



Gender Differences in Clinical Characteristics, Treatment and Long-Term Outcome in Patients With Stage C/D Heart Failure in Japan

– Report From The CHART-2 Study –

Yasuhiko Sakata, MD, PhD; Satoshi Miyata, PhD; Kotaro Nochioka, MD, PhD;
Masanobu Miura, MD, PhD; Tsuyoshi Takada, MD; Soichiro Tadaki, MD;
Jun Takahashi, MD, PhD; Hiroaki Shimokawa, MD, PhD

Background: The gender differences in patients with chronic heart failure (CHF) remain to be fully elucidated in the Japanese population.

Methods and Results: We examined gender differences in clinical characteristics, treatment and long-term outcome in 4,736 consecutive CHF patients in stage C/D (mean age, 69 years) out of 10,219 patients registered in the CHF Registry, named CHART-2 Study (NCT 00418041). Compared with male patients (68%, n=3,234), female patients (32%, n=1,502) were 3.8 years older and had lower prevalence of ischemic heart disease, diabetes, smoking, myocardial infarction and cancer. At baseline, women had higher prevalence of preserved left ventricular function but had higher NYHA functional class and increased brain natriuretic peptide level. In women, aspirin, β -blockers and statins were less frequently used and diuretics were more frequently used. Crude mortality rate was similar between the genders during the median 3.1-year follow-up (52.4/1,000 and 47.3/1,000 person-years for women and men, respectively, $P=0.225$). On multivariate Cox regression analysis, women had a reduced risk of mortality (adjusted HR, 0.791; 95% CI: 0.640–0.979, $P=0.031$).

Conclusions: Substantial gender differences exist in stage C/D CHF patients in real-world practice in Japan. Although female CHF patients had better survival than male patients after adjustment for baseline differences, crude mortality rate was similar between the genders, possibly reflecting relatively severer clinical manifestations in women. (*Circ J* 2014; **78**: 428–435)

Key Words: Gender difference; Heart failure; Observational study; Prognosis

It has been reported that women with chronic heart failure (CHF) have better survival than men in general.^{1–11} The Framingham Study reported that among the 5,192 subjects without CHF aged 30–62 at the time of entry in 1949,¹ overt heart failure (HF) developed in 142 during the 16-year follow-up, that the incidence rate was greater in men than in women and that the probability of death within 5 years after onset of HF was 62% in men and 42% in women.¹ After this report, a number of studies have been conducted that also found better survival in female patients compared with male patients,^{2–11} in the broad spectrum of HF, including advanced CHF⁷ and HF with preserved left ventricular (LV) ejection

fraction (HFpEF).^{10,11}

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In Japan, the number of CHF patients has been rapidly increasing along with the advancement of the aging society, particularly in women.^{12,13} It remains to be fully elucidated, however, whether gender differences exist among Japanese CHF patients. Thus, in the present study, we addressed this important issue using a CHF registry database, named Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2), a prospective multicenter observational study, in

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Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

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Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryō-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp

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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·min ⁻¹ ·1.73m ⁻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 \geq 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 \pm 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.

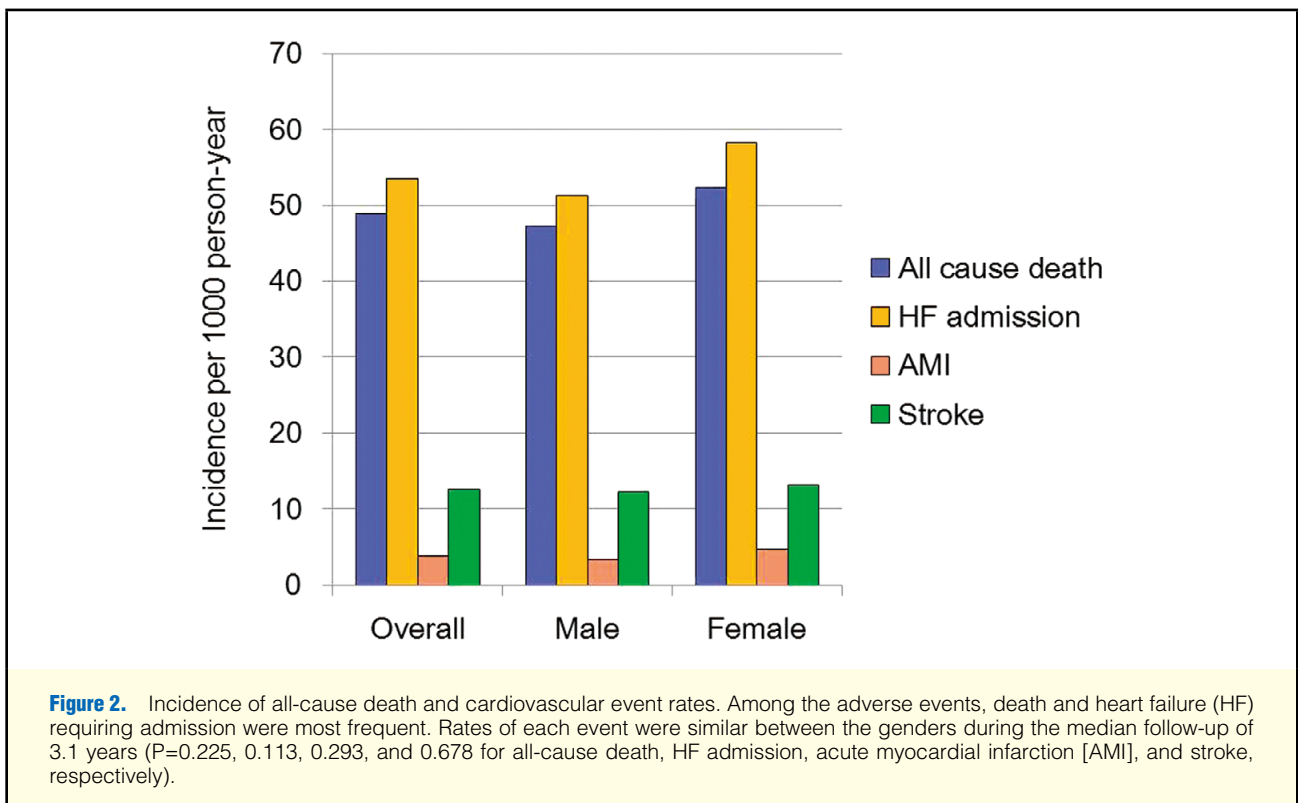
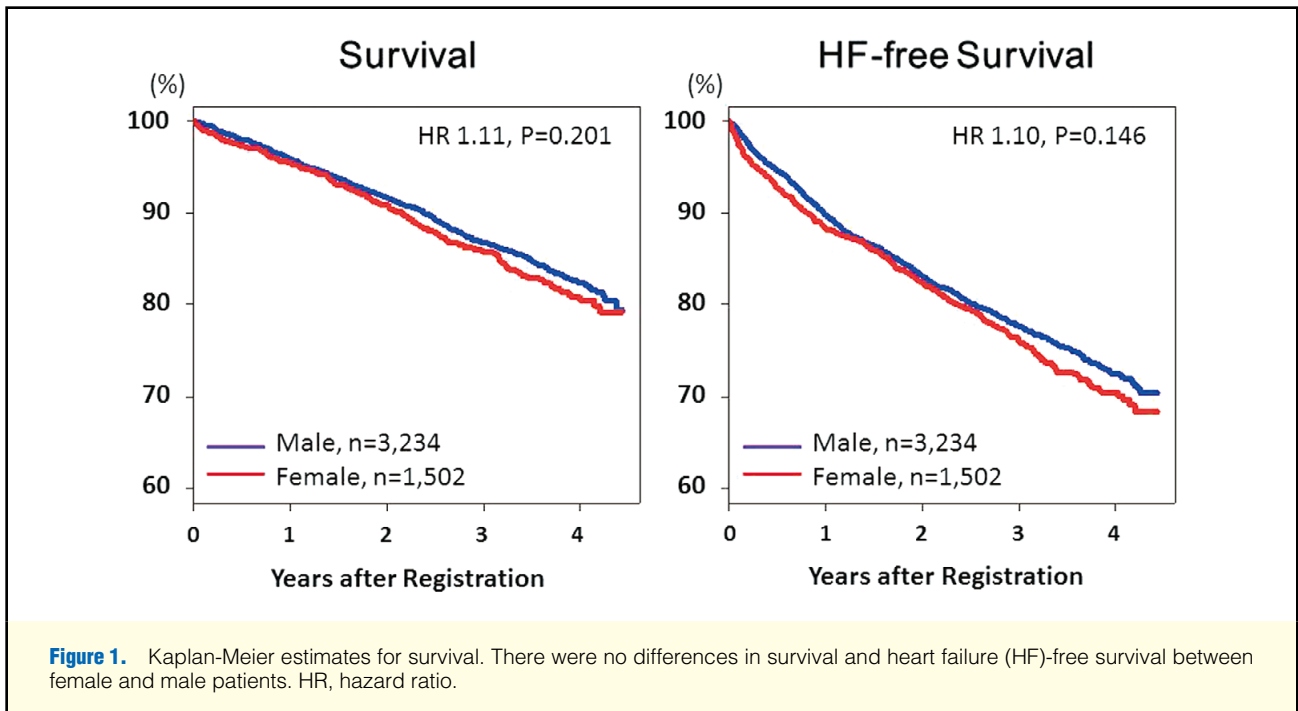
Results

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-



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

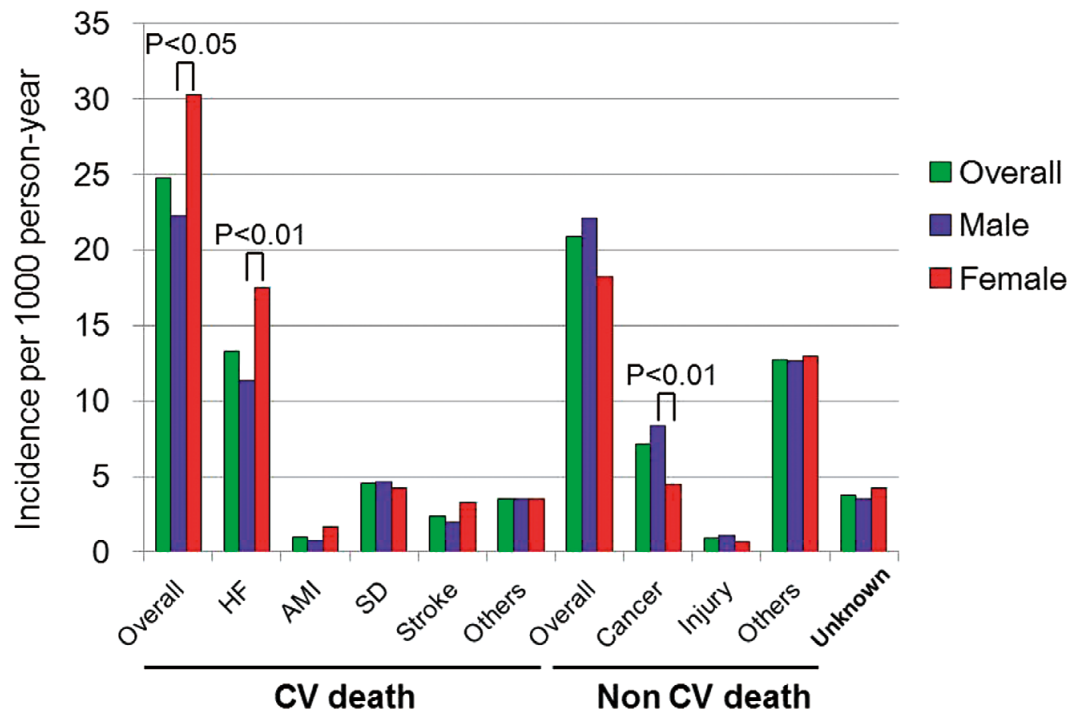


Figure 3. Gender and mode of death. Prevalence of modes of death was different between the genders. Particularly, incidence of death due to heart failure (HF) was more frequent in women, whereas that of malignant disease was more frequent in men. AMI, acute myocardial infarction; CV death, cardiovascular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

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

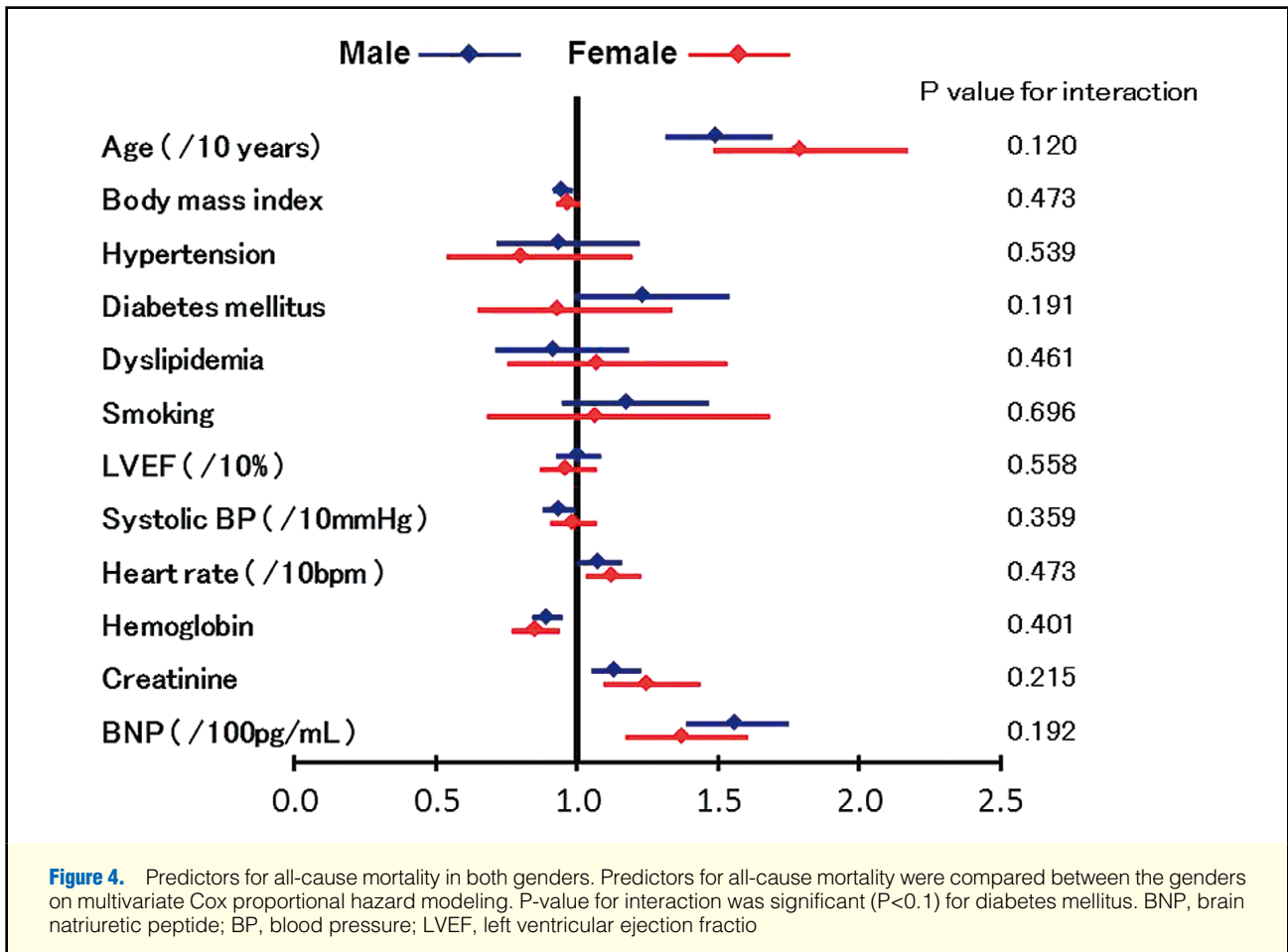
	All-cause death			CV death			HF admission		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Female gender	0.791	0.640–0.979	0.031	1.027	0.767–1.374	0.859	0.858	0.701–1.051	0.139
Age per 10 years	1.568	1.413–1.741	<0.001	1.541	1.333–1.782	<0.001	1.084	0.995–1.181	0.066
BMI	0.955	0.929–0.981	0.001	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



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 per-

son-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.

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Appendix

CHART-2 Study Investigators

1. Executive Committee

Hiroaki Shimokawa (Chair), Toshikazu Goto, Eiji Nozaki, Tetsuya Hiramoto, Mitsumasa Fukuchi, Kanichi Inoue, Atsushi Kato, Masafumi Sugi, Masatoshi Ohe, Tsuyoshi Shinozaki, Satoru Horiguchi, Hiroshi Kato.

2. Steering Committee

Kanichi Inoue, Tetsuya Hiramoto, Masahiko Ogata, Atsushi Kato, Shoichi Sato, Masafumi Sugi.

3. Collaborating Hospitals and Active Investigators by Prefecture

Aomori Prefecture

Shigeto Oyama (Towada City Hospital).

Iwate Prefecture

Eiji Nozaki, Akihiro Nakamura, Tohru Takahashi, Hideaki Endo, Sota Nakajima (Iwate Prefectural Central Hospital). Makoto Nakagawa, Tetsuji Nozaki, Takuya Yagi (Iwate Prefectural Isawa

Hospital).

Akita Prefecture

Satoru Horiguchi, Etsuko Fushimi, Yoshinao Sugai, Kohei Fukahori, Satoru Takeda, Kentaro Aizawa (Hiraka General Hospital).

Yamagata Prefecture

Masatoshi Ohe, Katsuhiko Sakurai, Takuro Tashima, Tadashi Kobayashi (Kojirakawa Shiseido Hospital). Toshikazu Goto, Tomoyasu Yahagi, Motoyuki Matsui, Yoshiaki Tamada, Akio Fukui, Kentaro Takahashi, Katsuaki Takahashi, Yoku Kikuchi (Yamagata Prefectural Central Hospital).

Miyagi Prefecture

Akihiko Sugimura, Minako Wakayama, Junko Ohashi (Sendai Red Cross Hospital). Kotaro Nochioka (Kanagami Hospital). Hiroyuki Kanno, Junji Kaneko (Katta General Hospital). Shu Suzuki, Kikuyo Takahashi (KKR Tohoku Kosai Hospital). Kenjiro Akai (Kurihara Central Hospital). Dai Katayose (Miyagi Rifu Ekisaikai Hospital). Sachio Onodera, Tetsuya Hiramoto, Seiji Komatsu, Masanobu Chida, Kaoru Iwabuchi, Masaharu Takeuchi, Hirokazu Yahagi (Osaki Citizen Hospital). Keiji Otsuka, Yoshito Koseki, Masaki Morita (Saito Hospital). Tsuyoshi Shinozaki, Takeshi Ishiduka, Noriko Onoue, Nobuhiro Yamaguchi (Sendai Medical Center). Atsushi Kato, Shigeto Namiuchi, Tadashi Sugie, Kenya Saji, Toru Takii (Sendai Open Hospital). Mitsumasa Fukuchi, Masahiko Ogata, Toshinori Tanikawa, Osamu Kitamukai (Sendai Tokushukai Hospital). Yoshihiro Fukumoto (Shizugawa Public Hospital). Kanichi Inoue, Jiro Koyama, Tomoko Tomioka, Yuki Shioiri, Yoshitaka Ito (South Miyagi Medical Center). Hiroshi Kato, Chikako Takahashi (Tohoku Rosai Hospital). Yasuhiko Sakata, Yoshihiro Fukumoto, Kenta Ito, Masaharu Nakayama, Koji Fukuda, Jun Takahashi, Yuji Wakayama, Koichiro Sugimura, Kimio Sato, Yasuharu Matsumoto (Tohoku University Hospital).

Fukushima Prefecture

Masafumi Sugi, Yoshito Yamamoto, Sunao Toda, Yutaka Minatoya, Yusuke Takagi (Iwaki Kyoritsu Hospital). Koji Fukuda (Watanabe Hospital).

4. Head Office and Coordinating Center

Yasuhiko Sakata, Jun Takahashi, Satoshi Miyata, Kotaro Nochioka, Masanobu Miura, Tsuyoshi Takada, Soichiro Tadaki, Chiharu Saga, Junko Suenaga, Hiromi Mihara, Yoko Yamada, Junko Kimura, Hiromi Ogino, Izumi Oikawa, Sanae Watanabe, Miki Washio, Keiko Nagasawa, Sachiko Nagasawa, Sachie Kotaka, Wakiko Komatsu, Reiko Hashimoto, Madoka Saga, Yasuko Ikeno, Hiroko Hamada.