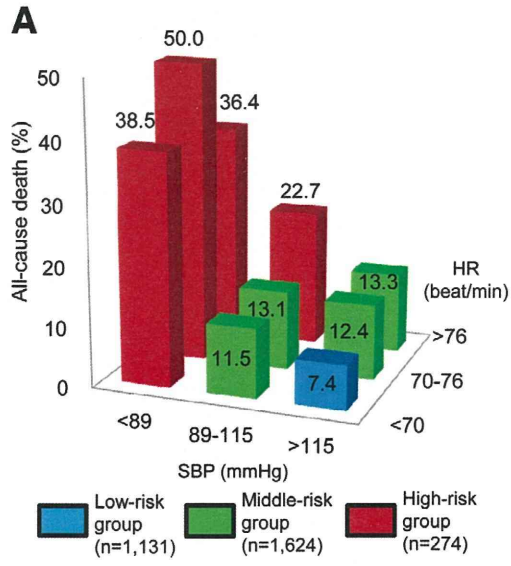


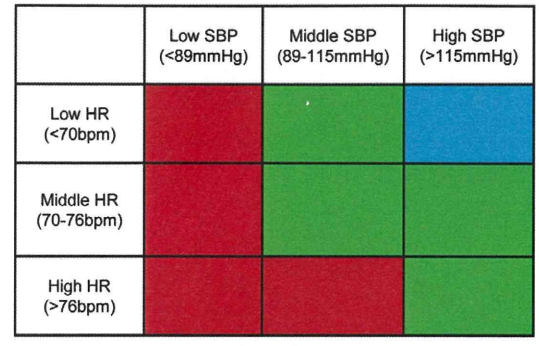
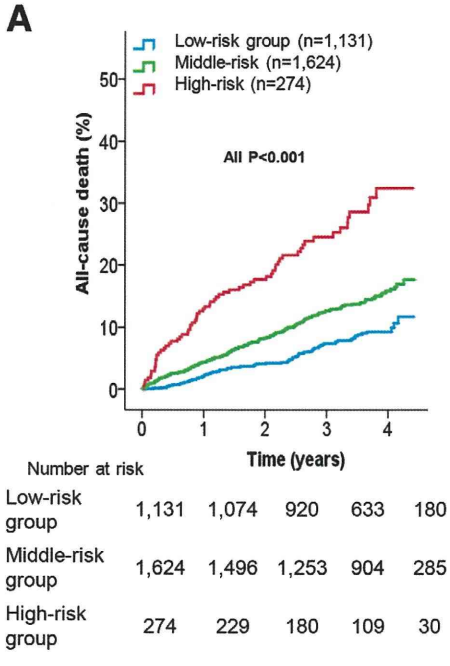


Figure 2. (**A**) Crude mortality rate for all-cause death. (**B**) Stratification of mortality risk according to heart rate (HR) and systolic blood pressure (SBP) in patients with chronic heart failure.



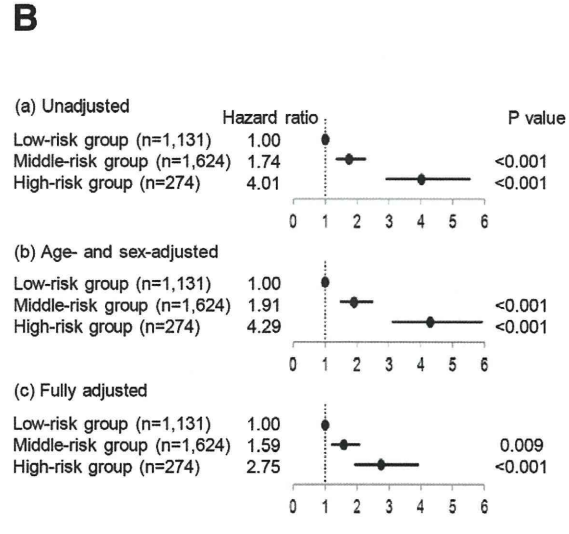
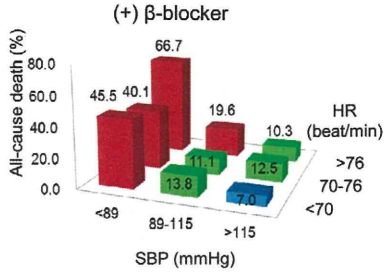


Figure 3. (**A**) Kaplan-Meier curves for all-cause death. (**B**) Cox regression hazard model for all-cause death: (a) unadjusted, (b) age- and sex- adjusted, and (c) fully adjusted.

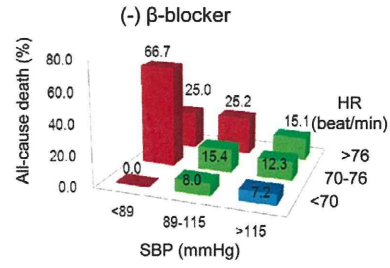
SBP and HR values were 128±19 mmHg and 71± 4 beats/min, respectively. The prevalence of β-blocker use was 47.5% at baseline. In the patients using β-blockers, the prescription ratio and mean doses of carvedilol, bisoprolol, and metoprolol were 79.7% and 7.5±1.5 mg, 8.6% and 4.0±1.8 mg, and 6.7% and 55.3±37.8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

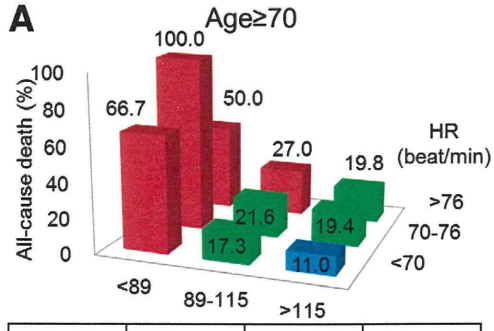
Figure 4. Comparison of the mortality rates between patients with and without β-blocker therapy.

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

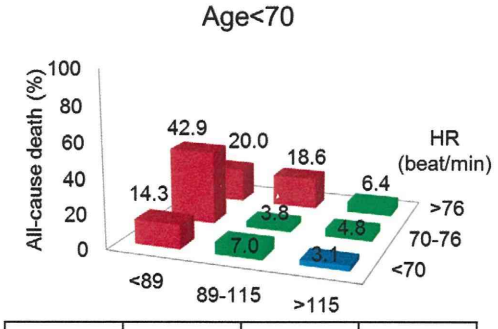
Category	HR	95% CI	P value	HR	95% CI	P value	P for interaction
	Male			Female			
Low-risk (reference)	1.00			1.00			
Middle-risk	1.66	1.24–2.23	<0.001	2.05	1.22–3.46	0.007	0.49
High-risk	3.79	2.59–5.53	<0.001	4.80	2.59–8.90	<0.001	0.52
	Age ≥70 years			Age <70 years			
Low-risk (reference)	1.00			1.00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

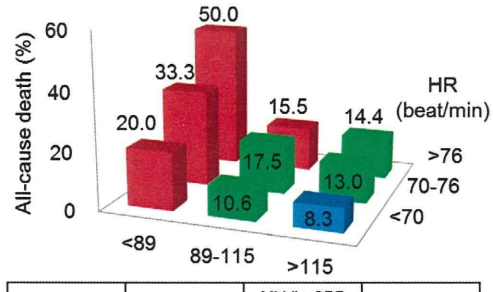
ond discriminator was the split value with HR of 76 beats/min (16.0% vs. 13.2% in mortality rate for HR >76 beats/min and HR 70–76 beats/min, respectively). Thus, we defined the risk values of HR as follows: low-risk = HR <70 beats/min; middle-risk = HR 70–76 beats/min, and high-risk = >76 beats/min (**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



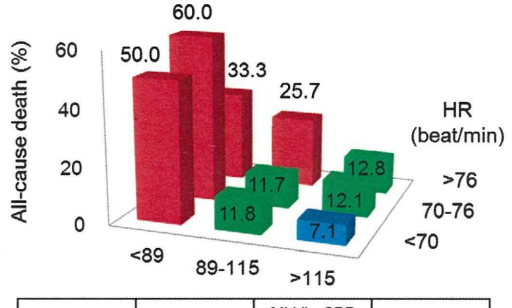
	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	3/6	34/128	67/338
Middle HR (70-76bpm)	1/1	19/88	44/227
Low HR (<70bpm)	4/6	27/156	68/621



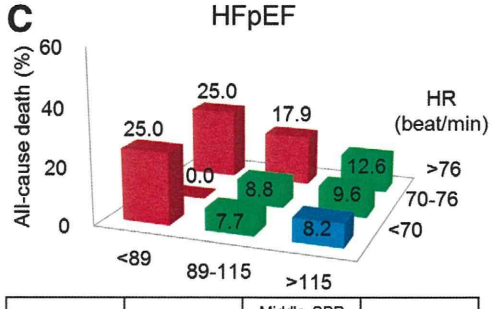
	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	1/5	21/116	21/326
Middle HR (70-76bpm)	3/7	3/80	10/209
Low HR (<70bpm)	1/7	14/200	16/510



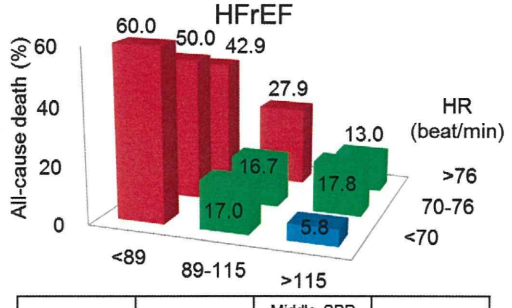
	Low SBP (<89mmHg)	Middle SBP (89-115mmHg)	High SBP (>115mmHg)
High HR (>76bpm)	1/2	11/71	28/195
Middle HR (70-76bpm)	1/3	7/40	17/131
Low HR (<70bpm)	1/5	9/85	28/195



	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.

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Disclosures

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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

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Epidemiology of Heart Failure in Asia

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Heart failure (HF) is a global epidemic in health care and a leading cause of mortality and morbidity worldwide. In Asian countries, causes of mortality and morbidity have shifted or have been shifting from infectious diseases and/or nutritional deficiencies to lifestyle-related diseases, such as cardiovascular disease, cancers and diabetes, in conjunction with the transition from developing to developed countries during the past decades (so-called "the epidemiologic transition"). Because the effect of this epidemiologic transition varies among countries, the etiology, prevalence, management and outcomes of HF also differ among the countries. Thus, we need to assemble and comprehensively analyze the available evidence to date for daily HF practice in Asia and to systematically conduct future epidemiologic approaches to establishing appropriate prevention programs against the burden of HF in Asia. This review article will briefly update the epidemiology of HF in Asia. (*Circ J* 2013; **77:** 2209–2217)

Key Words: Epidemiology; Heart failure; Prognosis

Heart failure (HF) is a global epidemic in health care and a leading cause of mortality and morbidity worldwide.[1] For example, approximately 5 million individuals have HF and over 550,000 are newly diagnosed as having HF every year in the United States.[2] However, despite sufficient epidemiologic data in developed countries (mainly in the North America and Europe), there is insufficient information of HF epidemiology in other regions, including Asia. Considering the differences in clinical and social backgrounds and management of HF across geographic regions, we need to assemble the available information regarding HF epidemiology in Asia and make use of it in our daily clinical practice. In this review, we will overview available cohort and epidemiologic studies for HF in Asia, particularly focusing on those from the South, East and South-East Asian countries.

Burden of HF in Asia

In Western and other developed countries, epidemics of obesity, diabetes mellitus (DM) and/or metabolic syndrome have become clinically evident, while the management of ischemic heart disease (IHD) and infection-related heart disease (ie, rheumatic heart disease [RHD]) has improved with the recent progress in medical and public health programs. These epidemics have resulted in a marked increase in cardiovascular disease (CVD) and subsequently HF, a final common pathway of CVD. In Asian countries, the causes of mortality and morbidity have been shifting from infectious diseases and/or nutritional deficiencies to lifestyle-related diseases, such as CVD, cancers, and DM, together with the transition from developing to developed countries during the past decades (so-called "the epidemiologic transition").[3] However, the effect of the epidemiologic transition varies not only among countries but also among regions, communities or ethnicities in the same country, making it difficult to generalize evidence obtained not only from Western countries but also from Asian countries. Considering the relatively younger age of patients with HF and larger population at risk for HF in Asian countries as compared with Western countries, the socioeconomic and clinical effects of HF are estimated to be particularly large in Asia. However, the lack of standard definition of HF and proper surveillance systems makes estimation of the HF burden in Asia difficult.[4]

Prevalence, Incidence and Estimated Number of HF Patients in Asia

There are a limited number of reports regarding the prevalence of HF in Asia (range, 1.26–6.7%).[5–8] A survey of the adult (aged ≥35 years) population in Xinjiang, China (n=8,459), reported that the prevalence of CHF was 1.26% (0.89%, 1.11% and 2.14% in the Han, Uygur and Hazakh populations, respectively), with an increase in the proportion with aging of 0.29%, 0.60%, 1.32%, 2.55% and 4.10% for the 35–44, 45–54, 55–64, 65–74, and ≥75 years age groups, respectively.[5] A single center-based study in Malaysia reported that the prevalence of HF among 1,435 acute medical admissions to the Kuala Lumpur General Hospital over the 4-week study period was 6.7%.[6] The age distribution of HF prevalence was 6.7%, 10.7%, 18.8%, 23.5%, 30.8% and 9.53% for age <40, 40–49, 50–59, 60–69, 70–79 and ≥80 years, respectively, in a hospital-based study in

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Table 1. Characteristics of HF Patients in Asian and Western Studies

Authors	Hamaguchi et al[37]	Kajimoto et al[42]	Shiba et al[25]	Shiba et al[10]	Shiba et al[10]	Shiba et al[10]
Cohort	JCARE-CARD	ATTEND	CHART-1	CHART-2	CHART-2	CHART-2
Registration year	2004–2005	2007–2011	2000–2004	2006–2010	2006–2010	2006–2010
Location, country	164 hospitals, Japan	52 hospitals, Japan	26 hospitals Tohoku district, Japan	24 hospitals Tohoku district, Japan	24 hospitals Tohoku district, Japan	24 hospitals Tohoku district, Japan
HF status	Worsening HF as a primary cause of hospitalization	Acute HF Syndrome	Stable HF	Stage A/B/C/D	Stage B	Stage C/D
No. of patients	2,549	4,841	1,154	10,219	4,654	4,735
Setting	Prospective, multicenter, observational	Prospective, multicenter, observational	Prospective, multicenter, observational	Prospective, multicenter, observational	Prospective, multicenter, observational	Prospective, multicenter, observational
Age, years, mean/median	70.7/–	73.0/–	67.8/–	68.2/–	67.3/–	68.9/–
Male sex, %	60	58	66.5	69.8	71.2	68.4
Etiology						
Coronary artery disease, %	32	31.2	25.3	53.1	51.0	47.1
Cardiomyopathy, %	–	–	–	13.6	10.0	19.5
Dilated cardiomyopathy, %	18.4	12.6	28.1	8.2	3.4	14.4
Hypertrophic cardiomyopathy, %	–	–	–	4	5.6	3.2
Valvular heart disease, %	27.7	19.4	28.1	19.8	19.1	23.8
Hypertensive heart disease, %	24.2	17.7	–	–	–	–
Congenital heart disease, %	–	–	–	–	–	–
Cor pulmonale, %	–	–	–	–	–	–
Comorbidity						
Hypertension, %	52.8	69.1	39.2	77.6	77.8	74.3
Diabetes mellitus, %	30	36.6	19.3	25.3	23.9	23.3
Prior myocardial infarction, %	27	–	–	29.9	31.2	33.8
Atrial fibrillation, %	35.2	–	39.3	–	–	–

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; HF, heart failure; RAS, renin-angiotensin system.

(**Table 1** continued the next page.)

Hubei Province, China (n=12,450),[9] and 3.1%, 29.0%, 33.7%, and 34.2% for age <40, 40–64, 65–74 and ≥75 years, respectively, in our Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-2 Study in Japan (n=10,219).[10]

In Japan, it is estimated that 1.0 million individuals have HF,[11,12] but the number of Japanese outpatients with left ventricular (LV) dysfunction is predicted to gradually increase from 979,000 in 2005 to 1.3 million by 2030.[12] In China, CVD is the leading cause of death and 4.2 million individuals have HF.[13,14] It has also been reported in China that 1.8 million individuals have congenital cardiac abnormalities and 500,000 new cases of HF are diagnosed every year.[15] Unfortunately, there is no reliable estimate in South Asia.[16] Huffman et al reported that the estimated number of patients with HF related to CHD, hypertension (HT), obesity, DM and RHD in 2000 in India ranged from 1.3 to 4.6 million.[17] However, it is also reported that, if the prevalence rate of HF in the USA in 2010 was applied, the prevalence of HF would be 1.87% in India and that the number of HF patients would be 22.7 million if this prevalence rate was applied to the Indian population of 1.21 billion in 2011.[16] Furthermore, Pillai and Ganapathi also estimated that the prevalence of HF is approximately 30 million in South Asia when extrapolating the same prevalence rate to the whole of South Asia (total population of 1.63 billion in 2011).[16] Thus, it is highly possible that Asian countries will experience a further burden of HF, requiring systematic approaches to surmount this epidemic.

Etiology and Baseline Characteristics of HF Patients in Asia

During the past decades, the epidemiologic transition has occurred in Asia in conjunction with aging of the population and changes in lifestyle.[8,16] **Table 1** is a comparison of the etiology and comorbidity of HF among representative studies in East Asian,[5–7,9,18–43] Asian-Pacific,[44] and Western populations.[45–48] In general, patients registered were relatively younger in China and Malaysia as compared with Japan, Taiwan and Korea

Authors	Youn et al[10]	Tseng CH[21]	Yin et al[19]	Yu et al[9]	Chong et al[6]	Atherton et al[44]	Atherton et al[44]	Nieminen et al[48]
Cohort	KorHF					ADHERE-AP	ADHERE	EHFS II
Registration year	2004–2009	2005	1993–2007	2000–2010	NA	2006–2008	2005–2006	2004–2005
Location, country	Korea	Taiwan	Single center, Beijing, China	12 hospitals Hubei Province, China	Single center, Kuala Lumpur, Malaysia	43 hospitals, 8 Asia-Pacific countries	307 hospitals, USA	133 hospitals, 30 European countries
HF status	Hospitalized HF (survivor), LVEF <40%	ICD-9-CM	ICD-9-CM	NA	NA	Acute decompensated HF	Acute decompensated HF	Acute HF
No. of patients	1,527	2,692	6,949	12,450	97	10,171	17,382	3,580
Setting	Prospective, multicenter, observational	Retrospective, random sampling of insurants (n=1,000,000)	Retrospective, review of hospital records	Retrospective, multicenter	Retrospective, screening of acute admissions (n=1,435)	Prospective, multicenter, observational	Prospective, multicenter, observational	Prospective, multicenter, observational
Age, years, mean/median	69/–	73.1/–	60.1/–	62.0/–	63.6	67/66	75/–	69.9/–
Male sex, %	56	54.5	62.7	57.6	62.9	57	49	61.3
Etiology								
Coronary artery disease, %	40.1	31.5	45	28.2	49.5	50	57	53.6
Cardiomyopathy, %	21.9	–	7.42	–	–	–	–	–
Dilated cardiomyopathy, %	–	–	–	26.6	4.1	–	–	19.3
Hypertrophic cardiomyopathy, %	–	–	–	–	–	–	–	–
Valvular heart disease, %	10.7	–	27.5	17.5 (rheumatic)	4.1	–	–	34.4
Hypertensive heart disease, %	–	–	–	–	18.6	–	–	–
Congenital heart disease, %	–	–	3.2	–	–	–	–	–
Cor pulmonale, %	–	–	9.61	–	–	–	–	–
Comorbidity								
Hypertension, %	42	38.9	38.7	31.5	49.5	64	77	62.5
Diabetes mellitus, %	31.4	28.1	18.3	–	28.9	45	45	32.8
Prior myocardial infarction, %	15.4	–	12.8	–	–	–	–	–
Atrial fibrillation, %	20.8	–	23.2	–	4.1	24	31	38.7

(**Table 1**). In the ADHERE-AP (Asian-Pacific) Study, it was reported that patients registered in South-East Asia were generally younger (median age: 53, 60, 61, 67 and 71 years for Philippines, Indonesia, Malaysia, Thailand and Singapore, respectively) as compared with those in East Asia (median age: 77 years for both Hong Kong and Taiwan) and in Australia (median age: 77 years).[44] It also has been demonstrated that patients who develop HF are relatively younger in South Asia, although scant information is available.[16] A report in 2008 from a single center in Pakistan reported that the mean age of HF patients (n=276) was 54.4 years,[49] compared with a mean age of 73.1±13.9 years in 500,000 US patients[50] and 68.2±12.3 years in 10,219 Japanese patients registered in the CHART-2 study.[10] Accordingly, HF patients are generally younger in China and South/South-East Asian countries as compared with those in East Asian and Western countries. Among the studies, the prevalence of male sex ranged between 50% and 70%, which was consistent with the Western studies (**Table 1**).

As the underlying etiology of HF in East and South-East Asia, coronary artery disease (CAD) had the highest prevalence, ranging from 28.2% to 53.1%, followed by valvular heart disease (VHD) and cardiomyopathy in China,[5,9,18–20] Malaysia,[6] Taiwan,[21] Hong Kong,[22,23] South Korea,[24] and Japan.[10,25–43] The prevalence of VHD ranged from 10.7% to 27.5% of HF patients in most countries except Malaysia, where the prevalence of VHD was relatively low as compared with that of the Euro-Heart Failure Survey II (EHFS II).[6] As a comorbidity, the prevalence of HT was highest, with a wide range from 31.5% to 77.8% in China,[5,9,18–20] Taiwan,[21] Hong Kong,[23] Malaysia,[6] and Japan.[10,25–43] In contrast, the prevalence of DM in Asia was 18.3–45.0%.[5–8,16–35]

In South Asia, in addition to CAD and HT, RHD is a major contributor to HF.[16] Although there are few major studies, a small study from India in 1999 (n=125) reported that RHD was the commonest underlying heart disease (52.8%), followed by ischemic and/or hypertensive heart disease (27.2%).[24] On the other hand, a study from Pakistan reported in 2007 that 77% was related to IHD among 196 HF patients with systolic HF.[25]

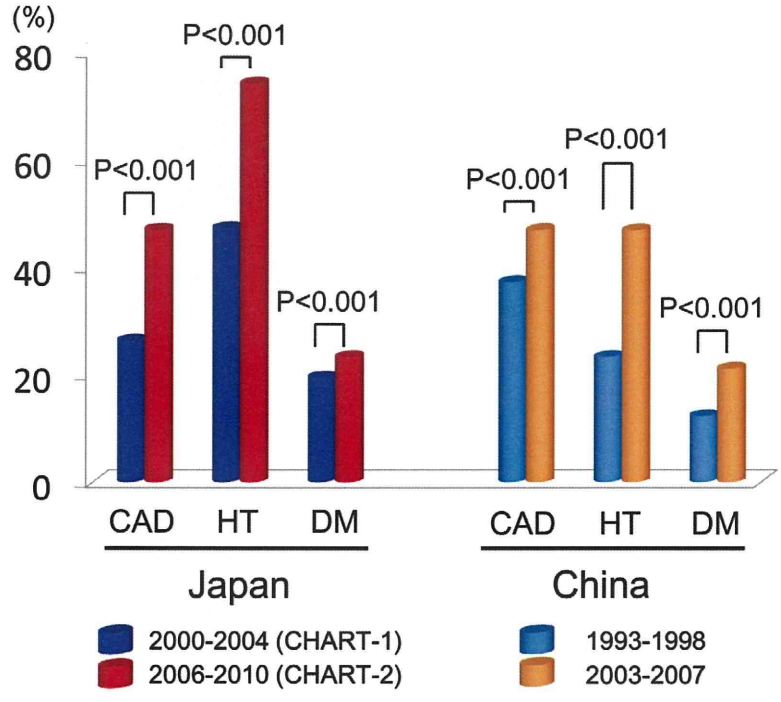

Figure 1. Recent trend towards ischemic etiology for heart failure in Asia. In both Japan (CHART studies)[10] and China,[18] the prevalence of coronary artery disease (CAD), hypertension (HT) and diabetes (DM) increased as a cause or comorbidity of heart failure.

In India, it is estimated that the number of patients aged 5–40 years with RHD at higher risk for HF development is at least 1.4 million,[51] although the incidence or prevalence of HF in RHD is unknown. Furthermore, the estimated number of children (0–15 years) with established congenital heart disease is 1.41 million in India, assuming an incidence of 4/1,000 live births for congenital heart diseases.[51] Because the risk of HF in patients with congenital heart disease increases with age, these estimates indicate that the number of adult patients with congenital heart disease is apparently huge in India, warranting a caution for a further burden of HF.[52] In addition, in India, the prevalence of chronic obstructive pulmonary disease (COPD) is 4.1% in adult subjects aged ≥35 years.[53] Considering the high prevalence of RHD, congenital heart disease and COPD in South Asia, it is highly possible that a considerable number of patients suffer from pulmonary hypertension and develop HF in this region.

Burden of Ischemic Etiology of HF in Asia

In North America, an increase in ischemic HF after acute myocardial infarction has been reported.[54,55] Our recent studies have also revealed an increasing trend towards ischemic etiology and comorbidities with DM and HT in Japanese HF patients.[10] The CHART-1 study, which enrolled 1,278 consecutive stable CHF patients between 2000 and 2005, revealed that the most prevalent etiology of HF was non-ischemic cardiomyopathy (28.6%) and CAD accounted for 25.4% of the total HF patients.[10,24–27] This prevalence of ischemic HF was considerably low as compared with Western studies.[45–48] In contrast, the CHART-2 study, which enrolled 10,219 consecutive patients with symptomatic HF, structural heart disease without HF and CAD between 2006 and 2010,[10,29–31] revealed that the prevalence of CAD, HT and DM in Stage C/D HF patients (n=4,735) increased to 47.1%, 74.3%, and 23.3%, respectively, demonstrating the rapid trend of westernization of etiology and clinical characteristics of HF patients in Japan (**Figure 1**).[10] A report from the Chinese People's Liberation Army General Hospital in Beijing, China, also showed that the prevalence of CAD, HT, and DM were increased in patients with HF from 37.2%, 23.3%, and 12.3% in 1993–1998 to 46.8%, 46.7%, and 21.1% in 2003–2007, respectively.[18] These lines of evidence suggest a burden of ischemic etiology for HF in East Asia (**Figure 1**).[8] In South Asia, it is also possible that etiologies of HF have changed during the past several decades, but there is little information available.[16]

HF With Preserved Ejection Fraction in Asia

Recently, HF with preserved ejection fraction (HFpEF) was recognized as a new entity of HF.[56,57] It was previously considered that HFpEF accounted for less than half of HF cases, mainly based on reports derived from hospitalized HF studies.[34,56] However, together with acceptance of the concept and definition of HFpEF, as well as an actual increase in the prevalence of HFpEF over time,[57] it is currently recognized that HFpEF represents more than half of HF patients in Japan[10,29] and Western countries.[58–60] In our CHART-2 Study, the prevalence of HFpEF, defined as Stage C/D HF patients with LV ejection fraction (LVEF) ≥50% was 65.2% (3,086 of 4,735).[29] Owan et al[57] examined consecutive patients hospitalized with decompensated HF at Mayo Clinic Hospitals in Olmsted County, Minnesota, USA, from 1987 through 2001. They found that the proportion of HFpEF cases increased over time, from 38% in 1986–1990 to 54% in 1996–2001.[57] This increase in HFpEF could be explained, at least in part, by a trend in the epidemiologic transition, as HFpEF patients are generally characterized by higher age, more females and a history of HT or atrial fibrillation and a lower prevalence of CAD,[29,34,56–60] all of which are highlighted during the epidemiologic transition. Thus, it is highly possible that the prevalence of HFpEF is also increasing in Asian countries, despite a lack of precise epidemiologic