Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

Usefulness of Combined Risk Stratification With Heart Rate and Systolic Blood Pressure in the Management of Chronic Heart Failure

– A Report From the CHART-2 Study –

Masanobu Miura, MD, PhD; Yasuhiko Sakata, MD, PhD; Satoshi Miyata, PhD; Kotaro Nochioka, MD, PhD; Tsuyoshi Takada, MD; Soichiro Tadaki, MD; Jun Takahashi, MD, PhD; Nobuyuki Shiba, MD, PhD; Hiroaki Shimokawa, MD, PhD on behalf of the CHART-2 Investigators

Background: The appropriate target ranges of heart rate (HR) and systolic blood pressure (SBP) for the management of chronic heart failure (CHF) patients remain to be elucidated in a large-scale cohort study.

Methods and Results: We examined 3,029 consecutive CHF patients with sinus rhythm (SR) (mean age, 67.9 years) registered in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study (CHART-2; NCT00418041). There were 357 deaths (11.8%) during the median follow-up of 3.1 years. We first performed the classification and regression tree analysis for mortality, identifying SBP <89 mmHg, HR >70 beats/min and SBP <115 mmHg as the primary, secondary and tertiary discriminators, respectively. According to these, we divided the patients into low- (n=1,131), middle- (n=1,624) and high-risk (n=274) groups with mortality risk <10%, 10–20% and >20%, respectively. The low-risk group was characterized by SBP >115 mmHg and HR <70 beats/min and the high-risk group by SBP <89 mmHg regardless of HR values or SBP 89–115 mmHg and HR >76 beats/min. Multivariate Cox regression analysis revealed that the hazard ratio of all-cause death for low-, middle- and high-risk groups was 1.00 (reference), 1.48 (95% confidence interval (CI): 1.10–1.99, P=0.009) and 2.44 (95% CI 1.66–3.58, P<0.001), respectively. Subgroup analysis revealed that age ≥70 years, diabetes, or reduced left ventricular function had higher hazard ratios in the high-risk group.

Conclusions: The results demonstrate the usefulness of combined risk stratification of HR and SBP in CHF patients with SR. (*Circ J* 2013; **77:** 2954–2962)

Key Words: CHART-2; Chronic heart failure; Heart rate; Prognosis; Systolic blood pressure

Elevated resting heart rate (HR) is an independent risk factor for mortality not only in the general population[1,2] but also in patients with coronary artery disease (CAD)[3] and those with chronic heart failure (CHF).[4] Furthermore, HR reduction is also associated with improvement in the prognosis of patients after myocardial infarction[5] and those with CHF.[6,7] According to the European Society of Cardiology (ESC) guidelines, HR should be controlled to less than 70 beats/min in CHF patients with reduced left ventricular ejection fraction (LVEF).[8] Thus, the management of HR is an important therapeutic strategy in CHF management. High systolic blood pressure (SBP) is also an adverse prognostic marker in both the general population[9] and patients with cardiovascular diseases.[10,11] However, increased SBP is associated with reduced mortality in CHF patients,[12] a phenomenon known as "reverse epidemiology".[13]

In the management of CHF, β-blockers are widely used because they have been shown to reduce mortality, particularly in patients with reduced LVEF.[14,15] However, physicians often hesitate to use β-blockers for CHF patients with reduced LVEF and lower SBP, because the drugs may further decrease SBP and HR. Indeed, in real-world practice, only a small percentage of CHF patients receive target doses of β-blockers despite

Received June 10, 2013; revised manuscript received July 24, 2013; accepted August 1, 2013; released online October 1, 2013 Time for primary review: 14 days

Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai (M.M., Y.S., S.M., K.N., T.T., S.T., J.T., H.S.); Department of Cardiology, International University of Health and Welfare Hospital, Nasushiobara (N.S.), Japan

The Guest Editor for this article was Hiroshi Ito, MD.

Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-13-0725

Table 1. Baseline Characteristics of the Patients With Chronic Heart Failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study

	All patients (n=3,029)	Low-risk group (n=1,131)	Middle-risk group (n=1,624)	High-risk group (n=274)	P value for 3 groups
Age (years)	67.9±12.8	69.0±11.8	67.4±13.1	66.9±14.6	0.002
Male (%)	70.1	73.4	68.4	66.1	0.006
History of admission for HF (%)	47.1	42.1	48.3	60.2	<0.001
Etiology					
Ischemic heart disease (%)	58.8	60.9	58.9	48.9	0.001
Cardiomyopathy (%)	16.8	16.1	15.8	25.5	<0.001
Valvular heart disease (%)	17.1	16.3	17.7	17.2	0.63
Hypertensive heart disease (%)	10.1	11.8	9.8	5.1	0.004
Comorbidities (%)					
Hypertension	78.7	85.5	76.8	61.3	<0.001
Diabetes	28.3	28.6	27.8	29.6	0.78
Hyperuricemia	42.1	42.5	41.1	46.0	0.29
Cerebrovascular disease	15.9	15.8	16.4	13.1	0.4
PAF	7.8	7.8	7.8	6.2	0.64
Clinical status					
NYHA class III or IV (%)	9.9	7.8	10.2	17.2	<0.001
Body mass index (kg/m^2)	23.7±4.7	24.2±4.3	23.7±4.8	22.0±5.5	<0.001
SBP (mmHg)	128±19	135±14	127±19	103±10	<0.001
DBP (mmHg)	73±12	74±10	73±13	64±10	<0.001
HR (beats/min)	71±14	60±6	76±13	86±11	<0.001
Measurements					
LVEF (%)	57.4±15.7	60.7±14.1	56.2±15.7	52.3±10.5	<0.001
LVDd (mm)	51.8±9.1	51.4±8.2	52.1±9.5	52.3±10.5	0.12
Hemoglobin (g/dl)	13.2±2.1	13.3±2.2	13.2±2.0	12.9±2.8	0.02
Blood urea nitrogen (mg/dl)	19.6±10.7	19.3±10.9	19.4±9.8	21.5±13.7	0.007
Serum creatinine (mg/dl)	1.1±0.9	1.0±0.6	1.1±1.0	1.2±1.1	0.008
Serum sodium (mEq/L)	141±2.8	141±2.7	141±2.7	140±3.3	<0.001
Serum potassium (mEq/L)	4.4±0.8	4.4±0.4	4.4±0.4	4.5±0.5	0.04
Brain natriuretic peptide (pg/ml)	76.3	70.7	73.2	135	<0.001
Medications					
ACE inhibitor (%)	44.1	42.4	44.3	50.0	0.07
ARB (%)	32.5	34.9	31.7	27.4	0.03
β-blocker (%)	47.5	50.3	45.9	46.0	0.06
Loop diuretics (%)	39.8	32.4	42.4	54.4	<0.001
Aldosterone inhibitor (%)	20.4	15.2	20.8	39.1	<0.001
Digitalis (%)	12.1	9.5	13.1	17.2	<0.001

Results of continuous values are presented as mean±SD. BNP levels are presented as medians.
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; SBP, systolic blood pressure.

being recommended in guidelines, especially those with lower SBP.[16,17] Furthermore, the appropriate target ranges of HR and SBP for the management of CHF have been studied separately[4,6,7] and the usefulness of combined risk stratification with HR and SBP remains to be examined in a large-scale cohort study.

In the present study, we addressed this important clinical issue in a registry, namely the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (n=10,219) (NCT 00418041).[18]

Methods

Population and Inclusion Criteria

Details of the design, purpose, and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[18] Briefly, eligible patients were aged ≥20 years with significant CAD or in stages B, C and D as defined by the Guidelines for the Diagnosis and Management of Heart Failure in Adults.[19] Patients were classified as having HF by experienced cardiologists of 24 participating hospitals, using the criteria of the Framingham Heart Study.[20] The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively enrolled after written informed consent was obtained. The CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients registered from the participating hospitals. All data and events will be surveyed at least once each year until September 2018.

In the CHART-2 Study, each patient's resting HR was measured by ECG after a 2–3-min rest while supine. SBP was mea-

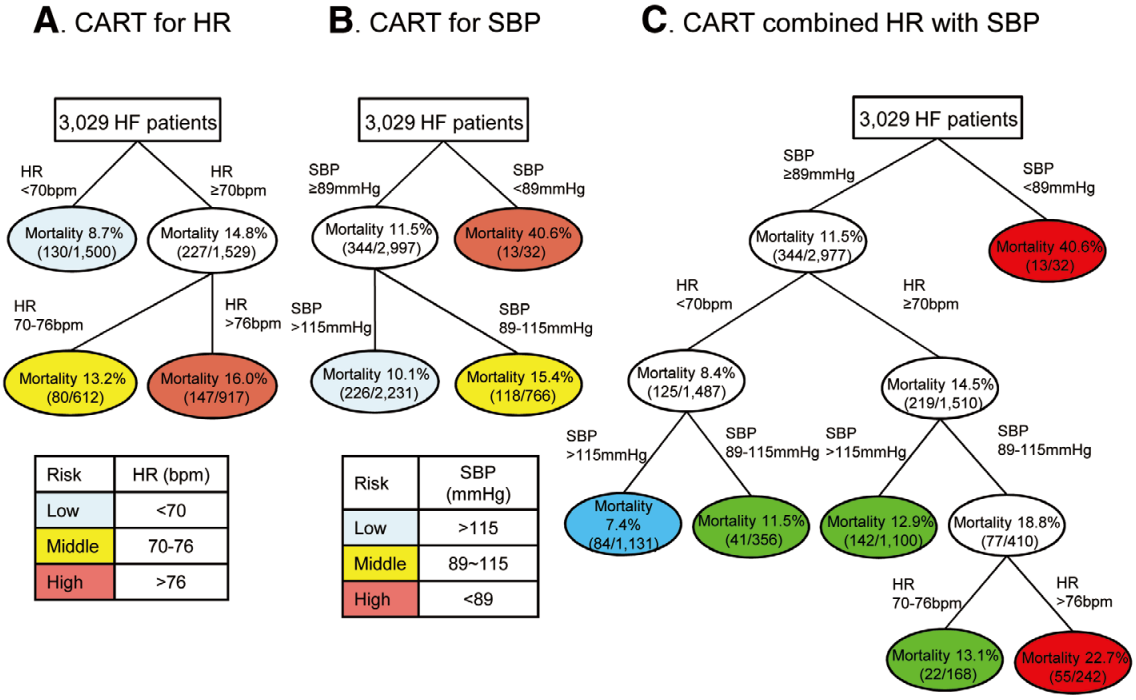


Figure 1. CART analysis for (**A**) heart rate (HR) and (**B**) systolic blood pressure (SBP). (**C**) CART analysis for combined HR and SBP. CART, classification and regression tree.

sured while seated after a 2–3-min rest. In the present study, we excluded asymptomatic patients in stage B (n=5,484) and patients with a pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy (n=486). We also excluded patients with chronic atrial fibrillation (n=1,079), those without sufficient data (n=89), and those who could not be followed up (n=53). Finally, 3,029 CHF patients in sinus rhythm (SR) at baseline were included in the present study. Among them, 236 patients had a history of paroxysmal atrial fibrillation (PAF).

Follow-up Survey and Study Outcomes

We conducted the second survey of survival in November 2011 and the median follow-up period of the study population was 3.1 years. The outcome of this study was all-cause death.

Statistical Analysis

In the present study, we performed classification and regression tree (CART) analysis[21] in order to identify the HR and SBP that would classify HF patients for all-cause death. CART analysis is an empirical, statistical technique based on recursive partitioning of the data space to predict the response.[21] The models are obtained by binary splitting of the data by the value of predictors, and the split variable and split-point are automatically selected from possible predictor values to achieve the best fit. Then, 1 or both "child nodes" are split into 2 or more regions recursively, and the process continues until some stopping rule is applied. Finally, the result of this process is represented as a binary decision tree.

First, we performed CART analysis for both HR and SBP to identify low-, middle-, and high-risk values of HR and SBP. Second, using these risk values of HR and SBP, we performed CART analysis by crossing over the risk values of HR and SBP. Then, we divided the study subjects into 3 risk groups according to the CART analysis and mortality rate: low-, middle-, and high-risk groups. We developed Kaplan-Meier curves and Cox proportional hazard models to compare the risk for all-cause death among the 3 groups. We constructed the following 3 Cox proportional hazard models; (a) unadjusted, (b) age- and sex-adjusted and (c) fully adjusted for clinical status, comorbidities and medications. We included the following covariates, which potentially influence the outcomes: age; sex; NYHA class; history of HF admission and malignant tumor; ischemic etiology of HF; LVEF; body mass index (BMI); serum sodium, serum potassium, serum creatinine, blood urea nitrogen (BUN) concentrations; comorbidities (anemia defined as hemoglobin <12 g/dl in females and <13 g/dl in males, diabetes mellitus, hyperuricemia and cerebrovascular disease); and medications (β-blockers, renin-angiotensin system inhibitors, calcium-channel blockers, loop diuretics, aldosterone antagonists and digitalis). We also performed subgroup analyses based on sex, age (<median or ≥median), history of PAF, LVEF (<50% or ≥50%), history of diabetes, cause of HF (ischemic or non-ischemic), and β-blocker therapy. Comparisons among the 3 groups were performed by chi-square test. Continuous data are described as mean±standard deviation and discrete-valued data as %.

The statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc, Chicago, IL, USA) and R 2.15.2.[22] Statistical significance was defined as a 2-sided P-value less than 0.05.

Results

Baseline Characteristics of All Study Subjects (Table 1)

Mean age was 67.9±12.8 years, and male patients accounted for 70.1% and ischemic HF for 58.8% of the study population. Mean

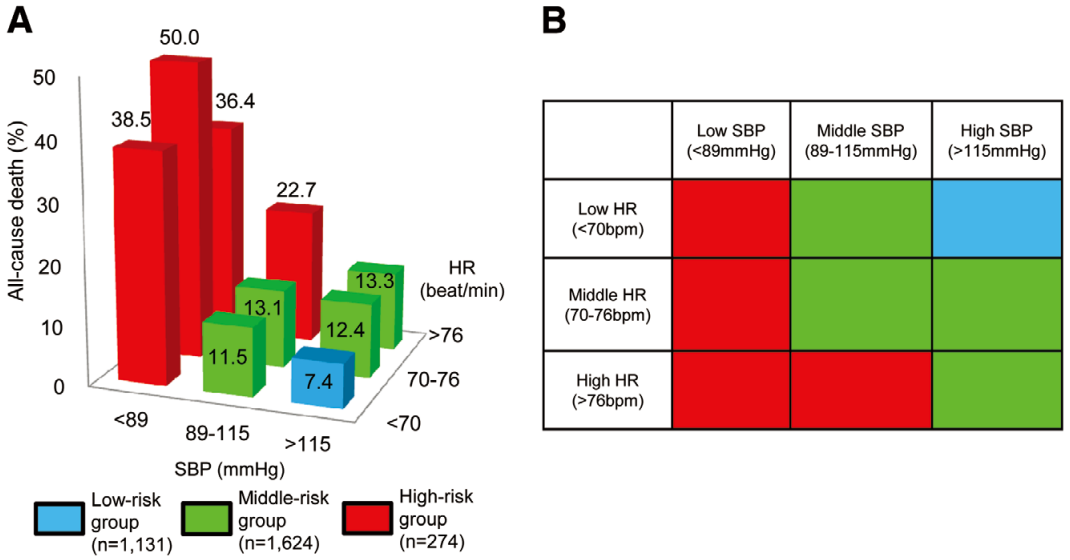


Figure 2. (**A**) Crude mortality rate for all-cause death. (**B**) Stratification of mortality risk according to heart rate (HR) and systolic blood pressure (SBP) in patients with chronic heart failure.

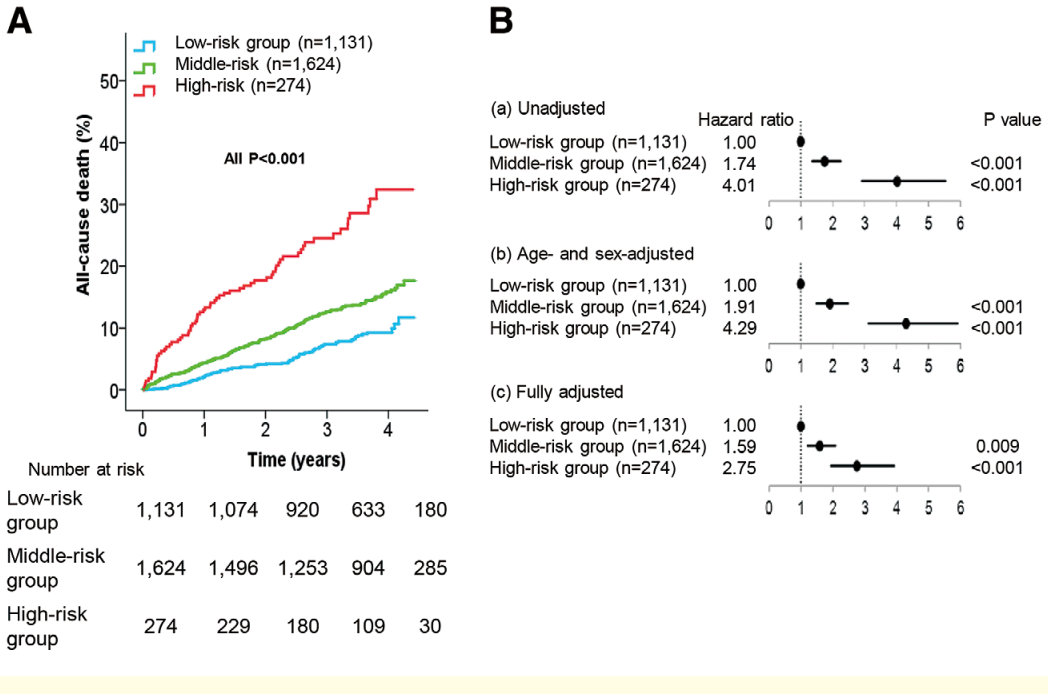
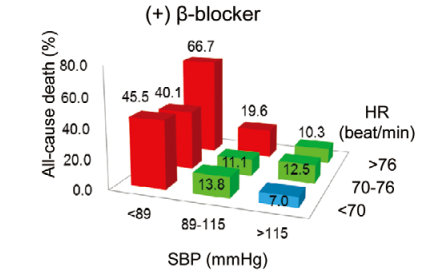


Figure 3. (**A**) Kaplan-Meier curves for all-cause death. (**B**) Cox regression hazard model for all-cause death: (a) unadjusted, (b) age- and sex- adjusted, and (c) fully adjusted.

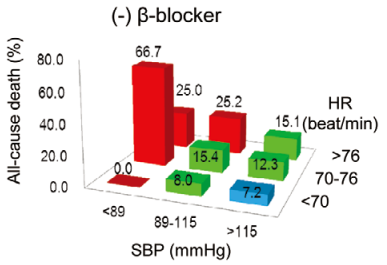
SBP and HR values were 128±19 mmHg and 71± 4 beats/min, respectively. The prevalence of β-blocker use was 47.5% at baseline. In the patients using β-blockers, the prescription ratio and mean doses of carvedilol, bisoprolol, and metoprolol were 79.7% and 7.5±1.5 mg, 8.6% and 4.0±1.8 mg, and 6.7% and 55.3±37.8 mg, respectively.

CART Analysis and Risk Model

During the median follow-up period of 3.1 years, 357 patients (11.8%) died. **Figure 1A** and **Figure 2B** show the CART results for HR and SBP, respectively, in all patients. The CART analysis for HR identified the first discriminator with the split value of 70 beats/min (8.7% vs. 14.8% in mortality rate for HR ≥70 beats/min and HR <70 beats/min, respectively). The sec-



	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	2/3	21/107	26/253
Middle HR (70-76bpm)	2/5	10/90	23/161
Low HR (<70bpm)	5/11	30/218	40/569



	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	2/8	34/135	62/411
Middle HR (70-76bpm)	2/3	12/78	31/252
Low HR (<70bpm)	0/2	11/138	44/562

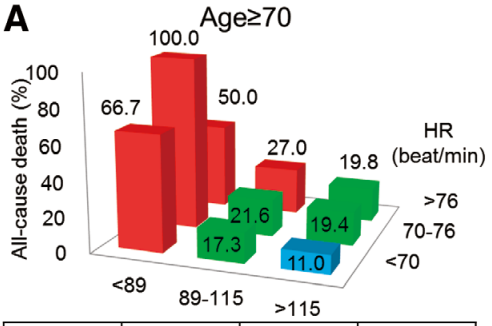
Figure 4. Comparison of the mortality rates between patients with and without β-blocker therapy.

Table 2. Subgroup Analyses for All-Cause Death of Patients With Chronic Heart Failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study

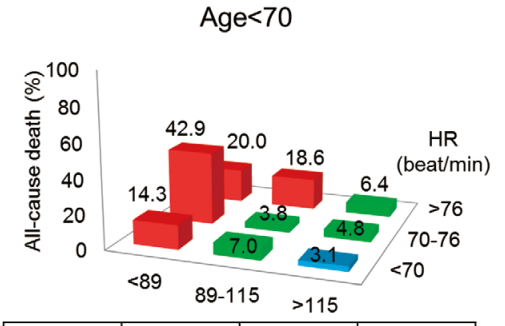
Category	HR	95% CI	P value	HR	95% CI	P value	P for interaction
		Male			Female		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.66	1.24–2.23	<0.001	2.05	1.22–3.46	0.007	0.49
High-risk	3.79	2.59–5.53	<0.001	4.80	2.59–8.90	<0.001	0.52
		Age ≥70 years			Age <70 years		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.89	1.07–3.33	0.03	1.85	1.40–2.47	<0.001	0.95
High-risk	7.47	4.01–13.93	<0.001	3.28	2.23–4.82	<0.001	0.03
		Sinus rhythm			PAF		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.45	0.62–3.35	0.39	1.77	1.36–2.32	<0.001	0.65
High-risk	4.81	1.67–13.87	0.004	3.97	2.84–5.55	<0.001	0.73
		LVEF≥50%			LVEF<50%		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.27	0.93–1.72	0.12	2.83	1.61–4.99	<0.001	0.01
High-risk	2.51	1.58–3.96	<0.001	6.85	3.72–12.61	<0.001	0.008
		(+) Diabetes			(–) Diabetes		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.80	1.33–2.45	<0.001	1.62	1.03–2.55	0.04	0.70
High-risk	4.97	3.42–7.21	<0.001	2.24	1.17–4.27	0.01	0.04
		Ischemic HF			Non-ischemic HF		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.74	1.13–2.69	0.01	1.74	1.27–2.39	<0.001	0.99
High-risk	4.67	2.85–7.67	<0.001	3.60	2.34–5.51	<0.001	0.42
		(+) β-blocker			(–) β-blocker		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.71	1.21–2.42	0.002	1.76	1.21–2.56	0.003	0.90
High-risk	4.03	2.61–6.22	<0.001	3.96	2.46–6.35	<0.001	0.96

Abbreviations as in Table 1.

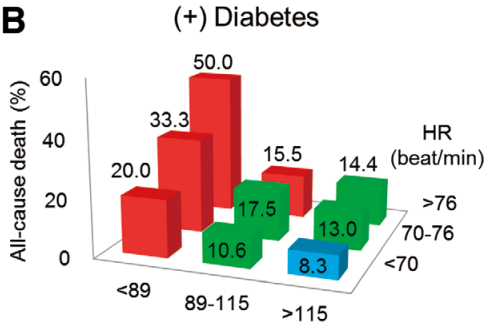
ond discriminator was the split value with HR of 76 beats/min (16.0% vs. 13.2% in mortality rate for HR >76 beats/min and HR 70–76 beats/min, respectively). Thus, we defined the risk values of HR as follows: low-risk = HR <70 beats/min; middle-risk = HR 70–76 beats/min, and high-risk = >76 beats/min (Figure 1A). The CART analysis for SBP identified the first discriminator with the split value of 89 mmHg (40.6% vs. 11.5% in mortality rate for SBP <89 mmHg and SBP ≥89 mmHg, respectively). The second discriminator was the split value with SBP of 115 mmHg (10.1% vs. 15.4% in mortality rate for SBP 89–115 mmHg and SBP >115 beats/min, respectively). Thus, we defined the risk of SBP as follows: low-risk = >115 mmHg; middle-risk = SBP



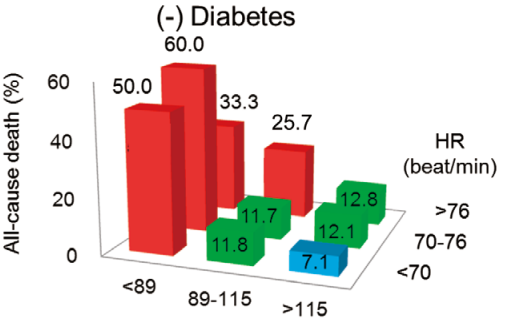
	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	3/6	34/128	67/338
Middle HR (70-76bpm)	1/1	19/88	44/227
Low HR (<70bpm)	4/6	27/156	68/621



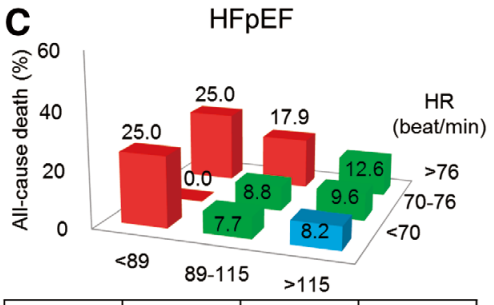
	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	1/5	21/116	21/326
Middle HR (70-76bpm)	3/7	3/80	10/209
Low HR (<70bpm)	1/7	14/200	16/510



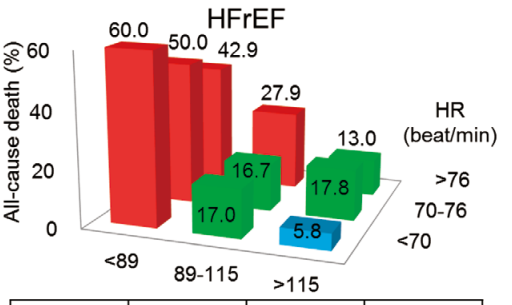
	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	1/2	11/71	28/195
Middle HR (70-76bpm)	1/3	7/40	17/131
Low HR (<70bpm)	1/5	9/85	28/195



	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	3/9	44/171	60/469
Middle HR (70-76bpm)	3/5	15/128	37/305
Low HR (<70bpm)	4/8	32/271	57/807



	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	1/4	22/123	55/438
Middle HR (70-76bpm)	0/0	8/91	28/292
Low HR (<70bpm)	2/8	16/207	68/828



	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	3/7	29/104	25/192
Middle HR (70-76bpm)	4/8	12/72	23/129
Low HR (<70bpm)	3/5	23/112	14/226

Figure 5. Comparison of the mortality rate according to subgroups for age (**A**), and heart failure with and without preserved ejection fraction (**B**).

89–115 mmHg, and high-risk = SBP <89 mmHg (Figure 1B).

Using these risk values of HR and SBP, we then performed the CART analysis for combined HR with SBP (Figure 1C). The CART analysis identified SBP as the first discriminator with the split value of 89 mmHg and the next spirit value was HR 70 beats/min. Thus, SBP <89 mmHg was strongly associated with higher mortality regardless of HR. The next split value was SBP 89–115 mmHg or >115 mmHg. The last split value was HR 70–76 beats/min or >76 beats/min. According to the mortality rate shown in Figure 2A, patients with SBP <89 mmHg and those with SBP 89–115 mmHg and with HR >76 beats/min were categorized as high risk (n=274) because the mortality of this group was >20% (red bars). The patients with SBP >115 mmHg and HR <70 beats/min were categorized as low risk with a mortality rate <10% (n=1,131, blue bar). The remaining patients were categorized as middle risk with similar mortality (n=1,624) (green bars). Therefore, we divided the patients into 3 groups as shown in Figure 2B.

The baseline characteristics of each group are shown in Table 1. The low-risk group was characterized by older age, more males, more ischemic etiology and lowest NYHA class and, by definition, by highest SBP and lowest HR. In contrast, the middle- and high-risk groups were characterized by higher NYHA class, higher prevalence of history of HF admission, more females, and lower prevalence of hypertension and ischemic HF. The high-risk group also had the highest concentrations of B-type natriuretic peptide and BUN, the lowest BMI and LVEF and higher use of diuretics and digitalis compared with the other groups. The prevalence of β-blocker use was comparable among the 3 groups. The prevalence of sudden death and death because of HF in the high-risk group was higher than that in the middle- and low-risk groups (Table S1).

Prognostic Impact of the Risk Model for All-Cause Death

Kaplan-Meier curves showed that the high- and middle-risk groups had significantly higher mortality as compared with the low-risk group (Figure 3A). Figure 3B shows the results of multivariable Cox hazard regression analysis for all-cause death. As compared with the low-risk group (reference), in the unadjusted model (a), the hazard ratio (95% confidence interval [CI]) for the middle-risk and high-risk groups was 1.74 (1.35–2.25) and 4.01 (2.91–5.52), respectively (both P<0.001), while in the model (c), the hazard ratio (95% CI) for all-cause death of the middle- and high-risk groups was 1.59 (1.21–2.08) and 2.75 (1.93–3.92), respectively.

Figure 4 shows the prognostic influence of β-blocker therapy. Although the number of the patients with SBP <89 mmHg was small regardless of therapy, the incidence of all-cause death did not statisticaly differ among the subgroups. Table 2 shows the results of subgroup analysis for all-cause death. The high- and middle-risk groups had higher hazard ratios for all-cause death regardless of sex, previous history of PAF, ischemic etiology, or β-blocker therapy. In contrast, age ≥70, diabetes, and LVEF <50% were associated with high mortality in the high-risk group (hazard ratio 7.47 (95% CI 4.01–13.93, P<0.001), 4.97 (95% CI 3.42–7.21, P<0.001) and 6.85 (95% CI 3.72–12.61, P<0.001) respectively) with a significant P value for interaction (0.03, 0.04 and 0.008, respectively) (Table 2, Figure 5).

Discussion

The novel findings of the present study using CART analysis of the CHART-2 registry were that SBP <89 mmHg, HR >70 beats/min, and SBP <115 mmHg were the primary, secondary and tertiary discriminators, respectively, for all-cause death in CHF patients in SR, and that HR control to <70 beats/min and BP control to ≥115 mmHg were associated with better outcomes in those patients. To the best of our knowledge, this is the first study to demonstrate in a large-scale cohort study the usefulness of combined risk stratification of HR and SBP in CHF patients in SR.

Importance of HR Reduction in HF

In the present study, CART analysis identified HR<70 beats/min as the primary discriminator for all-cause death in CHF patients with SR because those with HR ≥70 beats/min had an increased mortality by 1.7-fold in comparison with those with <70 beats/min (8.7% vs. 14.8%). This finding is consistent with that of the BEAUTIFUL subanalysis,[23] which revealed that HR >70 beats/min was associated with 34% increase in cardiovascular death and 53% increase in admission for HF compared with HR <70 beats/min in patients with CAD and left ventricular dysfunction (LVEF <40%).[23] The recent Guidelines of the ESC recommend that ivabradine should be considered to reduce the risk of HF hospitalization in patients in SR and with reduced LVEF (≤35%) when HR remains ≥70 beats/min with persistent symptoms (NYHA class II–IV) despite evidence-based medical treatment.[8] Furthermore, the European Medicines Agency has recently approved ivabradine for use in CHF patients with HR >75 beats/min or those with contraindication to β-blockers or β-blocker intolerance.[8] Thus, the present finding might be the first supporting evidence for the recommendation of the ESC Guidelines obtained from real-world clinical practice.

SBP in HF

The present study also demonstrated that even if HR is <70 beats/min, SBP <89 mmHg could be associated with a poor prognosis, supporting that SBP <89 mmHg is the primary discriminator for all-cause death regardless of HR status. It is widely known that higher SBP is an adverse prognostic marker in the general population[9] and in patients with cardiovascular diseases,[10,11] but not in CHF patients,[12,13] a finding that is known as "reverse epidemiology" in these patients.[13] Thohan and Little suggested that a SBP/diastolic BP (DBP) target of 110/70 mmHg may be a reasonable goal for the management of CHF.[24] However, it remains to be clarified whether low SBP is associated with increased mortality in CHF patients. In this context, the present study clearly demonstrated that CHF patients with SBP <89 mmHg had the highest risk of mortality regardless of their HR values, and that those with SBP 90–115 mmHg generally have a higher risk than those with SBP >115 mmHg (Figures 1, 2A,B). Concurrently, our results also demonstrated that different cut-off values of HR were associated with reduced mortality; <76 beats/min for patients with SBP 89–115 mmHg and <70 beats/min for those with SBP >115 mmHg (Figure 2A,B). Thus, it could be recommended that the mortality risk of CHF patients are stratified for the combination of SBP and HR. In the present study, we defined patients with SBP <89 mmHg regardless of HR values, or those with SBP 89–115 mmHg with HR >76 beats/min, as the high-risk group with a mortality rate >20% (hazard ratio 2.75) (Figure 3B). Interestingly, the hazard ratio for this high-risk group was increased especially in patients aged >70 years, those with diabetes, or with LVEF <50% (hazard ratios 7.47, 4.97 and 6.85, respectively), indicating the importance of combined risk stratification of HR and SBP in CHF patients (Table 2, Figure 5).

HR Reduction for Patients With Lower SBP

In the present study, HR <70 beats/min was shown to be associated with better prognosis in patients with SBP ≥89 mmHg, but

not in those with SBP <89 mmHg. Thus, although HR reduction is an important therapeutic strategy in CHF patients, we should simultaneously pay attention to SBP, as suggested in the COPERNICUS trial.[25] In the present study, hazard ratios for all-cause mortality were comparable in each risk group between patients with and those without β-blocker treatment (Table 2). Furthermore, mortality rates of patients with SBP <89 mmHg and β-blocker therapy were equivalent or even higher than those of patients with SBP <89 mmHg or 89–115 mmHg and without β-blocker therapy (Figure 4), suggesting that treatment with β-blockers for CHF patients with low SBP was not necessarily associated with reduced mortality, although caution in interpreting this observation is needed. In this context, ivabradine may be an ideal drug for CHF patients with lower SBP and lower LVEF as recommended in the ESC Guidelines,[8] because ivabradine is a pure HR-lowering agent in patients in SR[6,7] and does not affect SBP, myocardial contractility or intra-cardiac conduction.[23] However, it has recently been demonstrated in the SHIFT trial that the effects of ivabradine are prominent in patients with HR >77 beats/min but not so significant in those with HR <77 beats/min.[7] Thus, the potential benefits of HR reduction therapy for high-risk CHF patients remain to be further examined.

HR and SBP in HF Patients With Diabetes

In the present study, HF patients with diabetes in the high-risk group had significant higher hazard ratio for all-cause death compared with those without diabetes. In the present study, patients in the high-risk group had lower DBP levels (Table 1) and HF patients with diabetes had a higher prevalence of ischemic etiology compared with those without diabetes (66.7% vs. 41.5%, P<0.001). It has been reported that lower levels of BP, particularly DBP, are associated with decreased coronary perfusion and coronary vascular events in patients with CAD.[26–28] In the present study, however, the event rates of death from myocardial infarction or cardiovascular death were not high enough to detect statistical significance between patients with or without diabetes in the high-risk group. Thus, further study is warranted to reveal the association between diabetes and HR or BP for mortality in CHF patients.

Study Limitations

First, the present results came from analysis of data obtained at entry of subjects to the study and we did not take into consideration possible changes in SBP, HR and other covariates during the follow-up period. Second, both the prescription rate and dose of β-blocker were relatively low compared with other studies that enrolled patients hospitalized with HF.[15,29] In the present study, however, most of the patients (79.5%) were registered on an outpatient basis, and 65.7% had preserved LVEF (≥50%) and 52.9% did not have prior history of hospitalization for HF. These factors might have influenced the relatively low prescription ratio of β-blockers in the present study. Third, the primary design of the present study did not cover chronic lung disease, which has been recognized as an important prognostic factor of HF.[30] Finally, because CHART-2 is an observational study in real-world practice, the present results need to be carefully interpreted, especially when the effects of treatment are evaluated.

Conclusions

The present study demonstrates that SBP <89 mmHg regardless of HR values or SBP 89–115 mmHg and HR >76 beats/min is associated with poor prognosis in CHF patients in SR, indicating the importance of combined risk stratification of HR and SBP in the management of CHF patients.

Acknowledgments

We thank all members of the Tohoku Heart Failure Society and the staff of the Departments of Cardiovascular Medicine and Evidence-Based Cardiovascular Medicine, Tohoku University Graduate School of Medicine for their kind contributions (Appendix S1). This study was supported in part by Grants-in-Aid from the Ministry of Health, Labour, and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Disclosures

The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo Co, Ltd (Tokyo, Japan), Bayer Yakuhin, Ltd (Osaka, Japan), Kyowa Hakko Kirin Co, Ltd (Tokyo, Japan), Kowa Pharmaceutical Co, Ltd (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co, Ltd (Osaka, Japan), and Nippon Boehringer Ingelheim Co, Ltd (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd (Osaka, Japan), Daiichi Sankyo Co, Ltd (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan).

References

1. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005; **352:** 1951–1958.
2. Fujiura Y, Adachi H, Tsuruta M, Jacobs DR Jr, Hirai Y, Imaizumi T. Heart rate and mortality in a Japanese general population: An 18-year follow-up study. *J Clin Epidemiol* 2001; **54:** 495–500.
3. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005; **26:** 967–974.
4. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; **50:** 823–830.
5. Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am J Cardiol* 1986; **57:** 43F–49F.
6. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet* 2010; **376:** 875–885.
7. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010; **376:** 886–894.
8. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; **14:** 803–869.
9. Hozawa A, Ohkubo T, Kikuya M, Ugajin T, Yamaguchi J, Asayama K, et al. Prognostic value of home heart rate for cardiovascular mortality in the general population: The Ohasama study. *Am J Hypertens* 2004; **17:** 1005–1010.
10. Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. *BMJ* 2001; **323:** 75–81.
11. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903–1913.
12. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, et al. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart* 2009; **95:** 56–62.
13. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004; **43:** 1439–1444.
14. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344:** 1651–1658.
15. Kato N, Kinugawa K, Imamura T, Muraoka H, Minatsuki S, Inaba T, et al. Trend of clinical outcome and surrogate markers during titration of β-blocker in heart failure patients with reduced ejection fraction. *Circ J* 2013; **77:** 1001–1008.

16. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al. The Euro Heart Failure Survey programme: A survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* 2003; **24:** 464–474.
17. Fowler MB, Lottes SR, Nelson JJ, Lukas MA, Gilbert EM, Greenberg B, et al. Beta-blocker dosing in community-based treatment of heart failure. *Am Heart J* 2007; **153:** 1029–1036.
18. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H; CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the CHART-2 Study. *Circ J* 2011; **75:** 823–833.
19. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013 June 5, doi:10.1161/CIR.0b013e31829e8807 [Epub ahead of print].
20. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 1971; **285:** 1441–1446.
21. Breiman L, Friedman J, Stone JC, Olshen AR. Classification and regression trees. Monterey, CA: Wadsworth, Inc, 1984.
22. R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/. (accessed December 13, 2012).
23. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. *Lancet* 2008; **372:** 817–821.
24. Thohan V, Little WC. Is a higher blood pressure better in heart failure? *Heart* 2009; **95:** 4–5.
25. Rouleau JL, Roecker EB, Tendera M, Mohacsi P, Krum H, Katus HA, et al. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *J Am Coll Cardiol* 2004; **43:** 1423–1429.
26. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006; **144:** 884–893.
27. Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: Exactly how essential? *J Am Coll Cardiol* 2009; **54:** 1827–1834.
28. Sakata Y. Is "strict" conventional therapy enough for the treatment of coronary artery disease? *Circ J* 2011; **75:** 2046–2047.
29. Tsuchihashi-Makaya M, Kinugawa S, Yokoshiki H, Hamaguchi S, Yokota T, Goto D, et al. Beta-blocker use at discharge in patients hospitalized for heart failure is associated with improved survival. *Circ J* 2010; **74:** 1364–1371.
30. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C, et al. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail* 2010; **12:** 685–691.

Supplementary Files

Supplementary File 1

Table S1. Modes of death in the present study of patients with chronic heart failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study

Appendix S1. Organization of the CHART-2 study

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-13-0725