Table 2. Prevalence of Medical Treatment 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	ADHF	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
RAS inhibitor, %	76.5	–	69.1	67.4	62.8	72.3
ACEI, %	37.4	14.5	–	34.9	28.1	44.6
ARB, %	44.4	34.6	–	33.6	35.9	31.8
β-blocker, %	48.6	33.4	24.7	40.4	34.2	49.0
Diuretic, %	–	–	–	32.6	16.6	52.9
Aldosterone antagonist, %	41.6	19.5	–	–	–	–
Calcium-channel blocker, %	25.2	28.6	–	45.3	48.1	38.7
Digitalis, %	30.9	12.6	–	15.9	10.4	23.5

*Limited to discharged patients.
ADHF, acute decompensated heart failure. Other abbreviations as in Table 1.

Authors	Youn et al[24]	Tseng CH[21]	Yu et al[9]	Atherton et al[44]	Atherton et al[44]	Nieminen et al[48]
Cohort	KorHF			ADHERE-AP	ADHERE	EHFS II
Registration year	2004–2009	2005	2000–2010	2006–2008	2005–2006	2004–2005
Location, country	Korea	Taiwan	12 hospitals, Hubei Province, China	43 hospitals, 8 Asia-Pacific countries	307 hospitals, USA	133 hospitals, 30 European countries
HF status	*Hospitalized HF, LVEF <40%	ICD-9-CM	NA	ADHF	ADHF	Acute HF
No. of patients	1,527	2,692	12,450	10,171	17,382	3,580
RAS inhibitor, %	68.0	50.8	–	63	67	80
ACEI, %	45.6	–	50.7	–	–	–
ARB, %	24.5	–	–	–	–	–
β-blocker, %	40.9	25.4	44.1	41	74	61
Diuretic, %	–	76.3	68.8	–	–	–
Aldosterone antagonist, %	37.5	–	–	–	–	–
Calcium-channel blocker, %	–	29.3	–	–	–	–
Digitalis, %	–	32.4	47.5	34	26	31

data. Indeed, elderly, female and/or hypertensive HFpEF patients would be one of the main therapeutic targets in Asia in the near future.

Management of HF Patients

Table 2 summarizes the drug treatments in representative HF studies in Asia. Diuretics were the most commonly used medication, followed by renin-angiotensin system (RAS) inhibitors and β-blockers. The prevalence of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) use was almost comparable. The prevalence of treatment with β-blocker varied among Japan, China, Taiwan, and Malaysia, with the highest percentage in Japan (49%) and the lowest in Malaysia (9.3%). In the CHART studies, both the usage of RAS inhibitors and β-blockers for Stage C/D HF patients increased from 2000–2005 to 2006–2010, while that of loop diuretics and digitalis decreased (Figure 2).[10] In South Asian countries, the most commonly used medications are β-blockers, ACEI/ARB, diuretics and aldosterone antagonists,[16] although there are few reliable data.

Implantable cardioverter defibrillators (ICD) and/or cardiac resynchronization therapy (CRT) are indicated for patients with chronic HF to prevent sudden cardiac death and/or improve LV function. However, both therapies are likely under-used in Asian countries, particularly in South Asia, because of limitations of accessibility and affordability. Although data from reliable, large-scale studies are scarce in Asia, 2.9% of Stage C and 15.8% of Stage D patients with HF had received ICD and/or CRT at the time of registration in our CHART-2 Study and are currently being followed up.[10]

Clinical Outcomes of HF Patients in Asia

Table 3 summarizes the clinical outcomes of HF patients in Asia. As for acute decompensated heart failure (ADHF), the ATTEND Registry (n=4,841) revealed that the in-hospital mortality rate was 6.4% (n=311), with 218 cardiac (70%) and

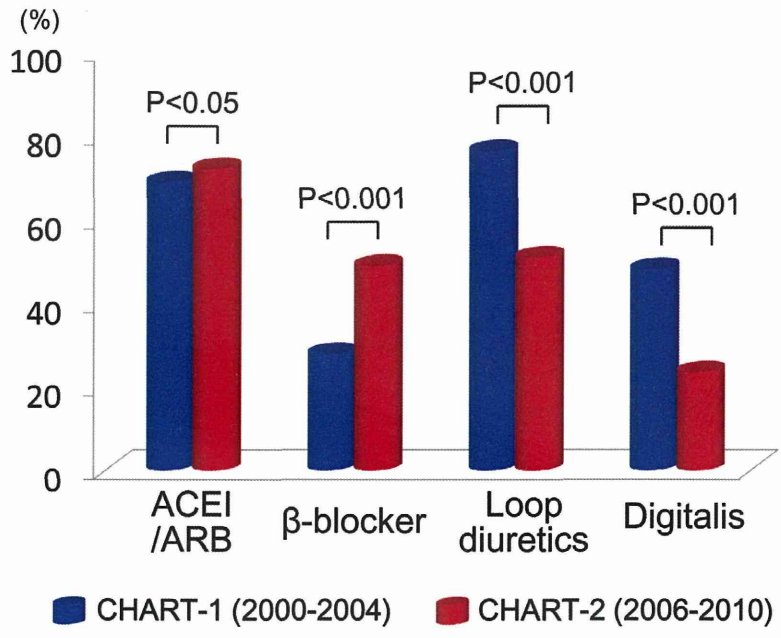

Figure 2. Recent trend in medication for patients with heart failure in Japan. In the CHART studies conducted in Japan, the prescription of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB) and β-blockers for Stage C/D HF patients increased from 2000–2005 to 2006–2010, whereas that of loop diuretics and digitalis decreased.[10]

Table 3. Clinical Outcomes of HF Patients in Asian and Western Studies

Authors	Tsuchihashi-Makaya et al[34]	Tsuchihashi-Makaya et al[34]	Kajimoto et al[42]	Nochioka et al[30]	Shiba et al[10]	Miura et al[29]
Cohort	JCARE-CARD	JCARE-CARD	ATTEND	CHART-2	CHART-2	CHART-2
Registration year	2004–2005	2004–2005	2007–2011	2006–2010	2006–2010	2006–2010
Location, country	164 hospitals, Japan	164 hospitals, Japan	52 hospitals, Japan	24 hospitals Tohoku district, Japan	24 hospitals Tohoku district, Japan	24 hospitals Tohoku district, Japan
HF status	Hospitalized HF, EF <40%	Hospitalized HF, EF ≥50%	ADHF	Stage B	Stage C/D	Stage C/D, EF ≥50%
No. of patients	985	429	4,841	3,421	4,736	2,465
In-hospital mortality, %	3.9	6.5	6.4	NA	NA	NA
Mortality at 1 year, %	11:4*	11.6*	NA	1.5†	4.2†	2.8†
Readmission because of HF at 1 year, %	23.7*	25.7*	NA	3.3†	14.3†	NA

*Limited to discharged patients. †calculated for this review.
Abbreviations as in Tables 1,2.

Authors	Youn et al[24]	Tseng CH[21]	Yin et al[19]	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	NA	2006–2008	2005–2006	2004–2005
Location, country	Korea	Taiwan	Single center, Beijing, China	Single center, Kuala Lumpur, Malaysia	43 hospitals, 8 Asia-Pacific countries	307 hospitals, USA	133 hospitals, 30 European countries
HF status	Hospitalized HF LVEF <40%	ICD-9-CM	ICD-9-CM	NA	Acute decompensated HF	Acute decompensated HF	Acute HF
No. of patients	1,636	2,692	6,949	97	10,171	17,382	3,580
In-hospital mortality, %	6.6	3.9	5.4	5.2	4.8	3	6.7
Mortality at 1 year, %	9.2*	NA	NA	NA	NA	NA	NA
Readmission because of HF at 1 year, %	9.8*	NA	NA	NA	NA	NA	NA

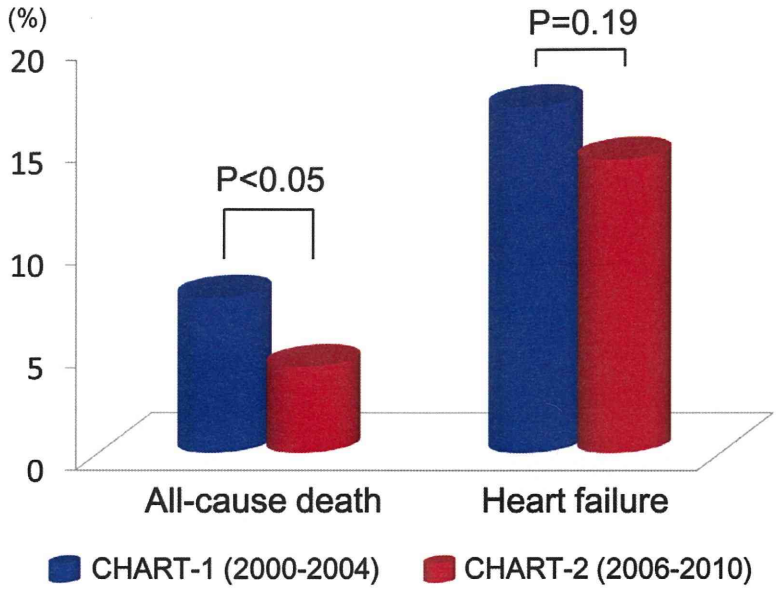

Figure 3. Incidence of all-cause death and heart failure in the CHART studies. Incidence of all-cause death and heart failure (HF) requiring hospitalization at 1 year was calculated for this review using the same cohort of Stage C/D HF patients reported by Nochioka et al (CHART-1)[28] and Shiba et al (CHART-2).[10] Incidence of all-cause death significantly and that of HF insignificantly decreased from CHART-1 to CHART-2.

93 non-cardiac deaths (30%),[42] which was almost comparable with that in the EuroHeart Failure Survey II (6.7%),[48] but slightly higher than in the ADHERE (4.0%) and OPTIMIZE-HF (3.8%) Studies.[45–47] In the Korean Heart Failure Registry (KorHF), in-hospital mortality was 6.6% among 1,653 hospitalized HF patients with LVEF <40% determined by echocardiography.[24] In a report from a single center in Beijing, China (n=7,319), the 30-day hospitalized mortality was 5.1% in 2003–2007, which had decreased significantly from 7.0% in 1993–1997.[16] The 1-year mortality of outpatients with HF varies from 3.6% to 17.1% (**Table 3**). As shown in **Figure 3**, the 1-year incidence of all-cause death significantly and that of HF requiring hospitalization insignificantly decreased from 2000–2004 to 2006–2010 in the CHART studies in Japan.[10,28] In Singapore, mortality from HF decreased from 7.3/10,000 in 1991 to 6.1/10,000 in 1998, with Indians and Malays having a worse outcome than Chinese, highlighting an ethnic difference in the same country.[7]

Prevention of HF in Asia

The American Heart Association (AHA) and the American College of Cardiology (ACC) Guidelines underscore the importance of early detection and treatment of patients at high risk for progression to symptomatic HF.[62] The AHA/ACC Guidelines classify asymptomatic subjects with structural and/or functional heart disease as Stage B, which is a category that is strongly associated with future development of HF.[63] Thus, the management of Stage B HF patients is important to prevent or better manage the risk factors for HF, such as HT, DM, smoking, obesity and other lifestyle-related diseases. Because the prevalence of these lifestyle-related diseases has been increasing in Asian countries,[66] management of these factors by lifestyle modification and medications are important. In particular, programs including diet, exercise, restriction of salt intake as well as medications are important to better manage HF patients with HT and DM. Indeed, several randomized clinical trials demonstrated that reduction in blood pressure with antihypertensive agents was associated with an absolute risk reduction in the incidence of HF,[64–66] whereas DM was associated with an increased risk of symptomatic HF.[67] In addition, early detection and management of RHD, congenital heart disease or pulmonary HT is important, particularly in South Asia. Improvement of affordability and accessibility are also important social issues to be addressed in Asia. Indeed, the ADHERE international study reported that patients hospitalized with ADHF in the Asia-Pacific region tended to present with more severe clinical symptoms and signs and are younger, especially in countries at an earlier stage in their epidemiological transition.[61] In these countries, it was reported that echocardiography and disease-modifying medications were less used, highlighting potential opportunities to improve outcomes.[61]

Conclusions

HF is a leading cause of mortality and morbidity in Asia. Because the causes of mortality and morbidity have shifted from infectious diseases and/or nutritional deficiencies to lifestyle-related diseases during the epidemiologic transition, it is highly possible that HF patients would further increase in Asia. To date, however, there is insufficient information available on HF epidemiology in Asia. Thus, we need to assemble and comprehensively analyze the available evidence in Asia to inform our daily clinical practice and to systematically conduct future epidemiologic approaches to establishing appropriate prevention programs against the burden of HF in Asia.

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Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 Study

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Aims It is still controversial whether elevated baseline heart rate (HR) is associated with higher mortality in patients with heart failure (HF) with preserved ejection fraction (HFpEF). We compared the impacts of baseline HR on mortality in patients with HFpEF and those with HF with reduced ejection fraction (HFrEF).

Methods and results We enrolled consecutive 2688 patients in Stage C or D HF with sinus rhythm from our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study ($n = 10\,219$). The prognostic impact of HR increase was compared between the two groups, defined as left ventricular ejection fraction of $\leq 50\%$ (HFrEF) and $> 50\%$ (HFpEF). Cox regression analysis revealed that elevated baseline HR was associated with increased all-cause mortality in both groups [hazard ratio for the highest tertile (HH) 1.77 in HFrEF, $P = 0.008$; HH1.82 in HFpEF, $P = 0.001$]. However, as for mode of death, elevated HR was associated with cardiovascular (CV) death in HFpEF (HH 2.17, $P = 0.012$), but the association was modest in HFrEF (HH1.49, $P = 0.14$): in particular, impact on HF death was different between HFpEF (HH 3.79, $P = 0.020$) and HFrEF (HH 1.07, $P = 0.864$). In contrast, the prognostic impact of baseline HR on non-CV death was noted only in patients with HFrEF. β-Blocker therapy was associated with reduced HF mortality in HFrEF (hazard ratio 0.49, $P = 0.038$) but not in HFpEF (hazard ratio 0.64, $P = 0.321$).

Conclusions Elevated HR was associated with increased CV death in HFpEF compared with HFrEF, although its impact on all-cause mortality was comparable between the two groups.

Keywords Heart failure • Heart rate • Prognosis

Introduction

Elevated baseline heart rate (HR) could be a reflection of activated sympathetic nervous system, a negative force-frequency response of failing myocardium and worsening myocardial ischaemia.[1–3] Furthermore, increased heart rate was associated with increased systemic inflammation and endothelial dysfunction.[4] Thus, it is widely considered to be a predictor of poor prognosis in patients with heart failure (HF). Indeed, unfavourable prognostic impact of elevated baseline HR has been repeatedly noted in patients with HF with reduced ejection fraction (HFrEF).[5–8] For instance, in addition to β-blocker, HR reduction with ivabradine has been reported as effective for patients with HFrEF.[9] In the European Society of Cardiology guidelines, ivabradine is recommended to

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reduce the risk of HF hospitalization in symptomatic (NYHA class II–IV) patients in sinus rhythm with an EF ≤ 35% and a heart rate remaining ≥ 70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).[10] However, it is still controversial whether elevated baseline HR is associated with poor prognosis in patients with HF with preserved ejection fraction (HFpEF).[11–13] This is possibly because these previous findings regarding the association between baseline HR and prognosis of HFpEF were derived from *post hoc* analysis of randomized control trials[11,13] or from an observational study with a relatively small sample size,[12] and thus likely involved selection bias. Furthermore, even in the positive studies,[11,12] it has not been elucidated which modes of deaths or cardiac events were particularly associated with elevated HR in HFpEF. Thus, it has been awaited to address the prognostic impacts of elevated HR in patients with HFpEF in more detail, using a large-scale prospective observational cohort.

In the present study, we thus examined the prognostic impact of baseline HR in HFpEF in our prospective observational multicentre cohort study, named the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study, where we successfully enrolled consecutive 10 219 patients in Stage B, C, and D HF.[14–16] The aim of the present study was to compare the impact of elevated HR on clinical outcomes between HFpEF and HFrEF, especially on cardiovascular (CV) death and HF death.

Methods

Design of the present study

The CHART-2 Study is a prospective observational multicenter cohort study, as previously reported in detail (NCT00418041).[14] Among 4735 stage C/D patients in the CHART-2 Study ($n = 10\ 219$),[14–16] 2863 in sinus rhythm without history of paroxysmal atrial fibrillation or implantable cardiac device were enrolled in the present study. They were divided into the two groups according to the baseline left ventricular ejection fraction (LVEF) of ≤ 50% (HFrEF) or > 50% (HFpEF) in the present study.[17] The prognostic impact of elevated baseline HR was examined by calculating relative risks in the highest and second highest tertiles of baseline HR compared with the lowest tertile. We also examined whether β-blocker therapy could affect the relationship between HR increase and prognostic endpoints between the HFrEF and the HFpEF groups. Furthermore, we explored optimal cut-off points of HR to split risk of mortality endpoints using the classification and regression tree (CART) method.[18,19]

Statistical analysis

The outcomes of all-cause death, CV death and non-CV death were estimated by Kaplan–Meier curve and log-rank test in both groups. The impact of each tertile defined by baseline HR for the endpoints was examined using the univariate and multivariate Cox proportional hazard model. The covariates for the multivariate analysis included gender, age, body mass index, systolic blood pressure (SBP), LV diastolic diameter (LVDd), LVEF, haemoglobin level, estimated glomerular filtration ratio, malignant diseases, β-blocker, RASI, enrolment location (inpatient or outpatient) and HR categories. The association between β-blockers and outcomes was assessed using univariate and multivariate Cox proportional hazard models with the same covariates except β-blocker use. Statistical analysis was performed using IBM SPSS Statistics 19 software (IBM, Armonk, NY, USA) and R software (version 2.5). To determine the optimal cut-off points of HR to split CV and non-CV mortality for overall, HFrEF and HFpEF patients, respectively, an open-source adaptation of the CART algorithm from R software was used.

Methods are mentioned in more detail in the Supplementary material online, Appendix S1.

Results

Baseline characteristics

Among the 2863 Stage-C/D HF patients in sinus rhythm enrolled in the present study, we finally analysed 2688 (93.9%) patients in whom both HR and LVEF data were available (mean age 67.5 ± 13.0 years, male 70%, and median follow-up period of 3.13 years). *Table 1* shows baseline characteristics of the patients in the HFrEF and HFpEF groups. The number of patients in the HFpEF group was twice that in the HFrEF group. The HFpEF group was characterized by more females, older age, higher SBP, lower HR and NYHA functional class, higher prevalence of hypertension and valvular heart disease, and lower serum brain natriuretic peptide levels. The prevalence of β-blocker use was significantly lower in the HFpEF group than in the HFrEF group (40% vs. 65%, $P < 0.001$). Supplementary material online, Table S1, shows the baseline characteristics of tertiles of baseline HR for both groups. Although almost all backgrounds except β-blocker use were comparable among the tertiles in the HFrEF group, the tertiles in the HFpEF group showed statistically significant trends in LVDd, LVEF value, ischaemic heart disease, prevalence of female sex and loop diuretics use, in addition to β-blocker use.

Impact of HR increase on clinical outcomes

During the follow-up period of median 3.13 years, 133 (15.0%) and 176 (9.8%) all-cause deaths, 79 (8.9%) and 76 (4.2%) CV deaths, 42 (4.7%) and 32 (1.8%) deaths for heart failure, 164 (18.5%) and 122 (6.8%) admission for heart failure, 42 (4.7%) and 86 (4.8%) non-CV deaths were noted in the HFrEF and HFpEF groups, respectively. There were 26 deaths due to unknown origins. The actual number of events and event rate in tertiles are shown in Supplementary material online, Table S2. The Kaplan–Meier curves and multivariate Cox regression analyses revealed that the higher HR tertile had more increased risk of all-cause death in both the HFrEF and HFpEF groups (*Figures 1A,B* and *2*). As for CV and HF death, a significant relationship between HR and mortality was noted in the HFpEF group (hazard ratios of the highest HR tertile 2.17, 95% CI 1.19–3.99, $P = 0.012$ for CV death and 3.79, 95% CI 1.24–11.62, $P = 0.020$ for HF death). In contrast, in the HFrEF group, elevated HR was not significantly associated with increased risk of CV mortality and HF mortality (hazard ratios of the highest HR tertile 1.49, 95% CI 0.87–2.54, $P = 0.143$ for CV death; and 1.07, 95% CI 0.50–2.27, $P = 0.864$ for HF death) (*Figures 1C,D* and *2*). Furthermore, a significant relationship between HR and non-CV

Table 1 Baseline characteristics of two groups defined by baseline LVEF

	Total $n = 2688$ (100%)	HFrEF $n = 885$ (32%)	HFpEF $n = 1803$ (67%)	*P*-value
Patients' characteristics				
Male sex	1874 (70%)	654 (74%)	1220 (68%)	0.001
Age (years)	67.5 ± 13	66.6 ± 13.0	67.9 ± 13.0	0.020
BMI	24.0 ± 3.9	23.5 ± 4.0	24.3 ± 3.8	< 0.001
Systolic BP (mmHg)	127.9 ± 19.0	123.3 ± 19.8	130.2 ± 18.2	< 0.001
Heart rate (bpm)	71.1 ± 13.5	72.9 ± 13.7	70.2 ± 13.3	< 0.001
LVDd (mm)	52.0 ± 9.2	58.6 ± 9.1	48.7 ± 7.3	< 0.001
LVEF (%)	57.2 ± 15.6	38.8 ± 8.8	66.2 ± 8.9	< 0.001
NYHA				< 0.001
I	702 (26%)	154 (17%)	548 (31%)	
II	1701 (64%)	605 (69%)	1096 (61%)	
III	254 (9%)	111 (13%)	143 (8%)	
IV	18 (1%)	11 (1%)	7 (0%)	
Medical history				
Hypertension	2109 (78%)	637 (72%)	1472 (82%)	< 0.001
Diabetes mellitus	758 (28%)	258 (29%)	500 (28%)	0.466
Dyslipidaemia	2079 (77%)	695 (79%)	1384 (77%)	0.327
Stroke	420 (16%)	122 (14%)	298 (17%)	0.070
Malignant disease	280 (10%)	92 (10%)	188 (10%)	1.000
Ischaemic heart disease	1594 (59%)	517 (58%)	1077 (60%)	0.531
Cardiomyopathy	469 (17%)	267 (30%)	202 (11%)	0.000
Valvular heart disease	472 (18%)	89 (10%)	383 (21%)	< 0.001
Laboratory data				
Haemoglobin (g/dL)	13.2 ± 2.0	13.2 ± 2.0	13.2 ± 1.9	0.667
Albumin (mg/dL)	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	0.005
LDL-C (mg/dL)	105.4 ± 30.7	105.6 ± 31.3	105.3 ± 30.4	0.840
eGFR (mL/min/1.73 m^2)	62.8 ± 25.3	60.7 ± 22.6	63.8 ± 26.5	0.002
BNP [pg/mL, median (IQR)]	71 (29–186)	135 (53–316)	53 (22–131)	< 0.001
Medication				
β-Blockers	1292 (48%)	575 (65%)	717 (40%)	< 0.001
RASI	1966 (73%)	706 (80%)	1260 (70%)	< 0.001
Loop diuretics	1073 (40%)	506 (57%)	567 (31%)	< 0.001
Aldosterone antagonists	548 (20%)	303 (34%)	245 (14%)	< 0.001
Statins	1240 (46%)	407 (46%)	833 (46%)	0.934

BMI, body mass index; BP, blood pressure; LVDd, left ventricular diastolic diameter; LDL-C, low-density lipoprotein-cholesterol; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; RASI, renin–angiotensin system inhibitors.

mortality was noted in the HFrEF group (hazard ratio of the highest HR tertile 2.33, 95% CI 1.09–4.97, $P = 0.029$), but not in the HFpEF group (*Figure 2*). Hazard ratio for HF admission tended to increase according to HR increment in the HFpEF group but not in the HFrEF group (*Figure 2*). The prognostic impact of baseline HR on CV and HF mortality were more evident in the HFpEF than in the HFrEF group, whereas such an impact on non-CV death was noted only in the HFrEF group (*Figure 2*).

β-Blocker use and prognostic impact of HR

When the baseline characteristics were examined according to LVEF and use of β-blockers, the patients treated with β-blockers were younger and had lower HR compared with those treated without β-blockers in both the HFrEF and the HFpEF groups (Supplementary material online, Table S3). SBP was lower in the patients with β-blockers compared with those without β-blockers in the HFrEF group (121.4 ± 19.6 vs. 126.8 ± 19.7 mmHg), but not in the HFpEF group (130.3 ± 18.4 vs. 130.1 ± 18.1 mmHg). Importantly, both univariate and multivariate Cox regression analyses revealed that use of β-blockers was significantly associated with a reduction in HF death in the HFrEF but not in the HFpEF group (*Table 2*). Risk reduction by β-blockers for all-cause death, CV death and HF death were observed in the HFrEF patients but not in the HFpEF patients (*Table 2*). In contrast, use of β-blockers was not associated with reduced risk of admission for HF in either group. The association of mortality with HR categories was notable for all-cause death and CV death only in patients with HFpEF and treated without β-blockers.

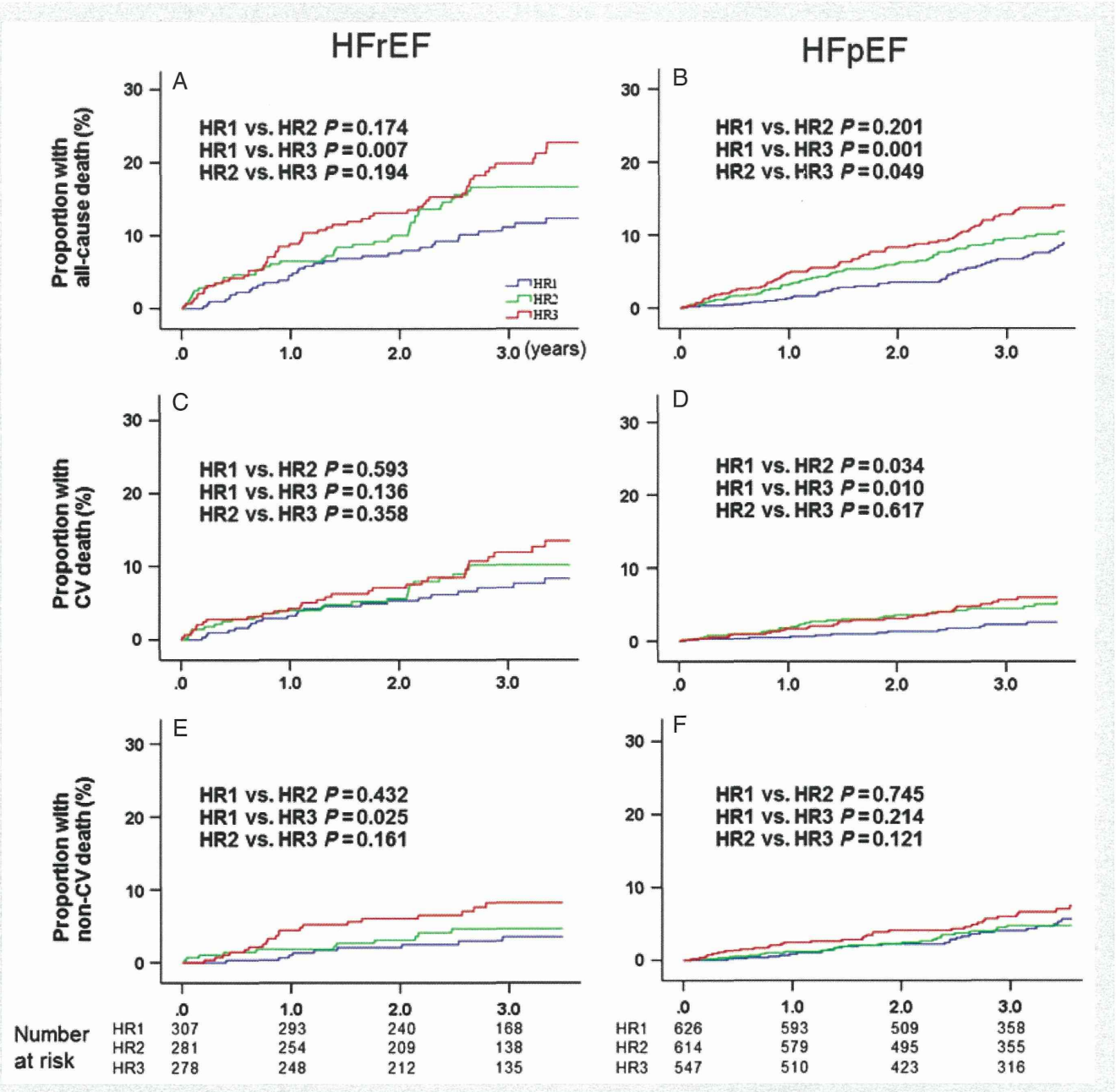

Figure 1 Kaplan–Meier curves for outcomes in HFrEF and HFpEF. Kaplan–Meier curves for all-cause death of HFrEF (*A*) and HFpEF (*B*), CV death of HFrEF (*C*) and HFpEF (*D*), and non-CV death of HFrEF (*E*) and HFpEF (*F*).

Cut-off value of HR for CV death

We attempted to search cut-off values of HR to split both HFrEF and HFpEF patients for CV death based on CART analysis (*Table 3*). CART analysis suggested that the primary cut-off value in baseline HR to discern a high-risk population for CV death were 63.5, 69.5, and 63.5 bpm in the overall, HFrEF, and HFpEF patients, respectively, and that those for non-CV death were all 71.5 bpm (*Table 3*). A total of 1683 (62.6%), 511 (57.7%), and 1172 (65.0%) patients had HR equal to or more than the cut-off values with hazard ratios of 1.85 (95% CI 1.26–2.73, $P = 0.002$), 1.60 (1.00–2.55, $P = 0.051$), and 2.04 (1.17–3.53, $P = 0.012$) for CV death in the overall, HFrEF, and HFpEF patients, respectively (*Table 3*).

Discussion

In the present study, we examined the difference in the prognostic impact of HR status between the HFpEF and HFrEF groups in the CHART-2 study, the largest-scale prospective observational study for patients in Stage B, C, and D HF in Japan.[14–16] The present study is the first to report an association in detail between elevated HR and modes of death in HFpEF in comparison with those

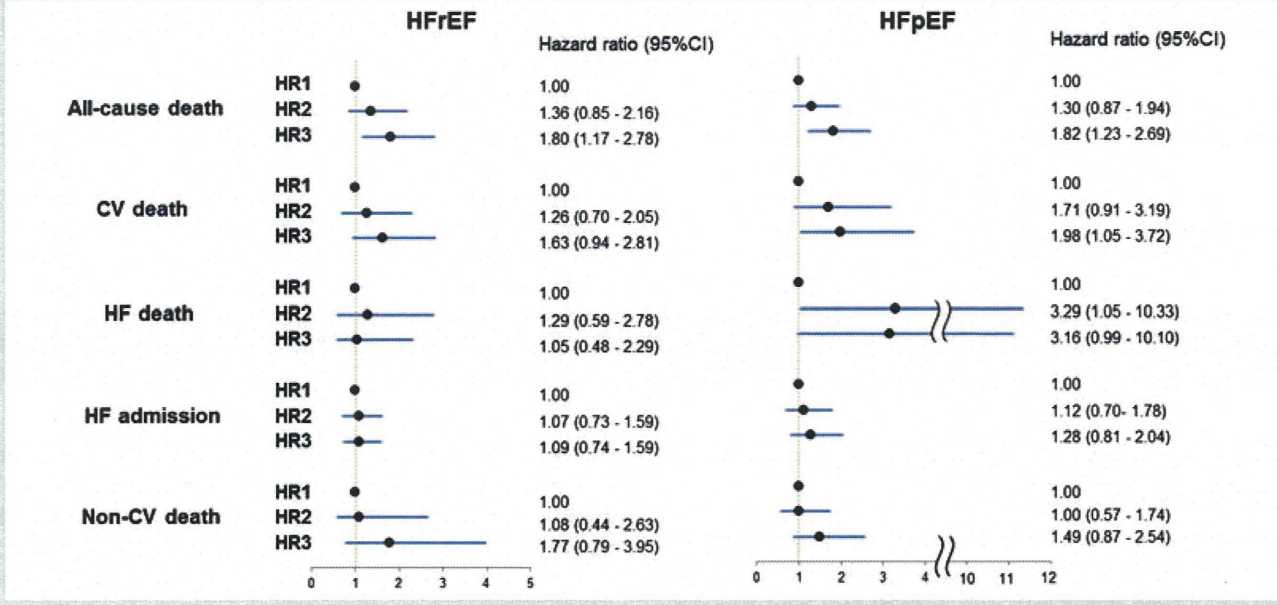

Figure 2 Association between baseline HR and outcomes in HFrEF and HFpEF. Adjusted hazard ratio for all-cause death, CV death, HF death, HF admission, and non-CV death in HFrEF and HFpEF.

Table 2 Unadjusted and adjusted hazard ratios of β-blocker for all-cause death, CV death, HF death, and HF admission in HFrEF and HFpEF

	Unadjusted				Adjusted[a]			
	HFrEF		HFpEF		HFrEF		HFpEF	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
All-cause death	0.70 (0.50–0.99)	0.042	0.81 (0.59–1.10)	0.174	0.71 (0.49–1.03)	0.075	1.11 (0.79–1.54)	0.553
CV death	0.68 (0.43–1.06)	0.088	0.79 (0.49–1.27)	0.326	0.68 (0.42–1.11)	0.123	0.96 (0.58–1.59)	0.874
HF death	0.51 (0.28–0.94)	0.030	0.51 (0.23–1.13)	0.096	0.49 (0.25–0.96)	0.038	0.64 (0.26–1.55)	0.321
HF admission	1.16 (0.84–1.63)	0.351	0.98 (0.68–1.41)	0.926	1.05 (0.74–1.49)	0.797	0.97 (0.66–1.43)	0.887

[a]Adjusted by age, sex, BMI, systolic blood pressure, LVEF, LVDd, Hb, eGFR, RASI, and HR catgories.
CV, cardiovascular; HF, heart failure.

in HFrEF. The results demonstrated that the impact of elevated baseline HR on CV mortality was notable in the HFpEF group compared with the HFrEF group, particularly on HF mortality.

Elevated baseline HR and all-cause mortality in HF

The present study demonstrated the impacts of HR status on all-cause mortality in both HFrEF and HFpEF patients, where the increased risk of all-cause deaths in patients with higher HR was noted even after adjustment for patient background, medication, and possible other confounders for mortality and morbidity. This relationship between elevated baseline HR and increased mortality appears to be reasonable in the clinical setting, because elevated HR could be a reflection of neurohumoral activation of the sympathetic nervous system, an excessive compensation for reduced cardiac output and myocardial ischaemia. However, it is still controversial whether elevated baseline HR is associated with increased all-cause mortality in HFpEF as in HFrEF. For example, in the subanalysis of the CHARM programmes, the correlation of baseline HR and risks for all-cause death was noted in both the HFrEF and HFpEF groups,[11] whereas the subanalysis of the DIG study revealed that elevated HR was associated with all-cause death in HFrEF but not in HFpEF patients.[13] Thus, our results regarding prognostic impacts of elevated HR on all-cause mortality are consistent with those of the CHARM programmes, but not with those of the DIG study, providing additional evidence for the relationship between baseline HR and clinical outcomes in a large cohort of patients receiving contemporary management for Stage C/D HF in the real-world setting.