Table 1. Baseline Characteristics

	Male (n=3,234)	Female (n=1,502)	P-value
Age (years)	67.7±12.1	71.5±12.3	<0.001
Body weight (kg)	64.5±11.3	52.1±11.2	<0.001
Height (cm)	163.7±7.1	149.4±6.8	<0.001
Body mass index (kg/m²)	24±3.5	23.3±4.5	<0.001
NYHA functional class			<0.001
I	841 (26.1)	251 (16.8)	
II	2,080 (64.6)	1,011 (67.6)	
III	277 (8.6)	217 (14.5)	
IV	23 (0.7)	16 (1.1)	
Baseline cardiovascular disease			
Ischemic heart disease	1,749 (54.1)	483 (32.2)	<0.001
Cardiomyopathy	638 (19.7)	284 (18.9)	0.533
Valvular heart disease	263 (8.1)	235 (15.6)	<0.001
Hypertensive heart disease	193 (6.0)	90 (6.0)	<1.000
Risk factors			
Hypertension	2,518 (77.9)	1,154 (76.8)	0.441
Diabetes mellitus	1,176 (36.4)	476 (31.7)	0.002
Dyslipidemia	2,371 (73.3)	1,062 (70.7)	0.066
Smoking	713 (23.4)	92 (6.6)	<0.001
Previous history			
Myocardial infarction	1,304 (40.3)	299 (19.9)	<0.001
Cerebral infarction	114 (3.5)	55 (3.7)	0.879
Atrial fibrillation	1,055 (32.9)	516 (34.7)	0.231
Malignant diseases	399 (12.3)	155 (10.3)	0.049
Hemodynamics and LV function			
SBP (mmHg)	126.1±18.9	126.7±19.8	0.32
DBP (mmHg)	72.7±11.8	71.2±12.2	<0.001
Heart rate (beats/min)	71.7±14.6	74.1±15.5	<0.001
LVDd (mm)	53.6±9	48.8±8.9	<0.001
LVEF (%)	55.5±15.2	60±15.4	<0.001
LVEF≥50%	2,041 (65.8)	1,083 (75.1)	<0.001
Laboratory findings			
Hemoglobin (g/dl)	13.6±2	12.3±2.2	<0.001
BUN (mg/dl)	20±10.4	20.3±10.8	0.337
Creatinine (mg/dl)	1.1±0.9	0.9±0.7	<0.001
Albumin (mg/dl)	4.1±0.5	4±0.5	<0.001
LDL-C (mg/dl)	103.5±30.6	108.3±31	<0.001
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	61.6±24.5	58.3±22.8	<0.001
BNP (pg/ml)	184.7±275.6	219.6±323.8	<0.001

Data given as mean±SD or n (%).
BNP, brain natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

which 10,219 patients have been enrolled in the Tohoku district, Japan (NCT 00418041).[13–16]

Methods

CHART-2 Study

Details of the CHART-2 study have been described previously.[13–16] Briefly, the CHART-2 study is a multicenter, prospective observational study, in which 10,219 patients >20 years of age with significant coronary artery disease (stage A) and those in stages B–D HF were enrolled between October 2006 and March 2010.[13–16] All information, including medical history, laboratory data, and echocardiography data, were recorded at the time of enrollment, and thereafter annually by trained clinical research coordinators. Baseline cardiovascular disease, risk factors, and previous history were determined according to the data obtained from the case records at the time of enrollment. Valvular heart disease was defined as moderate to severe aortic and/or mitral valve disease without a previous history of valvular surgery, while hypertensive heart disease was defined as the presence of concentric hypertrophy (mean thickness of the ventricular septum and LV posterior wall ≥12 mm) in patients with a history of hypertension but without a diagnosis of hypertrophic cardiomyopathy. The CHART-2 study was approved by the local ethics committee in each participating hospital and informed consent was obtained from all patients.

Table 2. Past History and Medication

	Male (n=3,234)	Female (n=1,502)	P-value
Past history			
PCI	1,231 (38.1)	304 (20.2)	<0.001
CABG	344 (10.6)	86 (5.7)	<0.001
ICD/CRT implantation	111 (3.4)	37 (2.5)	0.009
Other pacemaker implantation	209 (6.5)	165 (11)	<0.001
Medications			
Aspirin	2,016 (62.3)	706 (47)	<0.001
β-blocker	1,659 (51.3)	660 (43.9)	<0.001
RAS inhibitor	2,542 (78.6)	1,148 (76.4)	0.101
Diuretics	1,609 (49.8)	897 (59.7)	0.001
Calcium channel blocker	1,243 (38.4)	588 (39.1)	0.662
Statin	1,271 (39.3)	532 (35.4)	0.011

Data given as n (%).
CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system.

Study Design

Among the 10,219 patients enrolled, 4,736 had HF in stage C/D. Stages A–D were defined at the time of registration in the CHART-2 study, according to the ACC/AHA guidelines classification:[17] stage A, at high risk for HF but without structural heart disease or symptoms of HF; stage B, structural heart disease but without signs or symptoms of HF; stage C, structural heart disease with prior or current symptoms of HF; and stage D, refractory HF requiring specialized interventions. The diagnosis of HF was made based on the criteria of the Framingham study.[1] Among the 4,736 stage C/D patients, 3,234 (68%) were male and 1,502 (32%) were female. Using the registry data of these patients, we examined gender differences in terms of clinical characteristics, management and long-term outcome in patients with stage C/D HF.

Statistical Analysis

All continuous variables are shown as mean±SD. Clinical characteristics of female and male patients were compared using Welch's t-test and Fisher's exact test with 2-sided P-values. Primary outcome measures of survival and HF-free survival were estimated by the Kaplan-Meier curve, and tested by the log-rank test in both genders. Incidence rates per 1,000 person-years for all-cause death, modes of death, HF requiring admission, acute myocardial infarction (AMI) and stroke were compared with the exact binominal test. Determinants of all-cause death were examined by the multivariate Cox proportional hazard model. Potential confounding factors with regard to baseline characteristics and treatments were included in multivariate analysis. The covariates for the multivariate analysis included gender, age, body mass index (BMI), history of hypertension, diabetes mellitus, dyslipidemia, and smoking, LVEF, systolic blood pressure (SBP), heart rate, hemoglobin, serum creatinine and brain natriuretic peptide (BNP) and treatment with β-blocker, renin-angiotensin system inhibitor (RASI) and statin. Interactions of gender and subgroups were estimated by the Cox proportional hazard model including interaction terms using the same variables listed here. Continuous variables were transformed into binary variables for estimation of interactions in the Cox model. P<0.05 and P-value for interaction <0.1 were considered as statistically significant in the present study. Statistical analysis was performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, USA) and R version 3.0.2.

Results

Baseline Characteristics

Baseline characteristics are listed in **Table 1**. Among the 4,736 Stage C/D patients, 1,502 (32%) were female and were 3.8 years older than men. Compared with men, women were more likely to be less obese, and were characterized by lower prevalence of ischemic heart disease, and had higher prevalence of valvular heart disease. In contrast, the prevalences of diabetes, smoking, MI and malignant disease were lower in women than in men. Although women had a higher prevalence of preserved LV function, they had relatively severe manifestation of CHF compared with men, including higher heart rate, higher NYHA class and increased BNP level. Baseline information regarding CHF treatment at the time of registration is given in **Table 2**. Women were less frequently treated with aspirin, β-blocker and statin, but more frequently with diuretics. In accordance with the lower prevalence of ischemic heart disease, women were less likely to undergo percutaneous coronary intervention or coronary artery bypass grafting. Furthermore, women were less frequently treated with implantable cardioverter defibrillator and/or cardiac resynchronization therapy, while more frequently treated with other cardiac pacemaker.

Gender Differences in Long-Term Outcome

There were 674 deaths during a median follow-up of 3.8 years, of which 338 (50.1%), 285 (42.3%), and 51 (7.7%) were due to cardiovascular, non-cardiovascular and unknown causes, respectively. Incidence of all-cause death was similar between the genders (52.4/1,000 vs. 47.3/1,000 person-years for women and men, respectively, P=0.225; **Figures 1,2**). Incidences of CHF requiring admission, AMI and stroke were also similar between the genders (**Figure 2**). As shown in **Figure 3**, women had higher cardiovascular mortality than men, particularly that due to HF, while men died more frequently of cancer. Although incidence of all-cause death was similar between the genders, multivariate Cox regression analysis revealed that women had a reduced risk of all-cause events than men after adjustment for clinical variables (hazard ratio [HR], 0.791; 95% confidence interval (95% CI): 0.640–0.9798, P=0.031), while it was not evident for cardiovascular death (HR, 1.027; 95% CI: 0.767–1.374, P=0.859) or HF requiring hospitalization (HR 0.858; 95% CI: 0.701–1.051, P=0.139; **Table 3**). Subgroup anal-

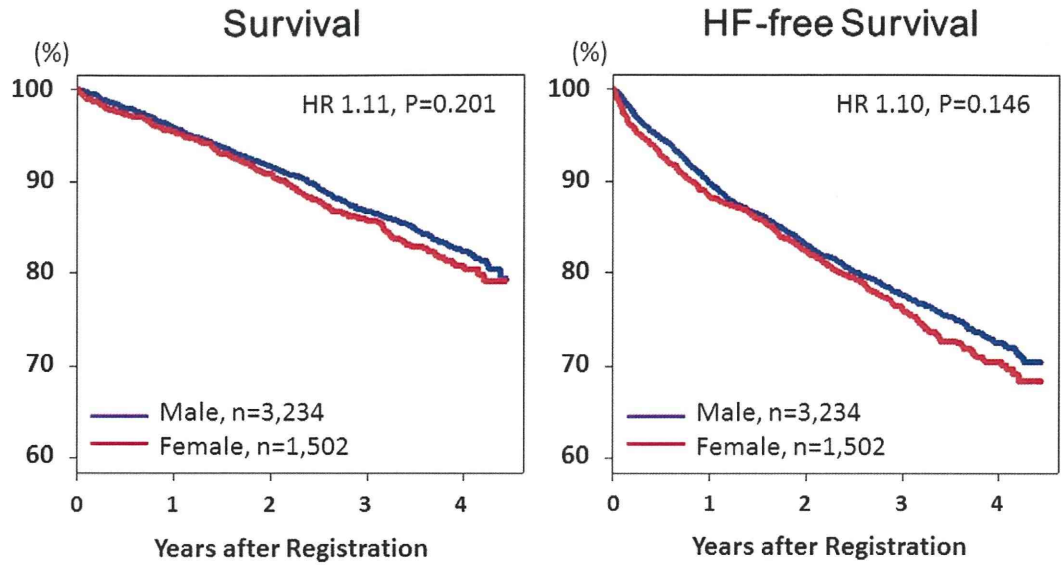

Figure 1. Kaplan-Meier estimates for survival. There were no differences in survival and heart failure (HF)-free survival between female and male patients. HR, hazard ratio.

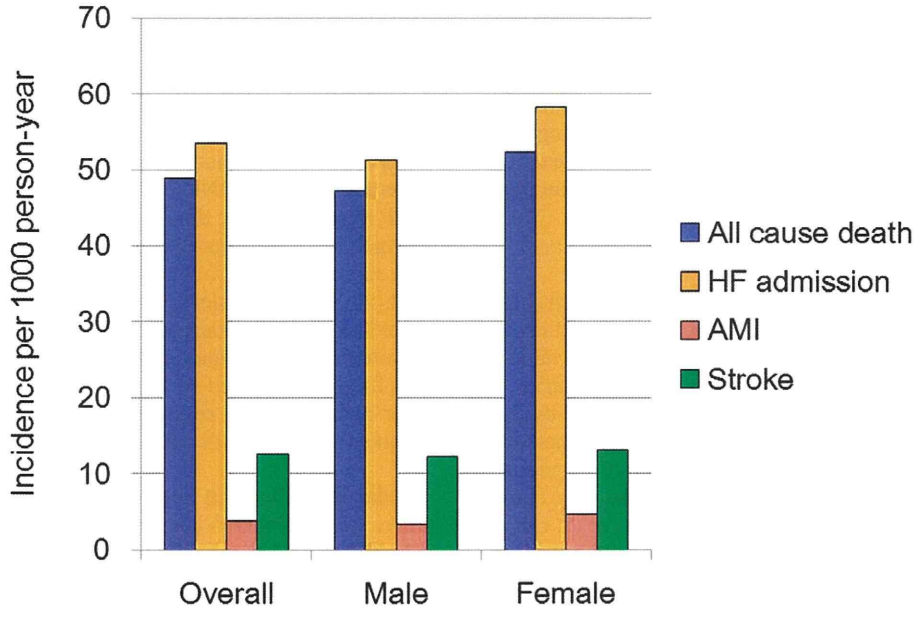

Figure 2. Incidence of all-cause death and cardiovascular event rates. Among the adverse events, death and heart failure (HF) requiring admission were most frequent. Rates of each event were similar between the genders during the median follow-up of 3.1 years (P=0.225, 0.113, 0.293, and 0.678 for all-cause death, HF admission, acute myocardial infarction [AMI], and stroke, respectively).

ysis showed that the prognostic impact of clinical variables on all-cause mortality was similar between the genders (**Figure 4**).

Discussion

The major findings of the present study are that substantial gender differences exist among Japanese HF patients, and that female CHF patients have better long-term survival compared with male CHF patients after adjustment for clinical parameters, although crude mortality rate was similar between the genders, possibly reflecting the relatively severer clinical manifestation in women. To the best of our knowledge, this is

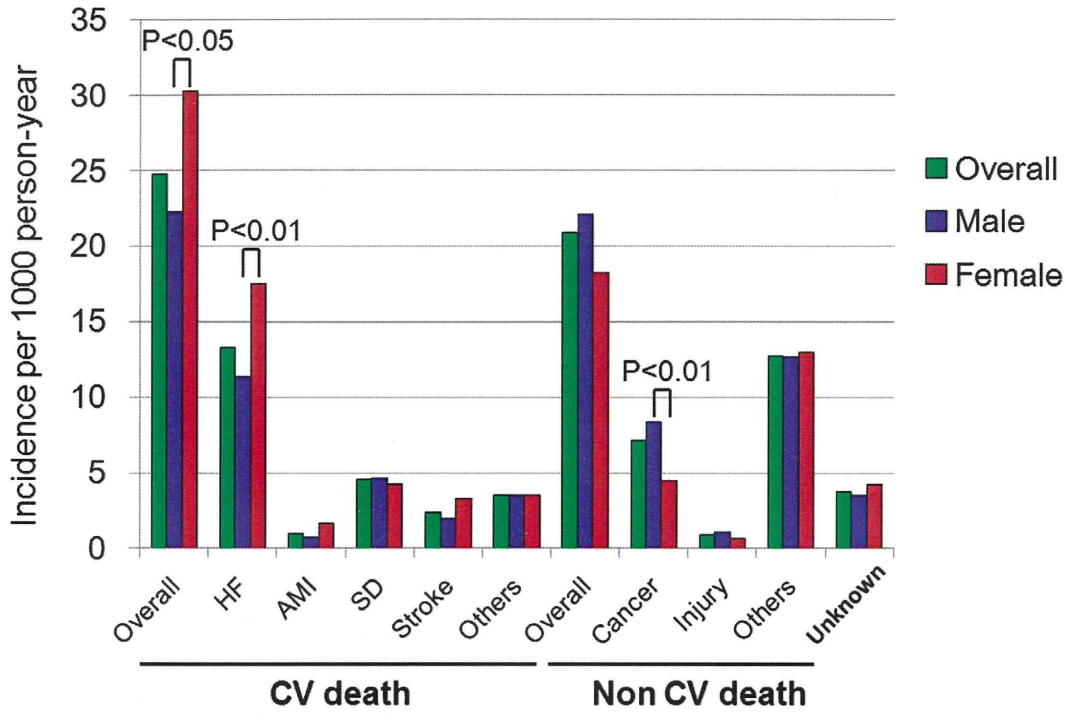

Figure 3. Gender and mode of death. Prevalence of modes of death was different between the genders. Particularly, incidence of death due to heart failure (HF) was more frequent in women, whereas that of malignant disease was more frequent in men. AMI, acute myocardial infarction; CV death, cardiovascular death; non-CV death, non-cardiovascular death; SD, sudden death.

Table 3. Predictors of All-Cause Death, CV Death and HF Admission

	All-cause death			CV death			HF admission		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Female gender	0.791	0.640–0.979	0.031	1.027	0.767–1.374	0.859	0.858	0.701–1.051	0.139
Age per 10 years	1.568	1.413–1.741	<0.001	1.541	1.333–1.782	<0.001	1.084	0.995–1.181	0.066
BMI	0.955	0.929–0.981	0.001	0.985	0.949–1.022	0.410	1.015	0.991–1.038	0.219
Hypertension	0.894	0.719–1.113	0.316	0.877	0.648–1.188	0.396	1.061	0.857–1.314	0.585
Diabetes mellitus	1.127	0.936–1.358	0.208	0.986	0.756–1.286	0.916	1.249	1.047–1.489	0.013
Dyslipidemia	0.961	0.782–1.181	0.708	1.062	0.790–1.428	0.691	0.794	0.649–0.972	0.025
Smoking	1.168	0.963–1.417	0.114	1.124	0.855–1.478	0.403	0.903	0.749–1.090	0.289
LVEF per 10%	0.988	0.929–1.051	0.704	0.920	0.844–1.003	0.057	0.855	0.806–0.907	<0.001
SBP per 10 mmHg	0.954	0.909–1.000	0.052	0.925	0.864–0.989	0.023	0.981	0.937–1.027	0.420
Heart rate per 10 beats/min	1.096	1.038–1.157	0.001	1.074	0.994–1.160	0.072	1.040	0.987–1.096	0.146
Hemoglobin	0.882	0.838–0.928	<0.001	0.910	0.848–0.977	0.009	0.866	0.826–0.908	<0.001
Creatinine	1.154	1.082–1.231	<0.001	1.166	1.065–1.277	0.001	0.987	0.906–1.075	0.762
BNP per 100 pg/ml	1.494	1.362–1.639	<0.001	1.696	1.484–1.938	<0.001	1.659	1.518–1.813	<0.001
β-blocker	0.826	0.683–0.998	0.048	0.767	0.588–1.000	0.050	0.870	0.726–1.043	0.131
RAS inhibitor	1.054	0.833–1.335	0.661	1.161	0.813–1.660	0.412	1.138	0.887–1.460	0.310
CCB	0.979	0.808–1.186	0.831	1.122	0.857–1.469	0.404	1.019	0.844–1.231	0.843
Statin	0.850	0.682–1.060	0.149	0.975	0.724–1.314	0.869	0.909	0.739–1.118	0.366
Diuretics	1.388	1.133–1.700	0.002	1.874	1.374–2.556	<0.001	2.337	1.878–2.909	<0.001

BMI, body mass index; CCB, calcium channel blocker; CV, cardiovascular; HF, heart failure. Other abbreviations as in Tables 1,2.

the first study to identify gender differences in clinical characteristics, management and long-term outcome in a large CHF cohort in Japan.

Gender Difference in Clinical Characteristics in Japanese CHF Patients

The present study identified gender differences in clinical characteristics, management and long-term outcome in patients

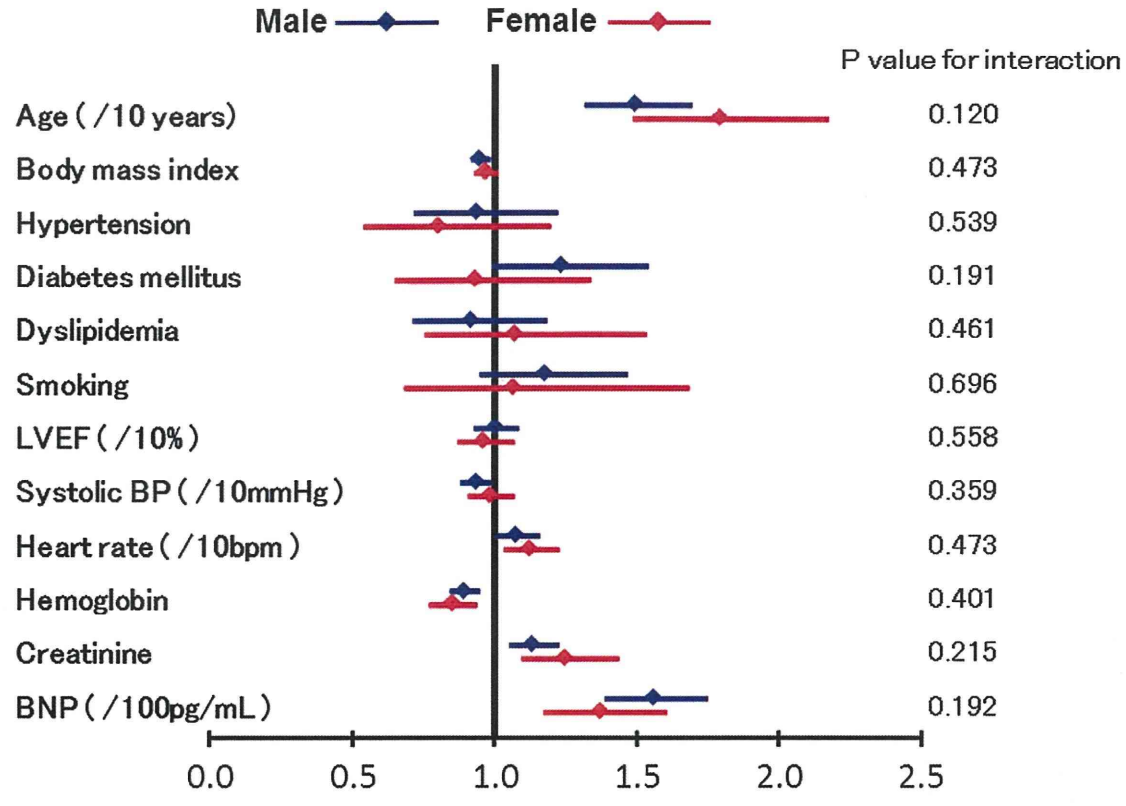

Figure 4. Predictors for all-cause mortality in both genders. Predictors for all-cause mortality were compared between the genders on multivariate Cox proportional hazard modeling. P-value for interaction was significant (P<0.1) for diabetes mellitus. BNP, brain natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fractio

with stage C/D HF registered in the CHART-2 study, the largest prospective observational study for HF in Japan. The present results are of great importance given that no studies have comprehensively reported gender differences in HF patients in a large cohort in Japan. We initially found that clinical characteristics were different between the genders in stage C/D HF patients. Particularly, female patients were characterized by higher age, higher prevalence of preserved LVEF, lower prevalence of ischemic heart disease and higher prevalence of valvular heart disease in the present study (**Table 1**), consistent with previous reports.[9–11] The clinical manifestations of HF appeared to be more severe in women compared with men, in that female patients had a higher NYHA functional class and elevated serum BNP despite the higher prevalence of preserved LVEF (**Table 1**). Treatment with evidence-based medication (EBM), however, was equally (RASI) or even less frequently (β-blockers and statins) given to women compared with men (**Table 2**). Thus, it is highly possible that female patients with stage C/D HF are less adequately treated and consequently manifest severer HF conditions compared with male patients. But it is also possible that EBM itself has not been fully established for female patients, who have a higher prevalence of preserved LVEF.[18–26]

Gender Difference in Long-Term Prognosis in Japanese HF Patients

One of the strengths of the present study is that we calculated the incidence of all-cause death and other events by the person-year method. The analysis found that female and male patients with stage C/D HF experienced 52.4 and 47.3 deaths per 1,000 person-years (P=0.225) and 58.3 and 51.3 cases of HF requiring admission per 1,000 person-years (P=0.189), respectively. Thus, there are no gender differences in all-cause death and HF requiring admission, although the incidences of both events are much higher than those of AMI or stroke (**Figure 2**). Regarding the modes of death in HF patients, the incidence of cardiovascular death, particularly that due to HF, was significantly higher in female patients, whereas that of cancer death was more frequent in male patients (**Figure 3**). It is thus conceivable that more severe clinical manifestations in female patients resulted in the increased cardiovascular mortality in the present study.

It has been generally accepted that female gender is associated with better survival (either crude and/or age-adjusted) compared with male gender in the broad spectrum of HF.[1–11] Several studies suggested that the gender difference in long-term prognosis of HF could be explained by the higher prevalence of preserved LVEF in women.[4–6] This, however, should be viewed with caution,[9] because gender differences in LVEF in HF patients are due to underlying disease, age and other factors. In the present study, the female CHF patients had better long-term survival than men after adjustment for clinical parameters including LVEF. Thus, unmeasured confounding factors other than LVEF could have affected the better mortality in female CHF patients in the present study.

It is noteworthy that the crude mortality rate did not differ

between the genders in the present study, whereas most of the previous studies reported better crude or unadjusted survival for female CHF patients.[1–3,7–10] One possible explanation for this discrepancy is the higher prevalence of HFpEF in the present study (65.8% for men and 75.1% for women, **Table 1**), given that similar crude mortality between the genders was also reported in patients with HFpEF enrolled in the ancillary arm of the Digitalis Investigation Group trial.[11] Another explanation would be that female CHF patients might have visited the hospital with a more advanced stage of HF than male CHF patients in the present study, a possible problem in daily practice in Japan.

Life Expectancy in Female CHF Patients

In Japan, the average life expectancy has been increasing in both genders. In 2010, the expectancy at birth was 79.55 years for men and 86.30 years for women,[28] with a 6.35-year difference between the genders that is greater than the 3.8-year difference between the genders in the present study (67.7 vs. 71.5 years, P<0.001). Given that the average life expectancy for a 67.7-year-old Japanese man and 71.5-year-old Japanese women is between 16.44 and 17.20 years, and between 17.73 and 18.58 years in 2010, respectively,[27] women could live an average of approximately 1.5 years longer than men in the general population if their age distribution is similar to that in the present study. The present study, however, found that female CHF patients did not have better survival than men in real-world practice. These lines of evidence suggest that life expectancy was shortened in female HF patients compared with male HF patients in the present study. Further studies are warranted to achieve better HF management based on gender differences, especially for women.

Study Limitations

Several limitations should be mentioned. First, the number of death events was relatively small, which might have limited the power to find significant observations. Second, because all subjects were recruited in the Tohoku district in Japan, caution may be needed when generalizing the present results to other cohorts.

Conclusions

Substantial gender differences were found in clinical characteristics, management and long-term outcome in the present CHART-2 Study. Although women had better survival than men after adjustment for baseline differences, crude mortality rate was similar between the genders, possibly reflecting the relatively severer clinical manifestations in female patients with HF in real-world practice.

Acknowledgments

We thank all the members of the Tohoku Heart Failure Society and the staff of the Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, for their contributions (**Appendix**). This study was supported by the Grants-in-Aid from the Ministry of Health, Labor, and Welfare (H.S.). H.S. received lecture fees from Bayer Yakuhin (Osaka, Japan), Daiichi Sankyo (Tokyo, Japan) and Novartis Pharma (Tokyo, Japan). The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by the unrestricted research grants from Daiichi Sankyo (Tokyo, Japan), Bayer Yakuhin (Osaka, Japan), Kyowa Hakko Kirin (Tokyo, Japan), Kowa Pharmaceutical (Tokyo, Japan), Novartis Pharma (Tokyo, Japan), Dainippon Sumitomo Pharma (Osaka, Japan), and Nippon Boehringer Ingelheim (Tokyo, Japan).

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Appendix

CHART-2 Study Investigators

1. Executive Committee

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Advance Publication by-J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Usefulness of Combined Risk Stratification With Heart Rate and Systolic Blood Pressure in the Management of Chronic Heart Failure

– A Report From the CHART-2 Study –

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Background: The appropriate target ranges of heart rate (HR) and systolic blood pressure (SBP) for the management of chronic heart failure (CHF) patients remain to be elucidated in a large-scale cohort study.

Methods and Results: We examined 3,029 consecutive CHF patients with sinus rhythm (SR) (mean age, 67.9 years) registered in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study (CHART-2; NCT00418041). There were 357 deaths (11.8%) during the median follow-up of 3.1 years. We first performed the classification and regression tree analysis for mortality, identifying SBP <89 mmHg, HR >70 beats/min and SBP <115 mmHg as the primary, secondary and tertiary discriminators, respectively. According to these, we divided the patients into low- (n=1,131), middle- (n=1,624) and high-risk (n=274) groups with mortality risk <10%, 10–20% and >20%, respectively. The low-risk group was characterized by SBP >115 mmHg and HR <70 beats/min and the high-risk group by SBP <89 mmHg regardless of HR values or SBP 89–115 mmHg and HR >76 beats/min. Multivariate Cox regression analysis revealed that the hazard ratio of all-cause death for low-, middle- and high-risk groups was 1.00 (reference), 1.48 (95% confidence interval (CI): 1.10–1.99, P=0.009) and 2.44 (95% CI 1.66–3.58, P<0.001), respectively. Subgroup analysis revealed that age ≥70 years, diabetes, or reduced left ventricular function had higher hazard ratios in the high-risk group.

Conclusions: The results demonstrate the usefulness of combined risk stratification of HR and SBP in CHF patients with SR.

Key Words: CHART-2; Chronic heart failure; Heart rate; Prognosis; Systolic blood pressure

Elevated resting heart rate (HR) is an independent risk factor for mortality not only in the general population[1,2] but also in patients with coronary artery disease (CAD)[3] and those with chronic heart failure (CHF).[4] Furthermore, HR reduction is also associated with improvement in the prognosis of patients after myocardial infarction[5] and those with CHF.[6,7] According to the European Society of Cardiology (ESC) guidelines, HR should be controlled to less than 70 beats/min in CHF patients with reduced left ventricular ejection fraction (LVEF).[8] Thus, the management of HR is an important therapeutic strategy in CHF management. High systolic blood pressure (SBP) is also an adverse prognostic marker in both the general population[9] and patients with cardiovascular diseases.[10,11] However, increased SBP is associated with reduced mortality in CHF patients,[12] a phenomenon known as "reverse epidemiology".[13]

In the management of CHF, β-blockers are widely used because they have been shown to reduce mortality, particularly in patients with reduced LVEF.[14,15] However, physicians often hesitate to use β-blockers for CHF patients with reduced LVEF and lower SBP, because the drugs may further decrease SBP and HR. Indeed, in real-world practice, only a small percentage of CHF patients receive target doses of β-blockers despite

Received June 10, 2013; revised manuscript received July 24, 2013; accepted August 1, 2013; released online October 1, 2013 Time for primary review: 14 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-13-0725

Table 1. Baseline Characteristics of the Patients With Chronic Heart Failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study

	All patients (n=3,029)	Low-risk group (n=1,131)	Middle-risk group (n=1,624)	High-risk group (n=274)	P value for 3 groups
Age (years)	67.9±12.8	69.0±11.8	67.4±13.1	66.9±14.6	0.002
Male (%)	70.1	73.4	68.4	66.1	0.006
History of admission for HF (%)	47.1	42.1	48.3	60.2	<0.001
Etiology					
Ischemic heart disease (%)	58.8	60.9	58.9	48.9	0.001
Cardiomyopathy (%)	16.8	16.1	15.8	25.5	<0.001
Valvular heart disease (%)	17.1	16.3	17.7	17.2	0.63
Hypertensive heart disease (%)	10.1	11.8	9.8	5.1	0.004
Comorbidities (%)					
Hypertension	78.7	85.5	76.8	61.3	<0.001
Diabetes	28.3	28.6	27.8	29.6	0.78
Hyperuricemia	42.1	42.5	41.1	46.0	0.29
Cerebrovascular disease	15.9	15.8	16.4	13.1	0.4
PAF	7.8	7.8	7.8	6.2	0.64
Clinical status					
NYHA class III or IV (%)	9.9	7.8	10.2	17.2	<0.001
Body mass index (kg/m^2)	23.7±4.7	24.2±4.3	23.7±4.8	22.0±5.5	<0.001
SBP (mmHg)	128±19	135±14	127±19	103±10	<0.001
DBP (mmHg)	73±12	74±10	73±13	64±10	<0.001
HR (beats/min)	71±14	60±6	76±13	86±11	<0.001
Measurements					
LVEF (%)	57.4±15.7	60.7±14.1	56.2±15.7	52.3±10.5	<0.001
LVDd (mm)	51.8±9.1	51.4±8.2	52.1±9.5	52.3±10.5	0.12
Hemoglobin (g/dl)	13.2±2.1	13.3±2.2	13.2±2.0	12.9±2.8	0.02
Blood urea nitrogen (mg/dl)	19.6±10.7	19.3±10.9	19.4±9.8	21.5±13.7	0.007
Serum creatinine (mg/dl)	1.1±0.9	1.0±0.6	1.1±1.0	1.2±1.1	0.008
Serum sodium (mEq/L)	141±2.8	141±2.7	141±2.7	140±3.3	<0.001
Serum potassium (mEq/L)	4.4±0.8	4.4±0.4	4.4±0.4	4.5±0.5	0.04
Brain natriuretic peptide (pg/ml)	76.3	70.7	73.2	135	<0.001
Medications					
ACE inhibitor (%)	44.1	42.4	44.3	50.0	0.07
ARB (%)	32.5	34.9	31.7	27.4	0.03
β-blocker (%)	47.5	50.3	45.9	46.0	0.06
Loop diuretics (%)	39.8	32.4	42.4	54.4	<0.001
Aldosterone inhibitor (%)	20.4	15.2	20.8	39.1	<0.001
Digitalis (%)	12.1	9.5	13.1	17.2	<0.001

Results of continuous values are presented as mean±SD. BNP levels are presented as medians.
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; SBP, systolic blood pressure.

being recommended in guidelines, especially those with lower SBP.[16,17] Furthermore, the appropriate target ranges of HR and SBP for the management of CHF have been studied separately[4,6,7] and the usefulness of combined risk stratification with HR and SBP remains to be examined in a large-scale cohort study.

In the present study, we addressed this important clinical issue in a registry, namely the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (n=10,219) (NCT 00418041).[18]

Methods

Population and Inclusion Criteria

Details of the design, purpose, and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[18] Briefly, eligible patients were aged ≥20 years with significant CAD or in stages B, C and D as defined by the Guidelines for the Diagnosis and Management of Heart Failure in Adults.[19] Patients were classified as having HF by experienced cardiologists of 24 participating hospitals, using the criteria of the Framingham Heart Study.[20] The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively enrolled after written informed consent was obtained. The CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients registered from the participating hospitals. All data and events will be surveyed at least once each year until September 2018.

In the CHART-2 Study, each patient's resting HR was measured by ECG after a 2–3-min rest while supine. SBP was mea-

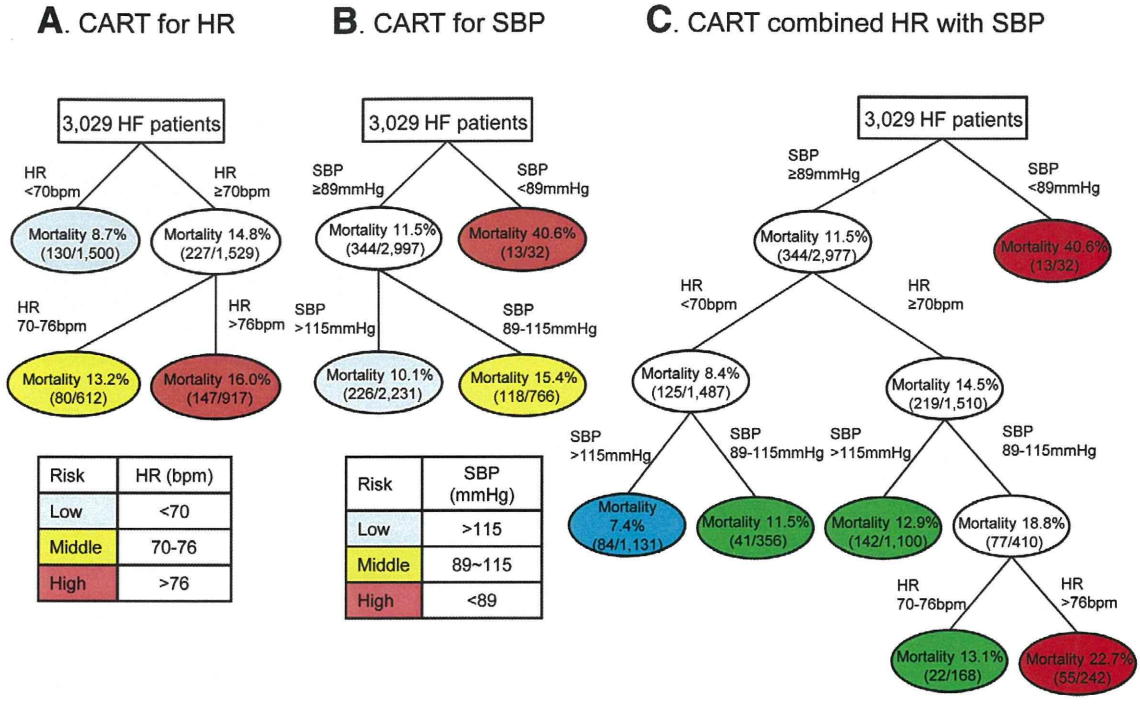

Figure 1. CART analysis for (**A**) heart rate (HR) and (**B**) systolic blood pressure (SBP). (**C**) CART analysis for combined HR and SBP. CART, classification and regression tree.

sured while seated after a 2–3-min rest. In the present study, we excluded asymptomatic patients in stage B (n=5,484) and patients with a pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy (n=486). We also excluded patients with chronic atrial fibrillation (n=1,079), those without sufficient data (n=89), and those who could not be followed up (n=53). Finally, 3,029 CHF patients in sinus rhythm (SR) at baseline were included in the present study. Among them, 236 patients had a history of paroxysmal atrial fibrillation (PAF).

Follow-up Survey and Study Outcomes

We conducted the second survey of survival in November 2011 and the median follow-up period of the study population was 3.1 years. The outcome of this study was all-cause death.

Statistical Analysis

In the present study, we performed classification and regression tree (CART) analysis[21] in order to identify the HR and SBP that would classify HF patients for all-cause death. CART analysis is an empirical, statistical technique based on recursive partitioning of the data space to predict the response.[21] The models are obtained by binary splitting of the data by the value of predictors, and the split variable and split-point are automatically selected from possible predictor values to achieve the best fit. Then, 1 or both "child nodes" are split into 2 or more regions recursively, and the process continues until some stopping rule is applied. Finally, the result of this process is represented as a binary decision tree.

First, we performed CART analysis for both HR and SBP to identify low-, middle-, and high-risk values of HR and SBP. Second, using these risk values of HR and SBP, we performed CART analysis by crossing over the risk values of HR and SBP. Then, we divided the study subjects into 3 risk groups according to the CART analysis and mortality rate: low-, middle-, and high-risk groups. We developed Kaplan-Meier curves and Cox proportional hazard models to compare the risk for all-cause death among the 3 groups. We constructed the following 3 Cox proportional hazard models; (a) unadjusted, (b) age- and sex-adjusted and (c) fully adjusted for clinical status, comorbidities and medications. We included the following covariates, which potentially influence the outcomes: age; sex; NYHA class; history of HF admission and malignant tumor; ischemic etiology of HF; LVEF; body mass index (BMI); serum sodium, serum potassium, serum creatinine, blood urea nitrogen (BUN) concentrations; comorbidities (anemia defined as hemoglobin <12 g/dl in females and <13 g/dl in males, diabetes mellitus, hyperuricemia and cerebrovascular disease); and medications (β-blockers, renin-angiotensin system inhibitors, calcium-channel blockers, loop diuretics, aldosterone antagonists and digitalis). We also performed subgroup analyses based on sex, age (<median or ≥median), history of PAF, LVEF (<50% or ≥50%), history of diabetes, cause of HF (ischemic or non-ischemic), and β-blocker therapy. Comparisons among the 3 groups were performed by chi-square test. Continuous data are described as mean±standard deviation and discrete-valued data as %.

The statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc, Chicago, IL, USA) and R 2.15.2.[22] Statistical significance was defined as a 2-sided P-value less than 0.05.

Results

Baseline Characteristics of All Study Subjects (Table 1)

Mean age was 67.9±12.8 years, and male patients accounted for 70.1% and ischemic HF for 58.8% of the study population. Mean