk factors proportional to the regression coefficient, 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. The model was validated in a cohort from a different institution: C statistic 0.80.

Conclusion: The mortality of patients with advanced HF who were managed conventionally was effectively stratified using a risk model. It might be useful for clinicians to be more proactive about adopting CRT to improve patients' prognosis.

Key words : Advanced heart failure, prognosis model, cardiac resynchronization therapy

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I. 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 (>120ms), device therapy such as cardiac resynchronization therapy (CRT) has been demonstrated 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 (COMPANION) study demonstrated that use of CRT was associated with a

significant 20% decrease in mortality of advance HF at 6 month follow-up [5-8]. The Cardiac Resynchronization–Heart Failure (CARE-HF) 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 for CRT but treated with conventional strategy. And 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.

II. MATERIALS AND METHODS

1. Study population

Between January 2007 and February 2009, 1,345 patients with HF visited the tertiary referral hospital (Severance Cardiovascular Hospital, South Korea). 239 patients (18%) who had advanced HF (New York Heart Association (NYHA) functional class II~IV and LVEF ≤35%) with wide QRS interval (> 120ms) were consecutively enrolled. Patients (1) who received device therapy or heart transplantation and (2) who had a malignancy were excluded in this study (Figure 1). For the validation of a risk model, 66 patients were enrolled from a different affiliated institution (Gangnam Severance Hospital, South Korea) with the same inclusion and exclusion criteria (validation cohort) during the same period.

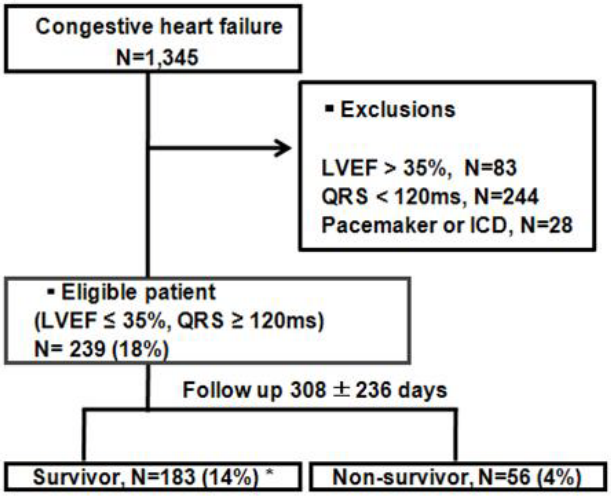


Figure 1. Diagram of Study workflow

2. Echocardiographic measurements

Echocardiography was performed on all patients at the index visit. A standard echocardiography was performed and the left ventricular end diastolic diameter (LVEDD), LVEF, left arterial volume index, and early mitral inflow velocity to early diastolic mitral annular velocity (E/E') were measured.

3. Clinical and biochemical data

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

4. Outcomes

In order to identify and evaluate risk factors associated with prognosis 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).

5. Statistical Analysis

Continuous variables were expressed as mean and standard deviations (SD). Baseline characteristics were compared by chi-square test 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 prediction model was evaluated by receiver-operating curve analysis (C statistic). P-values are all 2-sided and were 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.

III. RESULTS

1. Patient characteristics

The clinical characteristics and the use of various cardiac medications at the time of enrollment are presented in Table 1. Our patients 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. 56 (23%) patients died. The etiology of HF included 131 (55%) cases of ischemic and 108 (45%) cases of non-ischemic. There were 131 (55%) hypertensive and 94 (39%) diabetic, and 141 (59%) were chronic kidney disease (CKD) patients. 77 (32%) patients had atrial fibrillation. The mean LVEF was 25 ± 7% and the mean QRS interval was 145 ± 20ms. 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.

TABLE 1. Baseline demographic and clinical characteristics in the derivation cohort*

Variable	**Non-Survivor** (N=56)	**Survivor** (N=183)	p-value
Age (years)	70 ± 13	66 ± 11	0.046*
Male	35 (63)	125 (68)	0.419
Etiology of heart failure			
Ischemic	32 (57)	99 (54)	0.689
Non-ischemic	24 (43)	84 (46)	
NYHA class			<0.001
II	6 (11)	69 (38)	
III	16 (29)	72 (39)	
IV	34 (61)	42 (23)	
Co-morbidity			
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/㎡)	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 (mmHg)	115 ± 22	113 ± 14	0.773
Diastolic BP (mmHg)	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 (㎣/㎡)	50 ± 30	50 ± 31	0.998
E/E'	22 ± 10	24 ± 12	0.509
EKG findings			
Atrial fibrillation	20 (36)	57 (31)	0.626
QRS duration (ms)	142 ± 20	146 ± 21	0.147
Medications			
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 denotes New York Heart Association; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; BP: blood pressure; Hb: hemoglobin; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LA: left atrium; ACE: angiotension converting enzyme.

2. 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 to identify risk factors affecting all-cause death. The following demographic, clinical, biochemical, and echocardiography variables had significant correlations with all-cause death: NYHA class (III, IV vs. II) (hazard ratio 4.2; 95% CI: 1.81 to 9.87; p<0.001), body mass index (≥25kg/m ^{2}) (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 (≥55mm) (0.4; 95% CI : 0.21 to 0.65; p<0.001), heart rate (>90bpm) (6.3; 95% CI: 3.7 to 10.6; p<0.001), serum Hgb (2.7; 95% CI : 1.30 to 4.14; p<0.001), serum Na (≤135mEq/L) (2.74; 95% CI: 1.62 to 4.63; p<0.001), and serum creatinine (≥1.5mg/dl) (3.3; 95% CI: 1.96 to 5.69; p<0.001).

Then, we analyzed significant factors by stepwise multivariate analysis. Prior stroke (hazard ratio 2.7; 95% CI: 1.23 to 6.13; p=0.01), heart rate (>90bpm) (4.6; 95% CI: 2.51 to 8.59; p<0.001), and serum Na (≤135mEq/L) (2.9; 95% CI: 1.61 to 5.37; p<0.001) and serum creatinine (≥1.5mg/dL) (1.9; 95% CI: 1.02 to 3.64; p=0.04) were defined as significant predictors (Table 3).

TABLE 2. Univariate Cox Regression for all-cause mortality*

Variables	Regression coefficient	Hazard ratio	95% CI	p-value
Age	0.016	1.023	0.998~1.049	0.070
Male	0.082	0.790	0.460~1.357	0.393
Ischemic heart disease	-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/㎡)	-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

*CI denotes confidence interval; NYHA: New York Heart Association; CKD, chronic kidney disease; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; Hb: hemoglobin; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; SCr: serum creatinine.

TABLE 3. Multivariate Cox Regression Analysis for all-cause death and risk score *

	β Regression coefficient	Hazard ratio	95% CI	p-value	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

*CI denotes confidence interval; Scr: serum creatinine

†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].

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 (Figure 2). In multivariate analysis, NYHA class (III, IV vs. II) (2.0; 95% CI: 1.05 to 3.71; p=0.04), heart rate (>90bpm) (2.16; 95% CI: 1.29 to 3.62; p=0.01), serum Na (<135mEq/L) (2.53; 95% CI: 1.59 to 4.03; p<0.001) and serum creatinine (≥1.5mg/dL) (2.1; 95% CI: 1.20 to 3.58; p=0.01) were identified as significant risk factors.

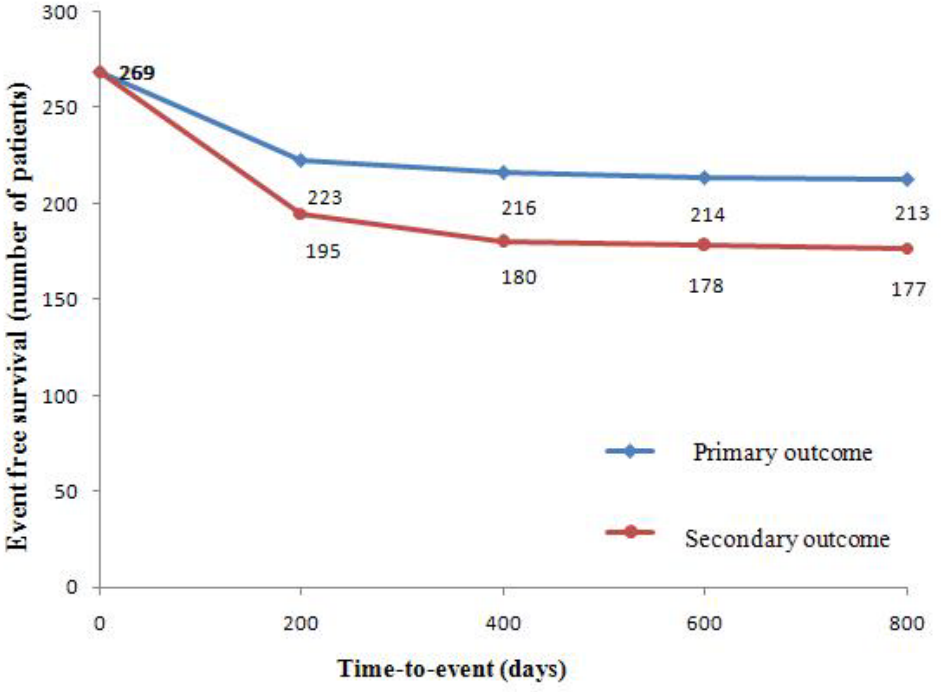


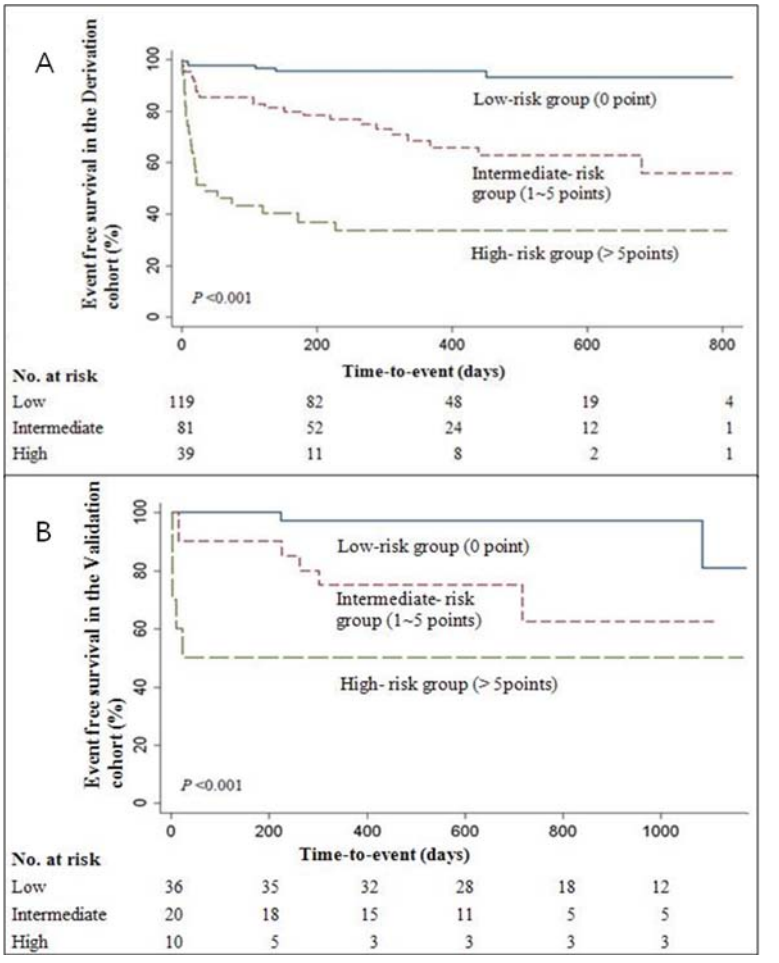
Figure 2. Primary outcome: all-cause death. Secondary outcome: the composite of all- cause death or unplanned hospitalization due to MACE.

4. Prognostic modeling and risk stratification

We assigned scores to risk factors based on a linear transformation of the corresponding β regression coefficients. The coefficient of each variable was divided by the lowest β value, then multiplied by a constant (2), and rounded to the nearest integer [10] (Table 3). The risk model calculated a score by adding together the points corresponding to patient's risk factors: [Risk score = 3 x prior stroke + 5 x heart rate (>90bpm) + 3 x serum Na (≤135mEq/L) + 2 x serum creatinine (≥1.5mg/dL)].

Based on the risk score, patients were stratified into three groups: 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. The difference in the probability of death between the high-risk and the low-risk groups was 0.59 at 2 years. Compared with the low-risk group, the hazard ratio 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 (Figure 3-A and Table 4).



3. Kaplan-Meier Survival Curves for the Derivation cohort (A) and the Validation Cohort (B). Risk group were determined by adding up the points of the following risk factors: Prior stroke (3 points), heart rate >90bpm (5 points), serum Na ≤135mEq/L (3 points), and serum creatinine >1.5 mg/dL (2 points).

TABLE 4. 2-year mortality *

Risk category	Derivation cohort (N= 239)		Validation cohort (N = 66)	
	No. (%)	Death at 2Yr	No. (%)	Death at 2 Yr
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 in 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 $(P_{high}-P_{low})/100$

5. 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 were dead. We re-classified patients by 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).

6. Validation of the prediction model

Sixty-six patients from a different hospital were selected as the validation cohort. During a mean follow-up of 686 ± 367 days, 13 patients (20 %) died. Classification of the validation cohort 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 group. 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 hazard ratio 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) (Figure 3-B and Table 4).

IV. DISCUSSION

Our study demonstrated that patients with advanced HF who were suitable for CRT but treated with conventional strategy exhibited high mortality (56 deaths, 23%) during the follow-up. The risk of death in advanced HF is predicted by the presence of 4 independent risk factors. These risk factors are prior stroke, heart rate (> 90bpm), serum Na (≤ 135mEq/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.

CRT 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, and reverse remodeling of 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 (IMPROVE-HF) 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 (EUCOMED) registry, the number of CRT implantations markedly increased from 46/million in 2004 to 99/million in 2008. However, this rate (99/million) still means 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 should be crucial. Using our model, the high-risk group showed a markedly grave prognosis compared with the low-risk group (2-year mortality 64% versus 5%, hazard ratio 20.9; 95% CI: 8.6 to 51.3; $p<0.001$).

Our prediction model is made 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 and pathophysiological mechanisms with coronary artery disease, which is the most common cause of HF [16,17]. In the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) 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. have shown that heart failure patients with renal insufficiency exhibited a 1% increase in mortality for each 1mL/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, which the prolongation of the QRS interval is associated with poor prognosis in HF [22]. This discrepancy is possibly due to the prolonged QRS interval (>120ms) in all enrolled patients.

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

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 have 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. Additionally, we enrolled patients from tertiary referral hospitals, which may not fully represent entire spectrum of advance HF.

V. Conclusion

The prognosis of patients with advanced HF with low LVEF and a wide QRS interval who were treated with a conventional strategy is mainly 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.

References

1. Mosterd A, Cost B, Hoes A, De Bruijne M, Deckers J, Hofman A, Grobbee D. The prognosis of heart failure in the general population. The Rotterdam Study. *European Heart Journal*2001;22(15):1318.
2. Jessup M, Abraham W, Casey D, Feldman A, Francis G, Ganiats T, Konstam M, Mancini D, Rahko P, Silver M. 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. *Circulation*2009.
3. Bardy G, Lee K, Mark D, Poole J, Packer D, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *The New England journal of medicine* 2005;352(3):225.
4. Epstein A, DiMarco J, Ellenbogen K, Mark Estes N, Freedman R, Gettes L, Gillinov A, Gregoratos G, Hammill S, Hayes D. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: Executive Summary 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. *Heart Rhythm* 2008.
5. Cleland J, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L, Klein W, Tavazzi L. The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. *European Journal of Heart Failure* 2001;3(4):481-9.
6. Feldman A, de Lissovoy G, Bristow M, Saxon L, De Marco T, Kass D, Boehmer J, Singh S, Whellan D, Carson P. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. *Journal of the American College of Cardiology* 2005;46(12):2311-21.
7. Bristow M, Saxon L, Boehmer J, Krueger S, Kass D, De Marco T, Carson P, DiCarlo L, DeMets D, White B. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *New England Journal of Medicine* 2004;350(21):2140.
8. Lee D, Austin P, Rouleau J, Liu P, Naimark D, Tu J. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *Jama* 2003;290(19):2581.
9. Fonarow G, Yancy C, Albert N, Curtis A, Stough W, Gheorghiade M, Heywood J, McBride M, Mehra M, O'Connor C. Heart failure care in the

outpatient cardiology practice setting: findings from IMPROVE HF. *Circulation: Heart Failure* 2008;1(2):98.
10. Rassi Jr A, Rassi A, Little W, Xavier S, Rassi S, Rassi A, Rassi G, Hasslocher-Moreno A, Sousa A, Scanavacca M. Development and validation of a risk score for predicting death in Chagas' heart disease. *New England Journal of Medicine* 2006;355(8):799.
11. Upadhyay G, Choudhry N, Auricchio A, Ruskin J, Singh J. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. *Journal of the American College of Cardiology* 2008;52(15):1239.
12. Jarcho J. Biventricular pacing. *The New England journal of medicine* 2006;355(3):288.
13. Curtis AB, Yancy CW, Albert NM, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Mehra MR, Oconnor CM, Reynolds D, Walsh MN, Fonarow GC. Cardiac resynchronization therapy utilization for heart failure: findings from IMPROVE HF. *Am Heart J* 2009 Dec;158(6):956-64.
14. van Veldhuisen DJ, Maass AH, Priori SG, Stolt P, van Gelder IC, Dickstein K, Swedberg K. 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 Dec;11(12):1143-51.
15. Hays A, Sacco R, Rundek T, Sciacca R, Jin Z, Liu R, Homma S, Di Tullio M. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. *Stroke* 2006;37(7):1715.
16. Adams R, Chimowitz M, Alpert J, Awad I, Cerqueria M, Fayad P, Taubert K. 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(10):1278.
17. Touze E, Varenne O, Chatellier G, Peyrard S, Rothwell P, Mas J. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. *Stroke* 2005;36(12):2748.
18. Patel J, Whittaker C. Tachycardia-Induced Heart Failure. *The Permanente Journal* 2007;11(3).
19. Oren R. Hyponatremia in congestive heart failure. *The American journal of cardiology* 2005;95(9S1):2-7.
20. McAlister F, Ezekowitz J, Tonelli M, Armstrong P. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;109(8):1004.
21. Sarnak M, Levey A, Schoolwerth A, Coresh J, Culleton B, Hamm L,

McCullough P, Kasiske B, Kelepouris E, Klag M. 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(17):2154.
22. Iuliano S, Fisher S, Karasik P, Fletcher R, Singh S. QRS duration and mortality in patients with congestive heart failure. *American Heart Journal* 2002;143(6):1085-91.
23. Thohan V. Prognostic implications of echocardiography in advanced heart failure. *Current opinion in cardiology* 2004;19(3):238.

ABSTRACT (IN KOREAN)

낮은 좌심실 구혈률과 넓은(≥120msec) QRS 간격을 갖는 만성 심부전 환자에서 예후 인자 분석 및 예후 예측모델 개발

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배경:

심장 재동기화 치료는 낮은 좌심실 구혈률과 넓은 QRS 간격을 갖는 만성 심부전 환자에서 예후를 향상시키는 것으로 잘 알려져 있다. 하지만 실제 임상에서는 대상 환자 군에 여전히 잘 적용되지 않고 있다. 본 연구에서는 심장 재동기 치료 적응증이 되는 환자 군에서 예후 예측모델을 개발하고 고위험군을 조기에 선별하고자 한다.

방법:

2007년 1월부터 2009년 2월까지 신촌 세브란스 병원에 심부전으로 내원한 환자들 중 심장초음파에서 LVEF 35% 이하, 심전도에서 QRS 간격이 120msec 이상이면서 약물 치료만을 받은 환자들을 대상으로 임상적, 생화학적 지표들을 분석하고 임상 경과를 조사하였다.

결과:

해당기간 동안 심부전으로 내원한 환자는 총 1345명이었으며 LVEF 35%이하, QRS 간격이 120msec 이상인 환자는 267명(남자 180명, 평균 67±12세, 평균 관찰 기간

288일)이었다. 사망에 대하여 심부전에 영향을 미치는 변수를 가지고 Cox 회귀분석을 시행하였으며, 다변량 분석에서 뇌경색의 과거력, 입원 시 심박동수, 혈청 Na 그리고 혈청 Creatinie 수치가 의미 있는 변수로 확인되었다. 이들 변수에 대하여 각각의 회귀 계수를 곱한 값을 점수화 하여 환자 군을 위험도에 따라 세 군으로 나누고 이들 그룹의 2년 사망률을 비교하였더니 고위험군이 저위험군에 대하여 매우 높은 사망을 보였다 (64 % vx 5%). 이 모델을 타병원 환자들에게 적용하였더니 역시 유효한 결과를 보였다.

결론:

해당 환자군에서 뇌경색의 과거력, 입원 시 심박동수, 혈청 Na 그리고 혈청 Creatinie 수치가 예후와 관련된 인자로 확인되었으며 이를 이용한 예측 모델을 통해 높은 사망 가능성을 갖는 환자 군을 선별할 수 있었다. 향후 이를 이용하여 심장 재동기화 치료 등 보다 적극적인 치료가 필요한 환자군을 초기에 선별함으로써 해당 환자군의 예후를 개선할 수 있는지에 대한 전향적 연구가 필요하겠다.

핵심되는 말: 진행성 심부전, 예후 예측 모델, 심장 재동기화 치료