

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, $P = 0.008$; HH 1.82 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 (HH 1.49, $P = 0.14$): 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 \leq 35% and a heart rate remaining \geq 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 HFrfEF, 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 \leq 50% (HFrfEF) 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 HFrfEF 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, HFrfEF 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 HFrfEF and HFpEF groups. The number of patients in the HFpEF group was twice that in the HFrfEF 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 HFrfEF 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 HFrfEF 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 HFrfEF 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 HFrfEF 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 HFrfEF 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				
I	702 (26%)	154 (17%)	548 (31%)	< 0.001
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

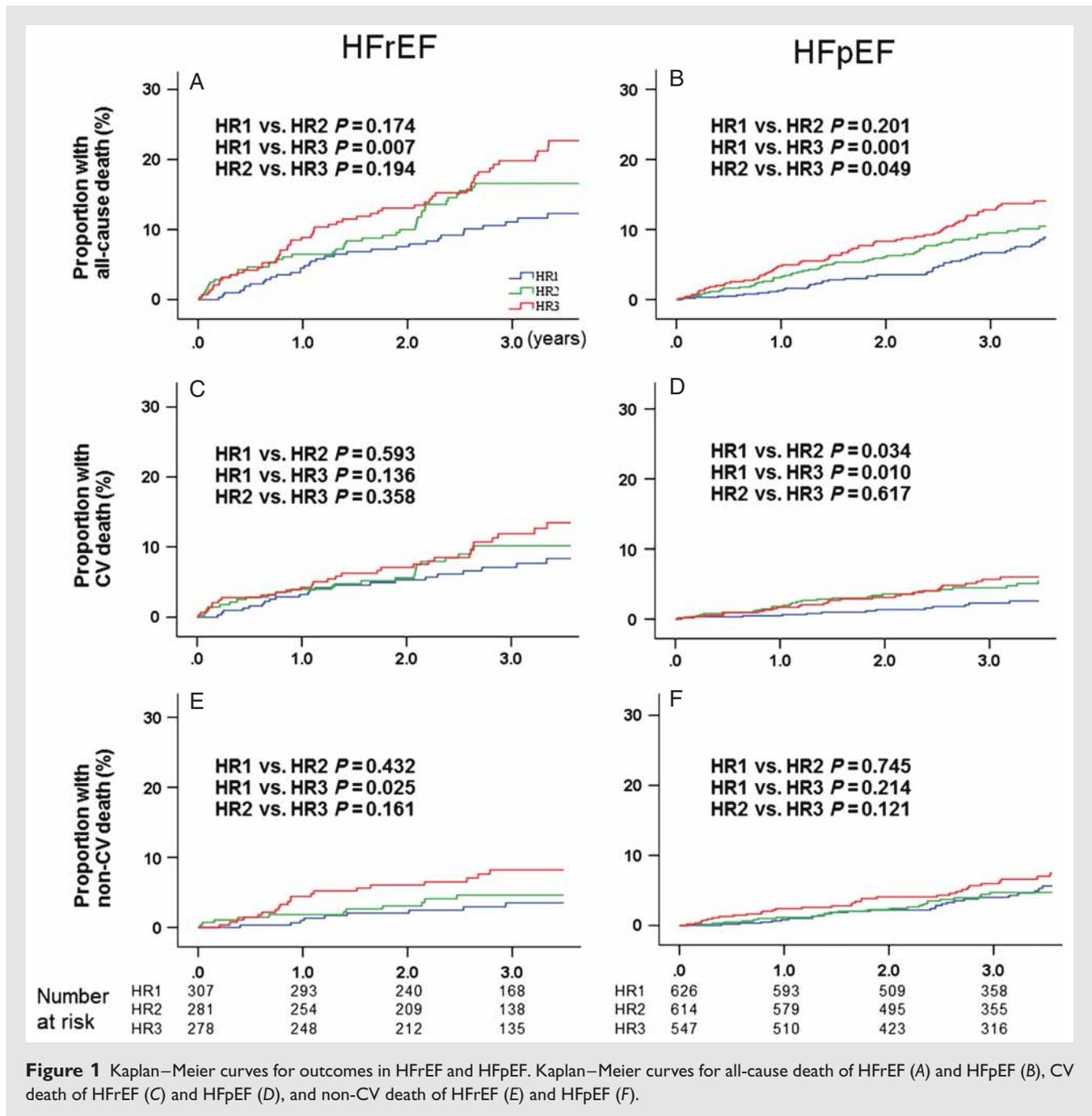
BMI, body mass index; BP, blood pressure; LVDd, left ventricular diastolic diameter; LDL-C, low-density lipoprotein-cholesterol; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; RASI, renin-angiotensin system inhibitors.

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.



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

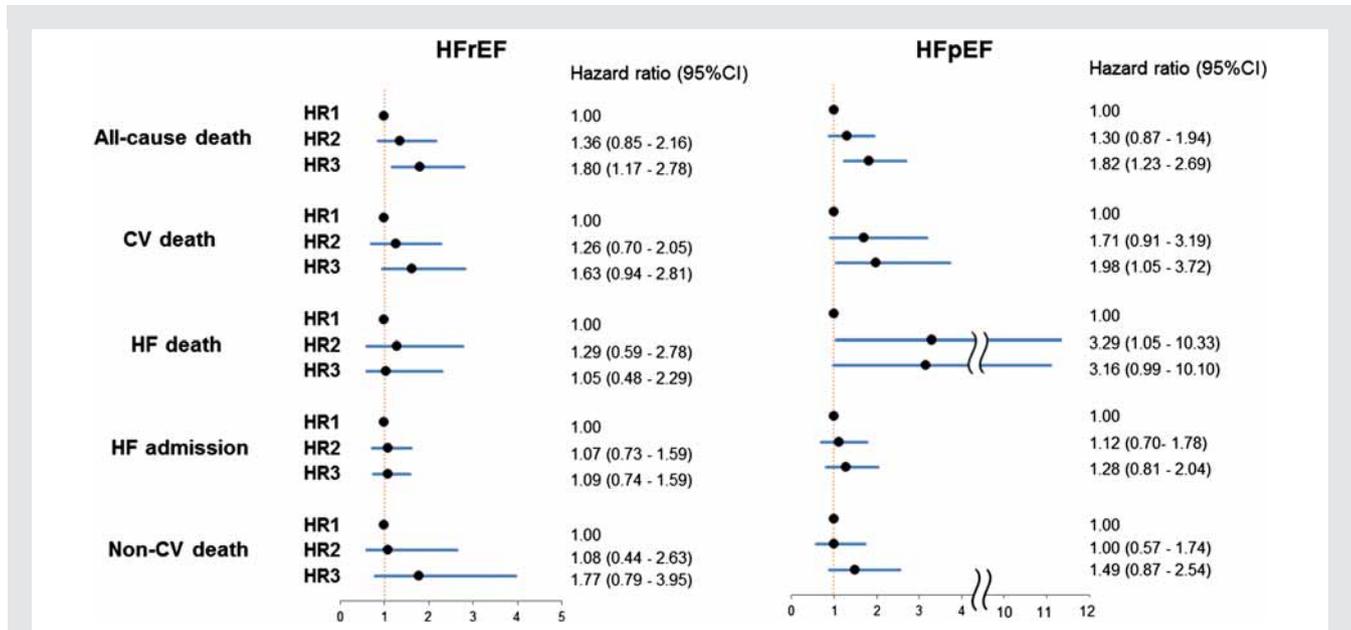


Figure 2 Association between baseline HR and outcomes in HFrEF and HFpEF. Adjusted hazard ratio for all-cause death, CV death, HF death, HF admission, and non-CV death in HFrEF and HFpEF.

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		HFpEF		Adjusted ^a		HFpEF	
	HFrEF		HFrEF		HFrEF		HFrEF	
	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

^aAdjusted by age, sex, BMI, systolic blood pressure, LVEF, LVDD, Hb, eGFR, RASI, and HR categories. 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.

Table 3 Split point of HR for outcomes in overall patients, HFrEF and HFpEF

		First split point of HR	Hazard ratio of higher HR group ^a	95% CI	P-value
CV death	All	63.5 bpm	1.85 (≥ 64 bpm)	1.26–2.73	0.002
	HFrEF	69.5 bpm	1.60 (≥ 67 bpm)	1.00–2.55	0.051
	HFpEF	63.5 bpm	2.04 (≥ 64 bpm)	1.17–3.53	0.012
Non-CV death	All	71.5 bpm	1.68 (≥ 72 bpm)	1.19–2.38	0.004
	HFrEF	71.5 bpm	1.34 (≥ 72 bpm)	1.22–4.50	0.011
	HFpEF	71.5 bpm	1.45 (≥ 72 bpm)	0.95–2.22	0.082

^aUnadjusted hazard ratios of patients with HR more than optimal split point indicated by CART analysis (higher HR group) over those with HR not more than indicated (lower HR group). The minimum HRs of the higher HR group are shown in parentheses next to the hazard ratios.

Different impact of baseline HR between HFrEF and HFpEF

Bui *et al.* demonstrated that HFpEF was associated with a higher risk of in-hospital mortality with increasing admission HR compared with HFrEF among patients hospitalized for HF, suggesting that higher HR might have imparted increased in-hospital mortality in HFpEF patients.²⁰ As for the impacts of elevated baseline HR on long-term CV mortality, the present study may provide the first evidence that such impacts on CV death, particularly on HF death, are rather significant in HFpEF compared with HFrEF (Figure 2). The relationship between elevated HR and increased CV mortality in HFpEF appears reasonable, since HFpEF is generally complicated by diastolic dysfunction and thus could be further worsened by shortening of the diastolic period according to an increase in HR.²¹ In the present study, there was no association between HR and hospitalization for HF in HFrEF or HFpEF (Figure 2). In addition, the present study may provide the first evidence for the association between baseline HR and non-CV death in HFrEF patients, following an association between HR and non-CV mortality being observed in the general population.^{22–24} Although the precise mechanisms remain to be elucidated, low physical activity, elevated adrenergic activity and smoking might be possible explanations for the association between elevated HR and increased non-CV mortality.^{22–24}

Cut-off value of HR for CV death in HFrEF and HFpEF

In order to determine the cut-off point for HR to partition Stage C/D patients according to the mortality rates, we performed CART analysis, demonstrating that 63.5, 69.5, and 63.5 bpm could be the primary splitting points for CV death among the overall, HFrEF, and HFpEF patients, respectively (Table 3). The univariate Cox regression analysis revealed that HFpEF patients with HR ≥ 63.5 bpm had an increased risk for CV death with a statistical significance (hazard ratio 2.04, $P=0.012$ for patients with HR ≥ 64 bpm), and HFrEF patients with HR ≥ 69.5 bpm with a tendency (hazard ratio 1.60, $P=0.051$ for patients with HR ≥ 67 bpm). These results may suggest that the therapeutic range of HR to reduce CV mortality could be lower in HFpEF compared with HFrEF patients (63.5 vs.

69.5 bpm). This was likely because a longer duration of the diastolic period is necessary to reduce CV mortality in patients with diastolic dysfunction compared with systolic dysfunction. In this context, HR reduction therapy could be an option to reduce CV mortality in HFpEF patients. Indeed, it has been reported that selective HR reduction by ivabradin improves vascular stiffness and left ventricular systolic and diastolic function in mice.²⁵ A sub-analysis of the SHIFT trial, which enrolled patients with HF and EF $< 35\%$, revealed that the prognostic impact of HR reduction by ivabradine was greater in patients who had baseline HR ≥ 75 and had achieved < 60 bpm or heart rate reductions > 10 bpm.²⁶ Although the cut-off point of HR to discern CV mortality may vary according to the baseline ejection fraction, further reduction of HR with ivabradine could be effective in patients with HFpEF. However, further investigations are required to elucidate whether HR reduction is effective in the management of HFpEF patients in real-world practice.

β -Blocker therapy in HFpEF

It is widely accepted that β -blocker therapy improves LVEF and reduces mortality in HFrEF patients through inhibition of sympathetic nervous activity and reduction in HR and oxygen consumption.^{27,28} The present study suggested different prognostic impacts of β -blockers between HFrEF and HFpEF, as β -blocker therapy was associated with decreased HF mortality in patients with HFrEF but not in those with HFpEF. β -Blockers could theoretically be beneficial in patients with HFpEF because shortening of the diastolic period could exacerbate diastolic dysfunction, a common feature of the disorder.²¹ However, it was previously reported that β -blockers may not be so useful in HFpEF patients,²⁹ a consistent finding of the present study. However, there remains a possibility that standard doses of β -blockers (for Japanese patients) in the present study was not sufficient to reduce CV mortality for HFpEF patients. In fact, Yamamoto *et al.* recently reported that a higher dose of carvedilol was associated with lower incidence of a composite of cardiovascular death and unplanned hospitalization for any cardiovascular cause in patients with HFpEF in the Japanese population.³⁰ Thus, further studies are warranted to examine whether higher doses of β -blockers could improve the mortality of HFpEF patients.

Study limitations

Several limitations should be mentioned for the present study. First, the number of HFrEF patients was smaller than that of HFpEF patients, and therefore the power might not be enough to detect a statistical significance in HFrEF patients; thus, interpretation should be made with caution. Second, the CHART-2 Study is a prospective, observational study that reflects the real-world practice of HF, as consecutive HF patients were enrolled with a minimal selection bias; however, we have to consider influences on the results by unknown confounders. Third, in the present study, we only used the data at the entry and did not take into consideration the possible changes in LVEF, HR, episodes of arrhythmia, particularly those of atrial fibrillation, medication, and other covariates during the follow-up period. In addition, no data were available for β -blocker therapy, such as timing of initiation, daily doses, adherence, discontinuation, and reasons for the presence or absence of prescription. Thus, it was difficult to elucidate the prognostic impact of β -blocker therapy in the present study. Fourth, in the present study, according to European Society of Cardiology guidelines,¹⁵ we chose the cut-off value of LVEF 50% to define HFpEF. However, caution is needed in interpreting the present results when comparing other cohorts with different cut-off values to discriminate between HFrEF and HFpEF, such as 35% or 40%.^{8,10} Finally, all subjects in the CHART-2 Study were Japanese people, which may limit generalization of the present results to patients in other countries.

Conclusions

We demonstrated the different impacts of elevated baseline HR on CV and non-CV mortality between HFrEF and HFpEF in the CHART-2 Study. Although the influence of elevated baseline HR on all-cause mortality was comparable, elevated HR was significantly associated with CV death in HFpEF, but insignificantly in HFrEF, particularly for HF death. Further studies are needed to elucidate the relationship between elevated baseline HR and mortality in order to improve the survival of HF patients.

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of tertiles defined by baseline heart rate of the two groups

Table S2. Actual number of event for tertiles in HFrEF and HFpEF

Table S3. Baseline characteristics across four groups defined by LVEF and β -blocker

Appendix S1. 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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