Letter to the Editor

Estimation of nocturnal cardiac output by automated analysis of circulation time derived from polysomnography

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ARTICLE INFO

To the Editors;

Two-thirds of heart failure (HF) patients are reportedly accompanied by comorbid sleep disordered breathing (SDB) [1]. Pulmonary congestion, low cardiac output and enhanced ventilatory response to carbon dioxide in HF have been observed to cause Cheyne–Stokes respiration [2,3]. Aside from the above, fluid accumulation and nocturnal rostral fluid shift may also predispose to obstructive sleep apnea in this particular group [4]. A community-based cohort study has shown that comorbid obstructive sleep apnea is associated with an increase in the risk of death in patients with HF [5]. Several existing non-randomized studies have suggested that treatment with continuous positive airway pressure improved the prognosis of such patients [5,6].

With the spread of awareness of these mutual relationships between SDB and HF, sleep study has become one of the most fundamental examinations in current HF management [7] and a large number of polysomnography studies are carried out on HF patients every year for this very reason. Among the data obtained in polysomnography study, the lag time from the start of re-breathing to the rising point of pulse oximetric saturation (SpO$_2$) during periodic breathing was reported to significantly correlate to the parameters of cardiac function [8,9]. Namely, the lag time from the lungs to the fingertips (lung-to-finger circulation time (LFCT), Fig. 1) is expected to lengthen in patients with lower cardiac output, and this relationship has a strong possibility of being used as an indicator of cardiac function in the subjects.

However, past studies conducted through the use of polysomnography have been far from satisfactory from the standpoint of daily clinical use. First, researchers had to manually and repeatedly measure numerous LFCTs from the long readout of a whole night of recorded polysomnography. Second, the precise causal association between cardiac output and LFCT was undetermined, even though LFCT is theoretically expected to correlate to the reciprocal value of cardiac output. Hence, we set out to develop a novel algorithm that could automatically and continuously detect LFCT from polysomnography data in an attempt to better clarify the relationship between LFCT and cardiac output.

The outlines of the algorithm detecting LFCT are illustrated in Fig. 1. The algorithm begins by fully rectifying the respiratory airflow signal, which then has a low-pass filter applied to it. Thereby, the resultant shape of the converted rectified airflow wave becomes more similar to that of the fingertip SpO$_2$ waveform. LFCT is then determined by a cross correlation analysis between the modified air-flow signal and the SpO$_2$ signal. This calculation can be automatically repeated every 2 min through to the end of the data collection period. Once the series of LFCT readouts are obtained, the algorithm automatically removes unreliable values and outliers.

As LFCT is expected to be shorter in smaller subjects in terms of height if they have similar cardiac output, we adopted the use of the measured cardiac index (CI), which is standardized by body surface area, for the values that were to be compared to those of the LFCT. Once again applying this algorithm, we performed following study to determine the relationship between LFCT and CI in 31 consecutive stable HF patients, who were admitted to our cardiovascular department due to various underlying cardiac diseases that required a right-sided standard cardiac catheterization: ischemic heart disease (n = 14), valvular heart disease (n = 6), cardiomyopathy (n = 4) and others (n = 7) (Table 1). The study protocol was approved by the institutional ethics committee, and conducted in strict accordance with the Helsinki Declaration. Cardiac output was measured principally by the standard technique (Fick's method) during the right-sided catheterization.

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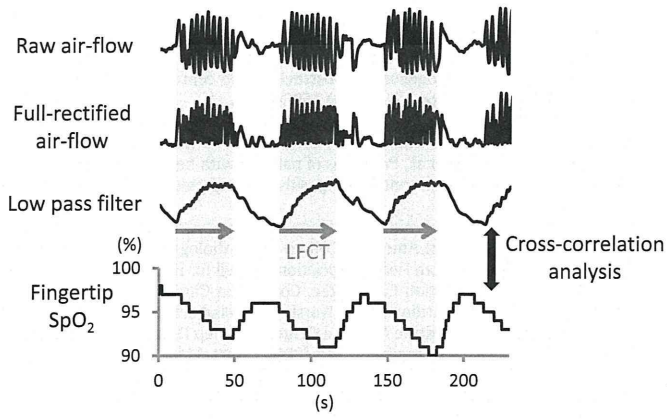E-mail address: shinando@sleep.med.kyushu-u.ac.jp (S. Ando).

Fig. 1. Outlines of the algorithm automatically detecting lung-to-finger circulation time (LFCT). Respiratory airflow and SpO$_2$ in a patient with Cheyne–Stokes respiration are shown. LFCT is defined as the lag time from the start of re-breathing to the rising point of SpO$_2$. First, the algorithm full-rectified airflow and applying a 1st order low-pass filter onto that without phase delay to attain a similar waveform to that of fingertip SpO$_2$. After preparing respiratory signal, the algorithm determined LFCT using a cross correlation analysis between respiratory signal and SpO$_2$. LFCT: lung to fingertip circulation time.

Table 1
Patient characteristics.

Age	66.7 ± 10.1	(y)
Male	61	(%)
Ischemic heart disease	45	(%)
3% ODI	19.1 ± 13.4	(/h)
LV ejection fraction	49.4 ± 15.3	(%)
BNP[a]	288 ± 303	(pg/ml)
PAW pressure	9.5 ± 5.2	(mm Hg)
Cardiac index	2.52 ± 0.51	(L/min/m^2)

[a] Data of 3 patients were not available. ODI: oxygen desaturation index, LV: left ventricle, BNP: brain natriuretic peptide, PAW pressure: pulmonary artery wedge pressure.

Portable polysomnography (SAS-2100 Nihon-Kohden Corp, Japan) was performed within 3 days of the catheterization.

After we confirmed that the algorithm had detected appropriate LFCT values compared with manually measured LFCT (RMSE of auto-detection vs. manual detection: 2.3 ± 1.9 s) in a representative patient, we averaged all the overnight LFCTs to yield one mean value for each patient, and then compared them to the respective individual's CI. As shown in Fig. 2, the overnight mean LFCT values significantly correlated to the measured CI ($R^2 = 0.44$, $p < 0.001$). We approximated the relationship to the hyperbolic function (Fig. 2, left), and calculated an estimated CI from each obtained LFCT. The RMSE of the estimated CI vs. the actual measured CI was limited to 0.33 ± 0.23 L/min/m^2, which we believe would be acceptable for clinical use. The nocturnal trend of LFCT and CI was clearly observed, as well as apnea/hypopnea events – as shown in Fig. 2, right – by overlaying this analysis on the polysomnographic data.

This study showed for the first time the feasibility of this newly-developed algorithm, and introduced an easy-to-use approach for automated LFCT detection and CI estimation, by utilizing airflow and fingertip oxygen saturation data. Most importantly from this study's viewpoint, this novel technique could visually represent not only cardiac output at one specific point in the sleep period, but also its nocturnal trend without the need for any additional apparatus or specialist operator skill.

We are aware of at least a couple of variable factors that could derange CI estimation. First, the estimation may be affected by sleeping position (i.e. lateral or supine position) due to the position of elevation of the monitored fingertip relative to the heart, which would alter hydrostatic pressure. Second, contributing factors that may affect blood flow or its distribution, such as significant arterial stenosis or dialysis shunt in the monitored arm, may result in a misleading CI estimation.

This analysis can be routinely performed during or after every polysomnography, and could become a helpful tool for screening HF or evaluating the effects of treatment in the daily management of HF, though a further, larger-sized study is needed in order to validate the
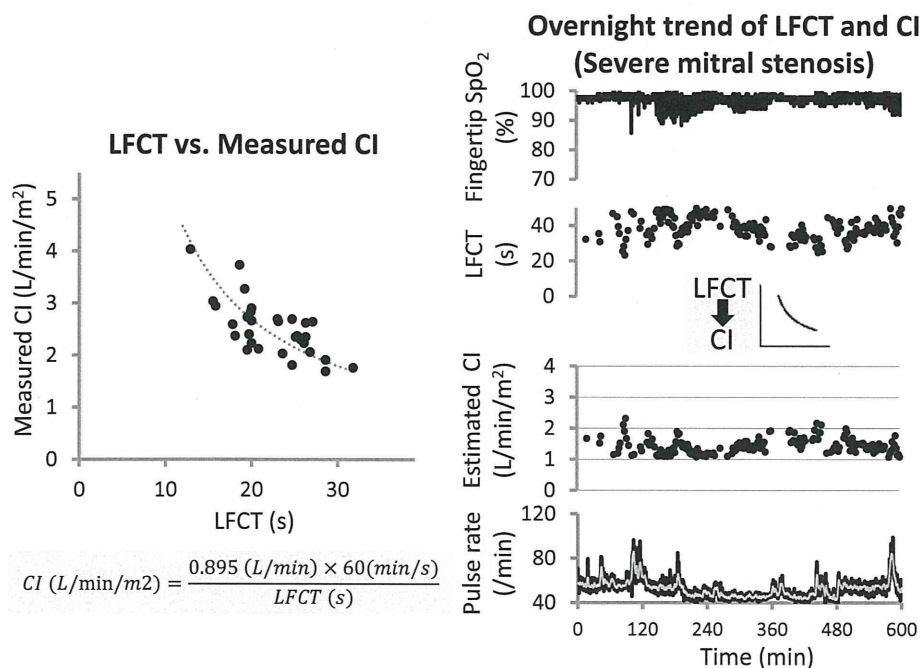

$$CI \ (L/min/m2) = \frac{0.895 \ (L/min) \times 60 (min/s)}{LFCT \ (s)}$$

Fig. 2. Relationship between lung-to-finger circulation time (LFCT) and cardiac index. Left panel: Automatically detected LFCT was significantly correlated to cardiac index ($R^2 = 0.44$, $p < 0.001$). The relationship was approximated to the hyperbolic function. Right panel: A representative overnight chart obtained from polysomnography data and our analysis in patients with severe mitral stenosis is demonstrated. LFCT was automatically derived from polysomnography data by our algorithm. Cardiac index was estimated by the identified hyperbolic function.

accuracy of this method in a wider range of the population with various cardiac diseases.

Conflict of interest

Acknowledgments

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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 –

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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.

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

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/m²)	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.
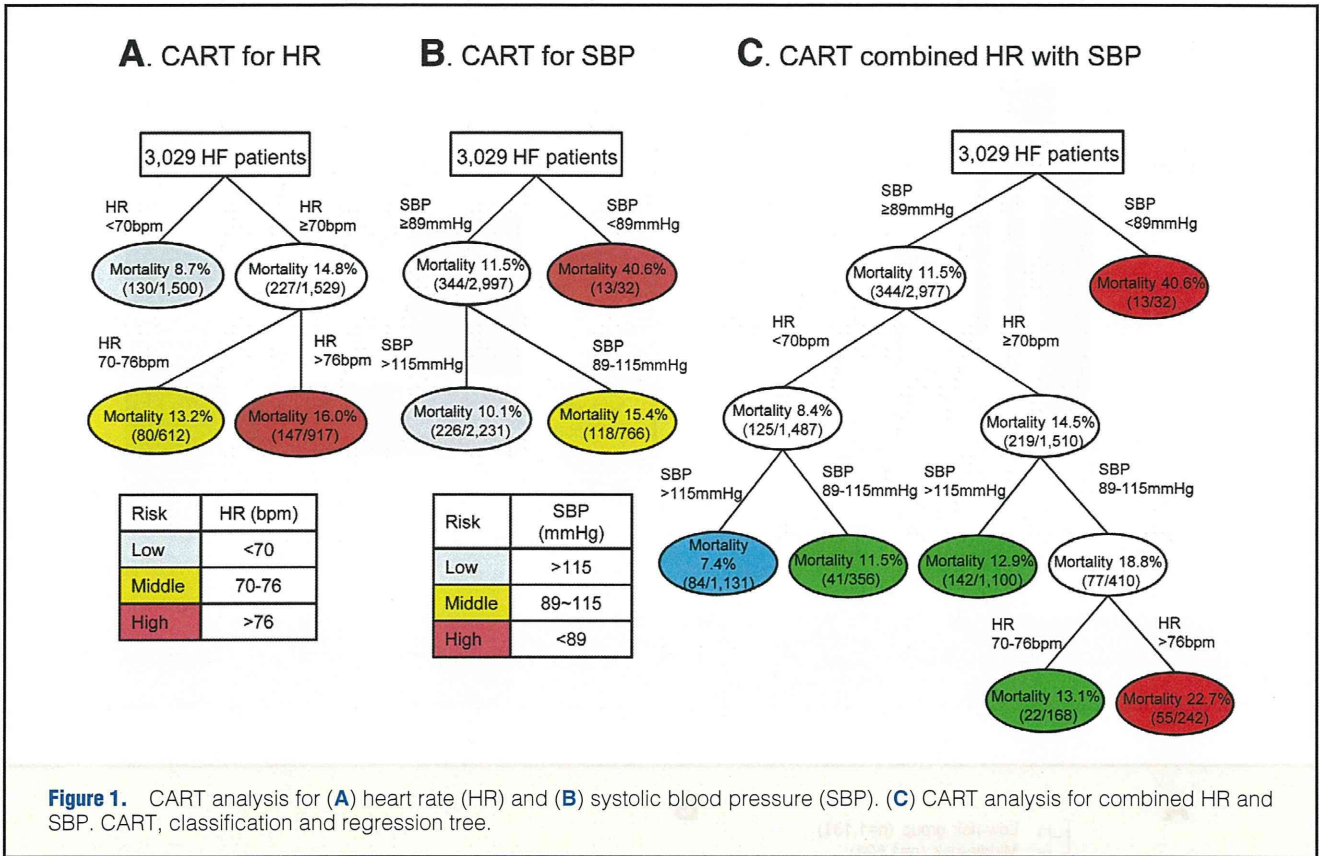
sured while seated after a 2–3-min rest. In the present study, we excluded asymptomatic patients in stage B (n=5,484) and patients with a pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy (n=486). We also excluded patients with chronic atrial fibrillation (n=1,079), those 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
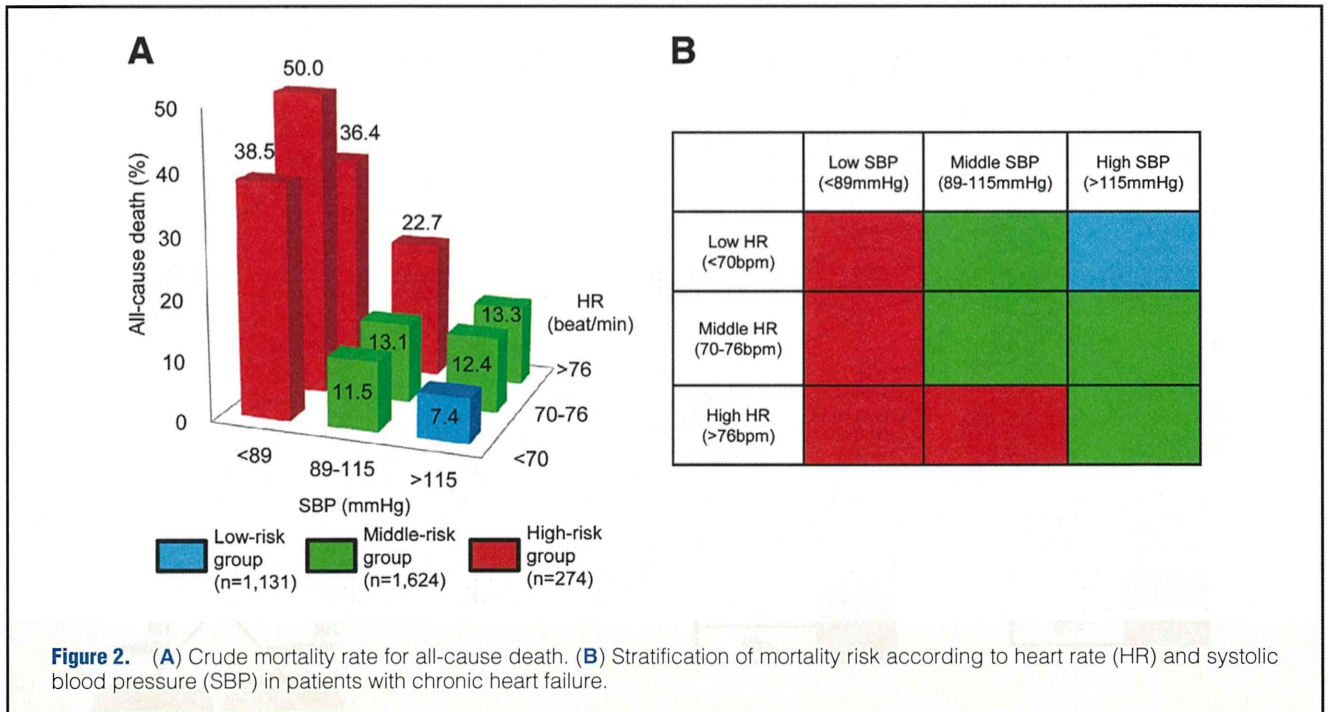
Figure 2. (**A**) Crude mortality rate for all-cause death. (**B**) Stratification of mortality risk according to heart rate (HR) and systolic blood pressure (SBP) in patients with chronic heart failure.
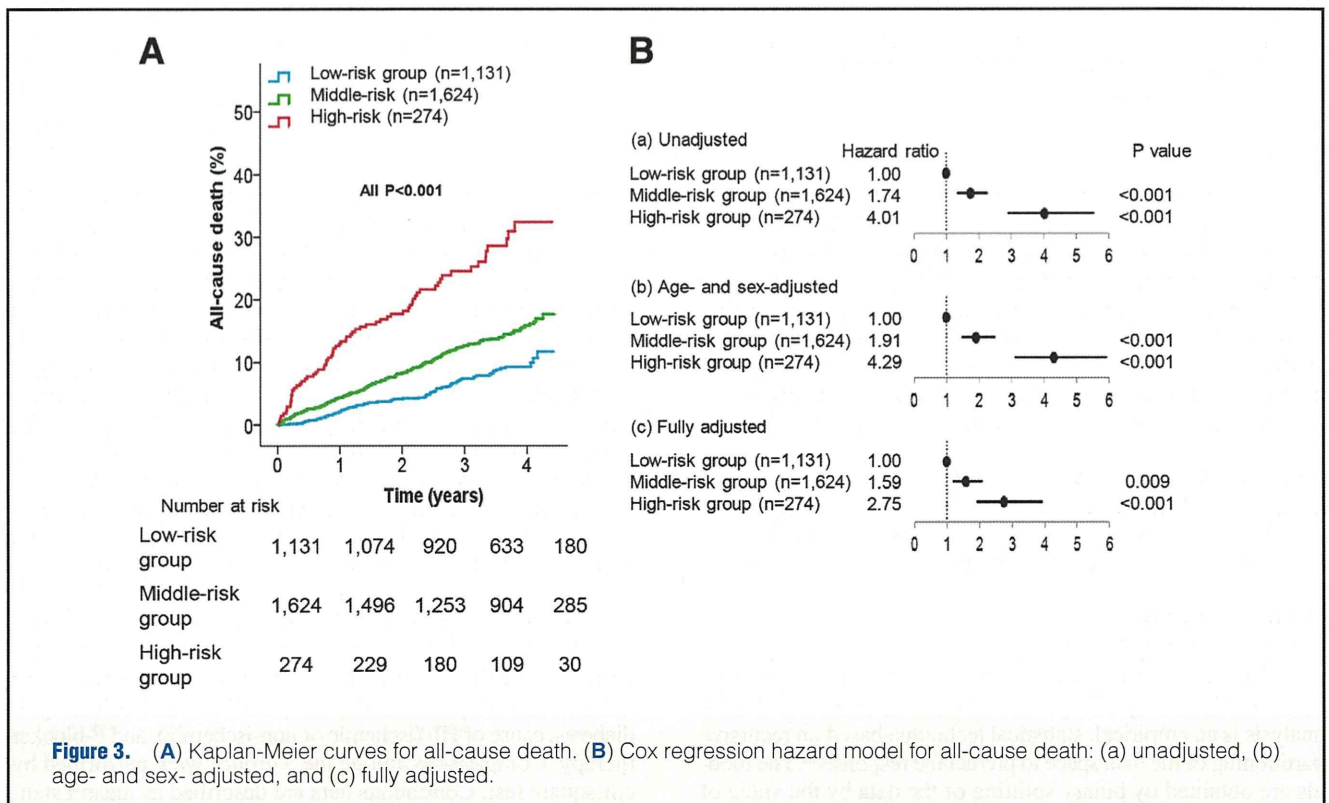
Figure 3. (**A**) Kaplan-Meier curves for all-cause death. (**B**) Cox regression hazard model for all-cause death: (a) unadjusted, (b) age- and sex- adjusted, and (c) fully adjusted.

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-

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

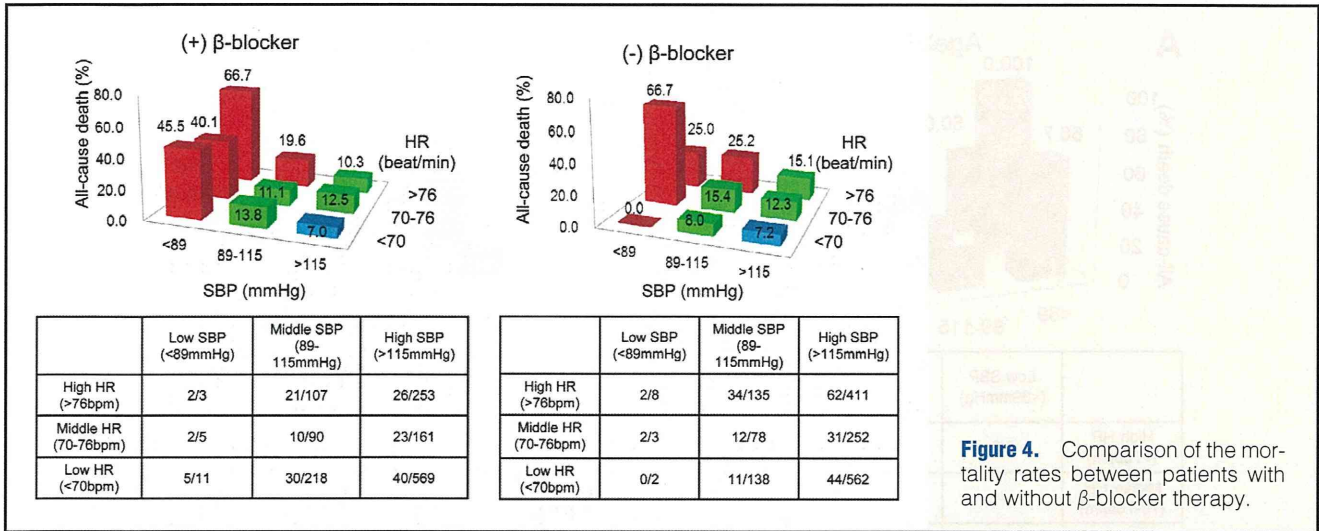| Category	HR	95% CI	P value	HR	95% CI	P value	P for interaction
		Male			Female		
Low-risk (reference)	1.00			1.00			
Middle-risk	1.66	1.24–2.23	<0.001	2.05	1.22–3.46	0.007	0.49
High-risk	3.79	2.59–5.53	<0.001	4.80	2.59–8.90	<0.001	0.52
		Age ≥70 years			Age <70 years		
Low-risk (reference)	1.00			1.00			
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

A

Age≥70

	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

Age<70

	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

B

(+) Diabetes

	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

(-) Diabetes

	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

C

HFpEF

	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

HFrEF

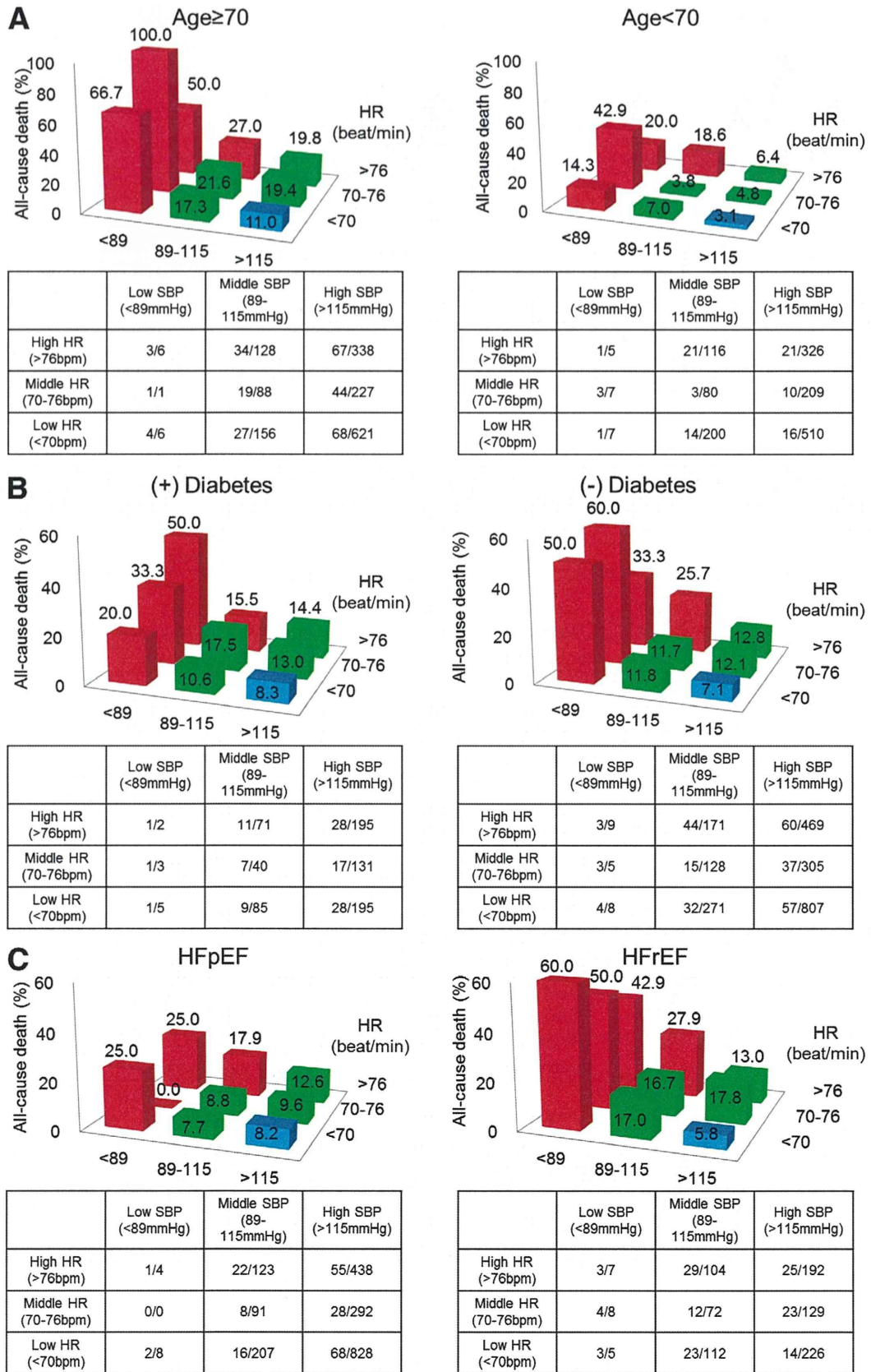|	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	3/7	29/104	25/192
Middle HR (70-76bpm)	4/8	12/72	23/129
Low HR (<70bpm)	3/5	23/112	14/226

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