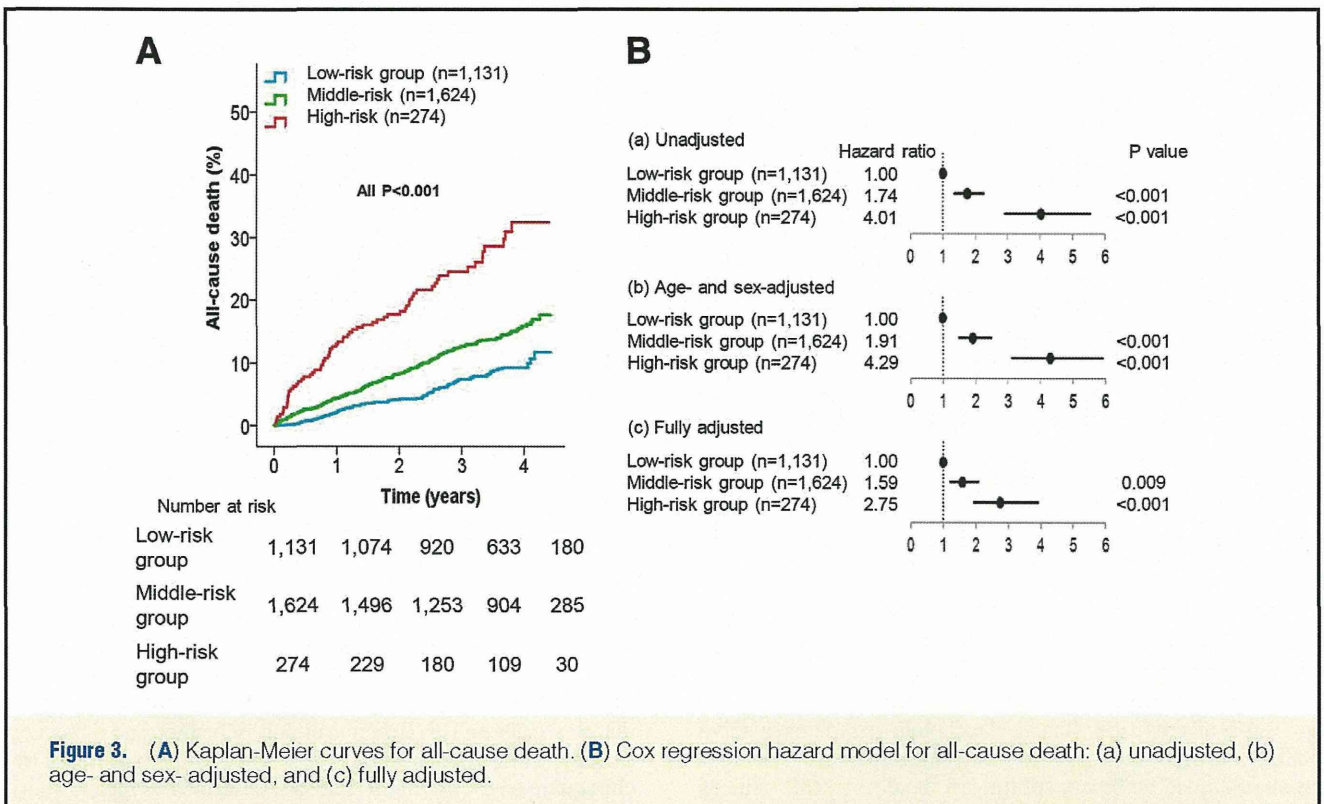**Figure 2.** (**A**) Crude mortality rate for all-cause death. (**B**) Stratification of mortality risk according to heart rate (HR) and systolic blood pressure (SBP) in patients with chronic heart failure.

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-
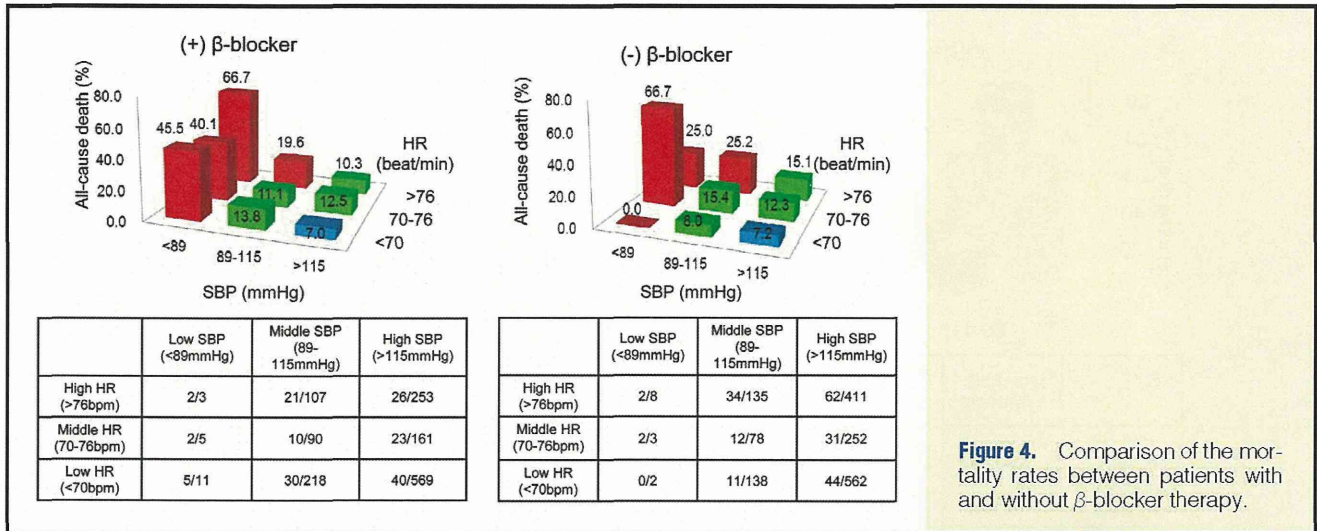
Figure 4. Comparison of the mortality rates between patients with and without β-blocker therapy.
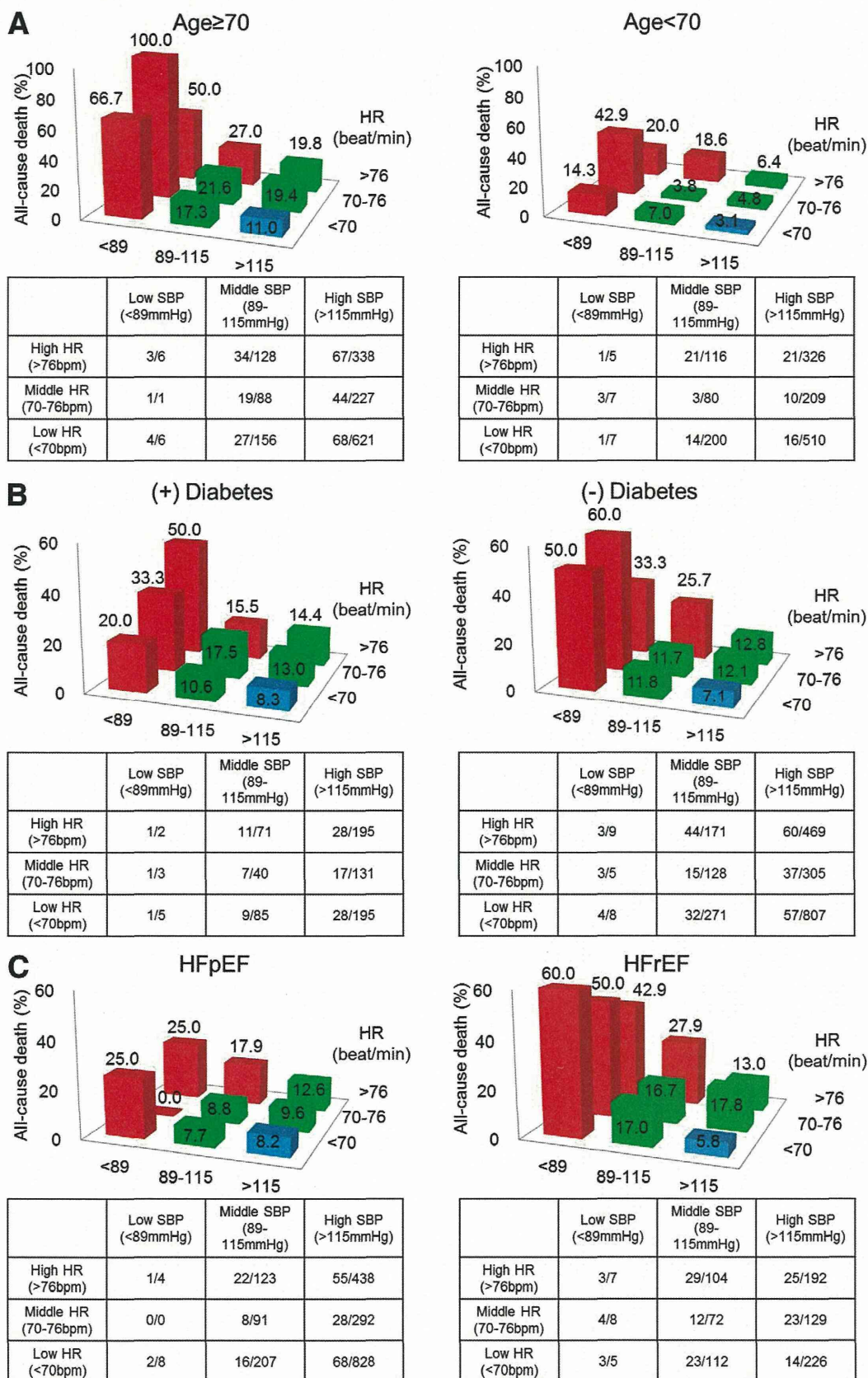
Table 2. Subgroup Analyses for All-Cause Death of Patients With Chronic Heart Failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study

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

not in those with SBP <89mmHg. 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 <89mmHg or 89–115mmHg 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 >77beats/min but not so significant in those with HR <77beats/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 <89mmHg regardless of HR values or SBP 89–115mmHg 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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Supplementary Files

Supplementary File 1

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

Appendix S1. Organization of the CHART-2 study

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

Impact of Physical Activity on Cardiovascular Events in Patients With Chronic Heart Failure
– A Multicenter Prospective Cohort Study –

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Background: We have previously demonstrated that the prevalence of metabolic syndrome in chronic heart failure (CHF) is more than double compared with the general population in Japan. However, the impact of physical activity on cardiovascular events in CHF patients remains to be fully elucidated.

Methods and Results: We performed a prospective, nationwide large-scale multicenter study of 9,178 patients with stage A/B/C/D CHF in Japan. We obtained the baseline physical activity data for 7,292 and yearly changes in physical activity data during a 3-year follow-up period for 4,353 patients. We divided the patients into high- and low-exercise groups by using the median value of physical activity in the stage A/B and C/D groups. In both groups, patients who exercised more were characterized by younger age and less advanced stage of CHF. Importantly, the baseline physical activity levels were significantly associated with all-cause death, heart failure (HF) hospitalization and other cardiovascular events (except acute myocardial infarction, stroke, HF hospitalization). Furthermore, the yearly change in physical activity level was also significantly associated with HF hospitalization and other cardiovascular events in both groups.

Conclusions: The baseline level of physical activity and its yearly changes are significantly associated with all-cause death and major cardiovascular events in both stage A/B and C/D patients, suggesting that physical activity could be an important therapeutic target to improve the long-term prognosis of CHF patients.   (*Circ J* 2013; **77**: 2963–2972)

Key Words: Chronic heart failure; Heart failure hospitalization; Physical activity; Prognosis

T he prevalence of lifestyle diseases, such as diabetes mellitus, dyslipidemia, hypertension, and their combination in metabolic syndrome (MetS), has been rapidly increasing in Japan over the past decades, because of westernization of lifestyle.[1] Recently, we performed a prospective, nationwide large-scale multicenter study supported by the Japanese government on the current status of chronic heart failure (CHF) patients in Japan, with a special reference to lifestyle diseases, and demonstrated that the prevalence of MetS in CHF patients is more than double compared with the general population in Japan.[2] This suggests that lifestyle diseases have a substantial impact on the development of both ischemic and non-ischemic CHF.[2,3]

CHF is a complex clinical syndrome in which both HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF) are substantially involved.[3–7] We have also demonstrated that the prevalence of the metabolic components is comparable between HFpEF and HFrEF.[2] In Japan, CHF has become a growing social issue as the number of CHF patients has been rapidly increasing because of the aging of the popu-

Table 1. Baseline Characteristics of CHF Patients with Low and High Physical Activity Levels in Stages A/B and C/D

	Stage A/B (n=4,435)			Stage C/D (n=2,857)		
	Low-Ex (n=2,097)	High-Ex (n=2,338)	P value	Low-Ex (n=1,525)	High-Ex (n=1,332)	P value
Age (years)	69.1±0.3	66.7±0.2	<0.001	69.5±0.3	66.4±0.3	<0.001
Sex (male)	1,498 (71.4%)	1,641 (70.2%)	NS	1,032 (67.7%)	925 (69.4%)	NS
Cigarette smoking, n (%)			NS			NS
Never	985 (66.7%)	1,136 (68.1%)		755 (68.2%)	693 (69.8%)	
Former	119 (8.1%)	144 (8.6%)		87 (7.9%)	70 (7.0%)	
Current	372 (25.2%)	387 (23.2%)		265 (23.9%)	230 (23.2%)	
Alcohol intake, n (%)			NS			0.001
Never	928 (49.0%)	1,010 (47.8%)		648 (47.1%)	644 (52.7%)	
Former	136 (7.2%)	178 (8.4%)		118 (8.6%)	65 (5.3%)	
Current	831 (43.9%)	926 (43.8%)		611 (44.4%)	512 (41.9%)	
BMI (kg/m^2)	24.0±0.8	24.0±0.8	NS	24.1±0.1	24.2±0.1	NS
Waist (cm)	86.0±0.2	86.1±0.2	NS	86.0±0.3	86.5±0.3	NS
Blood pressure (mmHg)						
Systolic	128.5±0.4	128.5±0.4	NS	128.0±0.5	128.9±0.5	NS
Diastolic	73.5±0.3	73.8±0.2	NS	73.5±0.3	73.6±0.3	NS
Heart rate (beats/min)	70.4±0.3	70.3±0.3	NS	70.9±0.4	71.3±0.4	NS
NYHA						
III/IV	–	–	–	99 (6.5%)	70 (5.3%)	NS
EF (%)	61.8±0.3	62.4±0.3	NS	61.3±0.4	61.2±0.4	NS
HFpEF (EF ≥50%)	1,616 (81.9%)	1,826 (82.6%)	NS	1,159 (79.6%)	1,007 (79.2%)	NS
HT	1,589 (76.1%)	1,803 (77.3%)	NS	1,208 (79.4%)	1,041 (78.5%)	NS
DM or fasting glucose ≥110mg/dl	515 (24.8%)	580 (24.9%)	NS	423 (27.9%)	330 (24.9%)	NS
Dyslipidemia	1,513 (72.6%)	1,692 (72.5%)	NS	1,145 (75.2%)	979 (73.9%)	NS
Serum creatinine ≥3.0mg/dl	33 (1.6%)	38 (1.6%)	NS	31 (2.0%)	27 (2.0%)	NS
Hemodialysis	23 (1.1%)	24 (1.0%)	NS	16 (1.1%)	19 (1.4%)	NS
IHD	1,124 (53.6%)	1,201 (51.4%)	NS	785 (51.5%)	708 (53.2%)	NS
HHD	217 (10.3%)	284 (12.1%)	NS	153 (10.0%)	144 (10.8%)	NS
CM	257 (12.3%)	281 (12.0%)	NS	221 (14.5%)	179 (13.4%)	NS
VHD	406 (19.4%)	474 (20.3%)	NS	299 (19.6%)	274 (20.6%)	NS
CHD	31 (1.5%)	42 (1.8%)	NS	27 (1.8%)	22 (1.7%)	NS
BNP	127.0±4.1	131.9±5.1	NS	140.3±5.6	155.6±9.0	NS
Exercise	2.0±0.03	14.3±0.2	<0.001	1.7±0.03	14.2±0.3	<0.001
Medications						
ACEI/ARB	1,261 (60.1%)	1,348 (57.7%)	NS	1,097 (71.9%)	957 (71.8%)	NS
β-blocker	776 (37.0%)	759 (32.5%)	<0.01	783 (51.3%)	679 (51.0%)	NS
Statin	988 (47.1%)	1,120 (47.9%)	NS	616 (40.4%)	568 (42.6%)	NS

Results are expressed as mean±SEM.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CHF, chronic heart failure; CM, cardiomyopathy; DM, diabetes mellitus; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHD, hypertensive heart disease; HT, hypertension; IHD, ischemic heart disease; NS, not significant; VHD, valvular heart disease.

lation,[3–7] so not only westernization of lifestyle but also reduced physical activity may be involved.[8]

Although physical activity is important for improvement lifestyle diseases, its impact on cardiovascular events in CHF remains to be elucidated, especially in terms of yearly changes in physical activity level. Thus, in the present study, we examined whether the baseline level of and yearly changes in physical activity influenced the occurrence of major cardiovascular events in CHF patients in our multicenter prospective cohort study.

Methods

The ethics committees of each institute approved the study protocol and all patients provided written informed consent.

Study Population

In this multicenter study, we prospectively enrolled 9,178 CHF patients in stages A/B/C/D by the ACC/AHA Guidelines[9] between September 2006 and December 2010 from 5 institutes in Japan.[2] For each patient, we used an online data collection system (Fujitsu Systems East Limited, Tokyo, Japan) to prospectively collect data from the participating hospitals: baseline demographic data; medications; comorbidities (previous myocardial infarction (MI) or stroke, dialysis, and atrial fibrillation); physical activity; cardiovascular events (acute MI [AMI], stroke, and HF hospitalization), and death.

Physical activity level (Exercise units) was assessed using a shortened version of the Japanese Exercise Guide 2006 published by the Japanese Ministry of Health, Labor, and Welfare

Table 2. Physical Activity Level at Baseline and Follow-up in Patients With Chronic Heart Failure

	Stage A/B (n=2,756)			Stage C/D (n=1,597)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Male	5.8, 9.4±0.2	4.3, 7.2±0.2	<0.001	5.0, 8.6±0.3	3.4, 6.3±0.2	<0.001
Female	4.9, 8.4±0.3	3.2, 5.6±0.3	<0.001	3.9, 7.7±0.5	2.3, 4.9±0.3	<0.001

Results are expressed as median, mean±SEM.
Abbreviation as in Table 1.

(**Table S1**): 1 Exercise (Ex) equals 1 METS×1 h (unit of physical activity).[10] Because of non-normal distribution, we divided the patients in stages A/B and C/D into high- and low-exercise groups according to the median value of physical activity in each group. Furthermore, we divided the patients into 4 groups, depending on each median of the baseline and follow-up physical activity levels: "low to low", "low to high", "high to low" and "high to high" groups.

Data Collection

Data for baseline demographics (age, sex, height, body weight, waist circumference, blood pressure and heart rate), CHF stage, medications (angiotensin-converting enzyme inhibitor [ACEI], angiotensin-receptor blocker [ARB], β-blocker, and statins), risk factors (hypertension, glucose intolerance/diabetes mellitus and dyslipidemia), biochemical data (lipid profile and glucose), plasma levels of brain natriuretic peptide (BNP), and comorbidities (ischemic heart disease [IHD], clinically diagnosed hypertensive heart disease, cardiomyopathy, valvular heart disease, and congenital heart disease) were based on the medical records.[2] Left ventricular ejection fraction (LVEF) was measured by echocardiography.[2]

The primary endpoints included all-cause death, AMI, stroke, HF hospitalization, and other cardiovascular events (except AMI, stroke, and HF hospitalization), such as percutaneous coronary intervention for stable effort angina and intervention for peripheral artery disease.

Definition of Metabolic Disorders

Dyslipidemia was diagnosed by use of lipid-lowering drugs and/or elevated lipid levels defined as low-density lipoprotein ≥140 mg/dl, plasma triglycerides ≥150 mg/dl or high-density lipoprotein <40 mg/dl in men and 50 mg/dl in women. Glucose intolerance/diabetes mellitus was diagnosed by use of antidiabetic drugs and/or fasting glucose ≥110 mg/dl. Hypertension was diagnosed by use of antihypertensive drugs and/or systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg.

Definition of Heart Failure

According to the ESC 2007 Guidelines, we further divided the patients with stages A/B/C/D CHF into 2 groups: HFpEF (LVEF ≥50%, n=5,608) and HFrEF (LVEF <50%, n=1,684).[11]

Statistical Analysis

Continuous variables are expressed as means and standard errors of mean (SEM), and categorical variables as counts and percentages. Comparisons between 2 groups were conducted with Welch's t-test for continuous variables and the chi-squared test for categorical variables. Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, USA) and the statistical computing software R version 2.15.1 (http://www.r-project.org). $P<0.05$ was considered to be statistically significant.

Results

Of the 9,178 consecutive patients with stages A/B and C/D of CHF, we were able to obtain baseline physical activity data for 7,292 (**Table S2**). There were 3,139 male and 1,296 female patients in stage A/B, and 1,957 male and 900 female patients in stage C/D (**Table 1**). Among them, data of the yearly changes in physical activity level during the 3-year follow-up were available for 4,353 patients (**Table S3**).

Baseline Physical Activity Level

The median level of physical activity was 8.9 Ex in men and 7.6 Ex in women in stage A/B, and 8.0 Ex in men and 6.6 Ex in women in stage C/D (**Table 2**). When the patients were divided into high- and low-exercise groups using the median value of physical activity, the high-exercise group was characterized by younger age, earlier stages of CHF, and less likelihood of taking medications such as ACEI/ARB or β-blocker (**Tables 1,S2**).

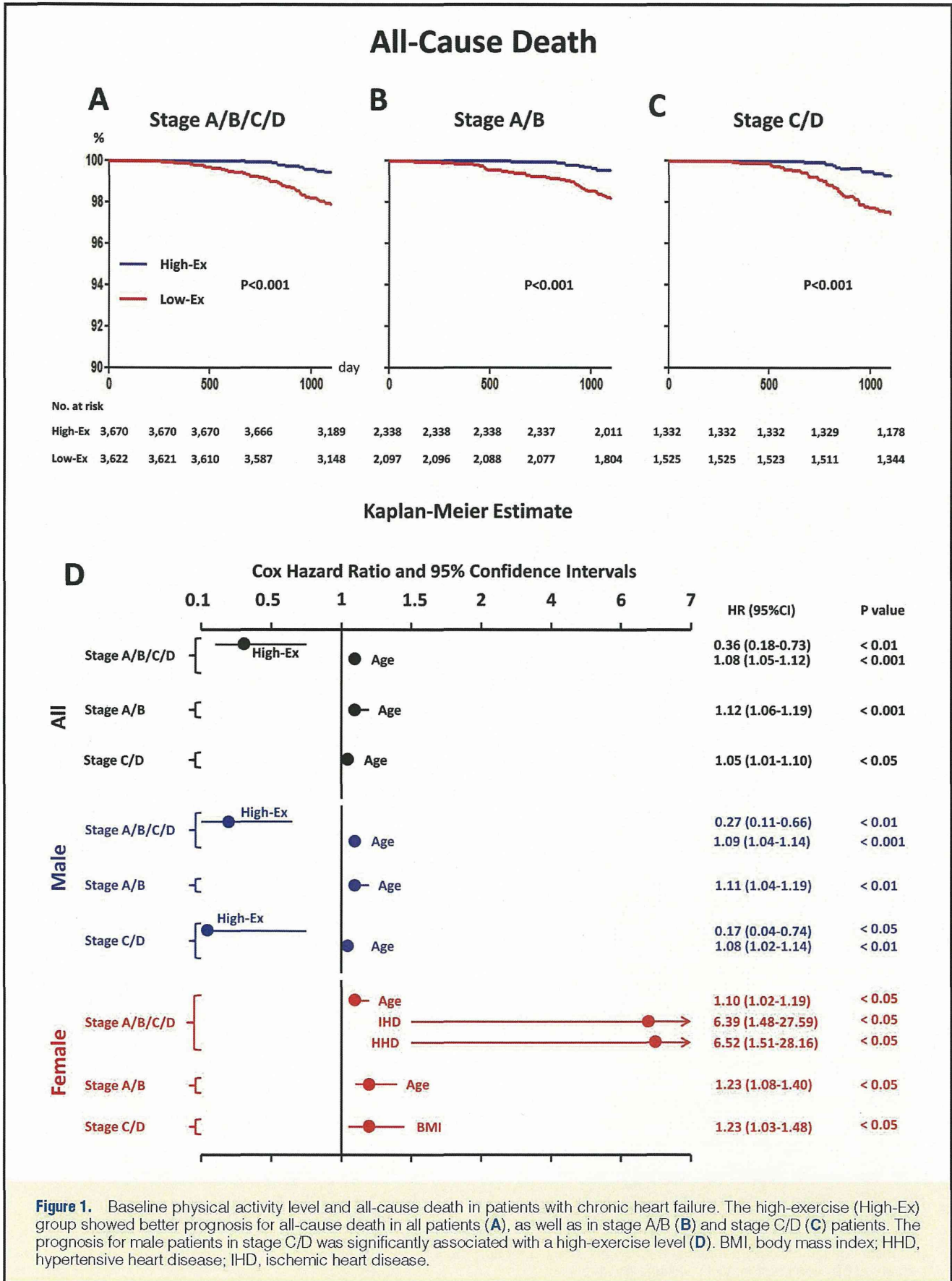### Baseline Physical Activity Level and Cardiovascular Events and Mortality

In all patients, as well as in both stages A/B and C/D, the prognosis for all-cause death was significantly better in the high-exercise group (**Figures 1A–C**), especially male patients in stage C/D (**Figure 1D**). It was also the case for admission for worsening HF except for female patients with stage A/B (**Figures 2A–D**).

Similarly, regarding other cardiovascular events (except AMI, stroke and HF hospitalization), the prognosis was significantly better in patients in the high-exercise group in both stage A/B and C/D (**Figures 3A–C**). In particular, multivariate analysis showed that a high level of physical activity is an independent prognostic factor for both male and female CHF patients in stages A–D (**Figure 3D**).

Regarding the occurrence of AMI, the prognosis of stage C/D patients was significantly better in the high-exercise group (**Figures S1A–C**); however, multivariate analyses showed only a significant correlation between baseline physical activity level and AMI in patients in stages A–D (**Figure S1D**). In stroke, the prognosis of stage A/B patients was significantly better in the high-exercise group (**Figures S3A–C**). Multivariate analyses showed a significant correlation between baseline physical activity level and stroke in stage A/B patients (**Figure S3D**).

Yearly Change in Physical Activity Level

During follow-up of 1.4±0.01 years, the physical activity level in male patients decreased from 9.4±0.2 to 7.2±0.2 Ex in stage A/B and from 8.6±0.3 to 6.3±0.2 Ex in stage C/D, and that in female patients also decreased from 8.4±0.3 to 5.6±0.3 Ex in stage A/B and from 7.7±0.5 to 4.9±0.3 Ex in stage C/D (**Table 2**). In the high-exercise group, a high level of physical activity was maintained in 809 (29%) stage A/B patients

All-Cause Death

A Stage A/B/C/D   **B** Stage A/B   **C** Stage C/D

High-Ex / Low-Ex   P<0.001 (A), P<0.001 (B), P<0.001 (C)

No. at risk

High-Ex	3,670	3,670	3,670	3,666	3,189	2,338	2,338	2,338	2,337	2,011	1,332	1,332	1,332	1,329	1,178
Low-Ex	3,622	3,621	3,610	3,587	3,148	2,097	2,096	2,088	2,077	1,804	1,525	1,525	1,523	1,511	1,344

Kaplan-Meier Estimate

D   Cox Hazard Ratio and 95% Confidence Intervals

Group		Variable	HR (95%CI)	P value
All	Stage A/B/C/D	High-Ex	0.36 (0.18-0.73)	< 0.01
		Age	1.08 (1.05-1.12)	< 0.001
	Stage A/B	Age	1.12 (1.06-1.19)	< 0.001
	Stage C/D	Age	1.05 (1.01-1.10)	< 0.05
Male	Stage A/B/C/D	High-Ex	0.27 (0.11-0.66)	< 0.01
		Age	1.09 (1.04-1.14)	< 0.001
	Stage A/B	Age	1.11 (1.04-1.19)	< 0.01
	Stage C/D	High-Ex	0.17 (0.04-0.74)	< 0.05
		Age	1.08 (1.02-1.14)	< 0.01
Female	Stage A/B/C/D	Age	1.10 (1.02-1.19)	< 0.05
		IHD	6.39 (1.48-27.59)	< 0.05
		HHD	6.52 (1.51-28.16)	< 0.05
	Stage A/B	Age	1.23 (1.08-1.40)	< 0.05
	Stage C/D	BMI	1.23 (1.03-1.48)	< 0.05

Figure 1. Baseline physical activity level and all-cause death in patients with chronic heart failure. The high-exercise (High-Ex) group showed better prognosis for all-cause death in all patients (**A**), as well as in stage A/B (**B**) and stage C/D (**C**) patients. The prognosis for male patients in stage C/D was significantly associated with a high-exercise level (**D**). BMI, body mass index; HHD, hypertensive heart disease; IHD, ischemic heart disease.