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Temporal Trends in Clinical Characteristics, Management and Prognosis of Patients With Symptomatic Heart Failure in Japan

– Report From the CHART Studies –

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Background: Temporal trends in clinical characteristics, management and prognosis of patients with symptomatic heart failure (HF) remain to be elucidated in Japan.

Methods and Results: From the Chronic Heart Failure Analysis and Registry in the Tohoku District-1 (CHART-1; 2000–2005, n=1,278) and CHART-2 (2006-present, n=10,219) Studies, we enrolled 1,006 and 3,676 consecutive symptomatic stage C/D HF patients, respectively. As compared with the patients in the CHART-1 Study, those in the CHART-2 Study had similar age and sex prevalence, and were characterized by lower brain natriuretic peptide, higher prevalence of preserved left ventricular ejection fraction (LVEF) and higher prevalence of hypertension, diabetes mellitus and ischemic heart disease (IHD), particularly IHD with LVEF ≥50%. From CHART-1 to CHART-2, use of renin-angiotensin system inhibitors, β-blockers and aldosterone antagonists was significantly increased, while that of loop diuretics and digitalis was decreased. Three-year incidences of all-cause death (24 vs. 15%; adjusted hazard ratio [adjHR], 0.73; P<0.001), cardiovascular death (17 vs. 7%; adjHR, 0.38; P<0.001) and hospitalization for HF (30 vs. 17%; adjHR, 0.51; P<0.001) were all significantly decreased from CHART-1 to CHART-2. In the CHART-2 Study, use of β-blockers was associated with improved prognosis in patients with LVEF <50%, while that of statins was associated with improved prognosis in those with LVEF ≥50%.

Conclusions: Along with implementation of evidence-based medications, the prognosis of HF patients has been improved in Japan. (Trial registration: clinicaltrials.gov identifier: NCT00418041) (*Circ J* 2015; **79:** 2396–2407)

Key Words: Beta-blocker; Prognosis; Statin; Symptomatic heart failure

Heart failure (HF) is a major public health problem worldwide, and the number of HF patients has been increasing worldwide.[1–4] In the USA, there are approximately 5.7 million patients with HF, 0.87 million HF patients are newly diagnosed every year, and the number of HF patients is expected to rise to 8 million by 2030.[1] In Japan, although the precise number of HF patients is unclear, the number of outpatients with left ventricular (LV) dysfunction was estimated at 979,000 in 2005, which would be expected to rapidly increase by 90,000 every 5 years until 2020, then gradually by 24,000 every 5 years until 2035, reaching 1.32 million in 2035.[5] The Japanese Ministry of Health, Labour and Welfare reported that the number of HF deaths was 46,460 (370/million) in 2000, 56,327 (446/million) in 2006, and 71,881 (572/million) in 2013 in Japan.[6]

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Between 2000 and 2005, we conducted a multicenter, prospective cohort of chronic HF (CHF) patients, named the

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Chronic Heart Failure Analysis and Registry in the Tohoku District-1 (CHART-1) Study (n=1,278).[7,8] The CHART-1 Study found that the prognosis of CHF patients in Japan was equally poor compared with those in Western countries.[7,8] In 2006, we then started the CHART-2 Study to further elucidate the characteristics and prognosis of CHF patients in stages B–D.[3,8] In the previous studies, we found a trend toward westernization of ischemic etiology for HF and better implementation of evidence-based medications from the CHART-1 to the CHART-2 Studies.[3,8] It is important to elucidate the temporal trend in symptomatic HF for better management of the disorder.

The aim of the present study was thus to elucidate the temporal trend in clinical characteristics, management and long-term prognosis of patients with symptomatic HF patients in Japan, by comparing the CHART-1 and the CHART-2 Studies.

Methods

CHART Studies

In the present study, a total of 4,682 symptomatic HF patients were enrolled from the database of the CHART-1 (n=1,278) and the CHART-2 (n=10,219) Studies.[3,6,7] The CHART-1 Study was conducted between February 2000 and December 2005 and a total of 1,278 patients with CHF from the 26 hospitals (Tohoku University Hospital and 25 affiliated hospitals) were enrolled.[7,8] The purpose of the CHART-1 Study was to elucidate the clinical characteristics, treatment and prognosis of Japanese CHF patients.[5,6] All patients had a structural disorder of the heart and were treated with standard therapies for CHF, including diuretics, digitalis, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and β-blockers. In 2006, we then started the CHART-2 Study, in which a total of 10,219 consecutive patients, including 5,483 cardiovascular patients at high risk for development of HF (stage A/B) and 4,736 patients with symptomatic CHF (stages C/D),[9] were registered by 2010 in the 24 hospitals (Tohoku University Hospital and 23 affiliated hospitals) and have been currently followed up. Tohoku University Hospital and 14 hospitals participated in both the CHART-1 and the CHART-2 Studies, enrolling patients accounting for 74.0% and 75.8% of the total subjects registered in the CHART-1 and the CHART-2 Studies, respectively. No patients were registered in the 2 Studies in a duplicate manner.

The CHART-1 Study was approved by the ethics committee of Tohoku University Hospital. The CHART-2 Study was approved by the human research committee of Tohoku University School of Medicine, conformed to the ethics guidelines of the 1975 Declaration of Helsinki and also by the local ethics committee in each participating hospital and registered in Clinical Trials.gov (Identifier: NCT00418041). Written informed consent was provided by each patient before enrollment. Information on medical history and baseline demographics, including medication and echocardiographic data, were obtained at the time of enrollment by clinical research coordinators.

Definition of Symptomatic HF and Etiology of HF

Diagnosis of HF was made based on the Framingham criteria,[10] while CHF stage was classified according to the ACCF/AHA HF Guidelines.[9] We defined symptomatic HF as HF in New York Heart Association (NYHA) II, III or IV. The cause of HF was diagnosed by an attending physician at each hospital and/or the investigators of the Tohoku Heart Failure Association. Ischemic heart disease (IHD) was defined as history of myocardial infarction or angina pectoris. Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) were diagnosed based on the definition of DCM and HCM in the Japanese Circulation Society guidelines.[11,12]

Subjects

In the CHART-1 Study (n=1,278), 24 patients with missing data were excluded. Of the remaining 1,254 patients, 1,006 patients (78.7%) were defined as having symptomatic HF in the CHART-1 Study. In the CHART-2 Study (n=10,219), 5 patients with missing data were initially excluded. Thereafter, in order to minimize selection bias, we selected 5,923 patients from the CHART-2 Study who met the following inclusion criteria of the CHART-1 Study: (1) LV ejection fraction (LVEF) <50%; (2) LV end-diastolic diameter (LVDd) ≥55 mm; or (3) at least 1 episode of congestive HF.[7,8] Among the 5,923 patients, 3,676 were defined as having symptomatic HF in the CHART-2 Study. Finally, in the present study, 1,006 and 3,676 symptomatic HF patients were enrolled from the CHART-1 and the CHART-2 Studies, respectively. In the present study, HF with LVEF ≥50% was defined as HF with preserved LVEF (HFpEF), while HF with LVEF <50% was defined as HF with reduced LVEF (HFrEF).[13]

Outcomes

The study endpoints were 3-year incidence of all-cause death, cardiovascular death and hospitalization for worsening HF. Mode of death was also examined. For all patients, only the main mode of death was used. A patient admitted for worsening HF had to show signs and symptoms of HF requiring treatment with i.v. diuretics.[14] Follow-up was made at least once a year by clinical research coordinators by means of review of medical records, survey and telephone interview.[3,8] All events were reviewed and assigned according to consensus of at least 2 independent physician members of the Tohoku Heart Failure Association, by reviewing case reports, death certificates, medical records and hospital course summaries provided by the investigators.

Statistical Analysis

The continuous results are expressed as mean±SE or median (IQR), as appropriate. The discrete results are expressed as count (percentage). Wilcoxon rank sum and Fisher's exact test were used to compare patient characteristics between the CHART-1 and the CHART-2 Studies. Kaplan-Meier curves were plotted to evaluate the association between symptomatic HF patients and all-cause death, cardiovascular death or hospitalization for worsening HF. Comparison of the survival time between the 2 Studies was done using log-rank test. To compare prognosis between the CHART-1 and the CHART-2 patients, we used the multivariate Cox proportional hazard model by adjusting for the following clinical backgrounds: age, sex and comorbidity (hypertension, diabetes mellitus [DM], dyslipidemia, atrial fibrillation and ventricular tachycardia). In addition, to evaluate the effect of medication, the covariates were selected as follows: first, univariate Cox models were fitted for all patients in both the CHART-1 and the CHART-2 Studies, with candidate variables of sex, age, body mass index (BMI), systolic blood pressure (SBP), heart rate, NYHA class, LVEF, LVDd, hypertension, DM, dyslipidemia, atrial fibrillation, ventricular tachycardia, brain natriuretic peptide (BNP) and estimated glomerular filtration rate (eGFR). Then, after the multivariate Cox models were fitted using all the covariates that had $P<0.2$ in the univariate model, the optimal subset of covariates was selected by backward stepwise elimination. Two-sided $P<0.05$ was considered to be

Table 1. Baseline Characteristics

	Total (n=4,682)		
	CHART-1 (n=1,006)	CHART-2 (n=3,676)	P-value
Age (years)	68.9±0.4	69.7±0.2	0.084
Male	642 (63.8)	2,412 (65.6)	0.287
BP (mmHg)			
Systolic	125.7±0.7	125.4±0.3	0.663
Diastolic	71.4±0.4	71.5±0.2	0.765
Heart rate (beats/min)	75.2±0.5	72.6±0.3	<0.001
BMI (kg/m^2)	22.9±0.1	23.2±0.1	0.070
NYHA classification			<0.001
II	786 (78.1)	3,142 (85.5)	
III	210 (20.9)	495 (13.5)	
IV	10 (1.0)	39 (1.1)	
Laboratory data			
Hb (g/dl)	12.9±0.1	13.0±0.0	0.184
Anemia	395 (39.3)	1,375 (37.4)	0.287
BUN (mg/dl)	21.8±0.5	20.6±0.2	0.007
Cre (mg/dl)	1.09±0.03	1.08±0.01	0.790
eGFR (ml/min/1.73 m^2)	60.0±0.8	59.4±0.4	0.485
BNP (pg/ml)	158.8 (69.0–334.0)	123.2 (50.3–267.0)	<0.001
Echocardiography			
LVEF (%)	49.8±0.5	55.7±0.3	<0.001
LVEF ≥50%	463 (46.0)	2,316 (63.0)	<0.001
LVDd (mm)	56.7±0.3	52.4±0.2	<0.001
LVDs (mm)	43.0±0.4	37.1±0.2	<0.001
Comorbidity			
Hypertension	468 (46.4)	3,203 (87.1)	<0.001
Dyslipidemia	163 (16.1)	2,879 (78.3)	<0.001
Diabetes mellitus	194 (19.4)	1,280 (34.8)	<0.001
Atrial fibrillation	423 (42.1)	1,529 (41.6)	0.829
Ventricular tachycardia	216 (21.5)	420 (11.4)	<0.001
Etiology			
Ischemic heart disease	269 (26.7)	1,749 (47.6)	<0.001
LVEF ≥50%	88 (8.7)	1,048 (28.5)	
LVEF <50%	181 (18.0)	701 (19.1)	
Cardiomyopathy	334 (33.2)	644 (17.5)	<0.001
DCM	267 (26.5)	505 (13.7)	
HCM	35 (3.5)	115 (3.1)	
Other cardiomyopathy	32 (3.2)	24 (0.7)	
Medication			
β-blockers	288 (28.6)	1,886 (51.3)	<0.001
RASI	689 (68.5)	2,677 (72.8)	0.006
ACEI	575 (57.2)	1,720 (46.8)	<0.001
ARB	125 (12.4)	1,105 (30.1)	<0.001
Aldosterone antagonists	182 (18.7)	984 (26.8)	<0.001
Loop diuretics	729 (76.7)	2,041 (55.5)	<0.001
Digitalis	478 (48.5)	921 (25.1)	<0.001
CCB	288 (29.2)	1,388 (37.8)	<0.001
Statins	NA	1,332 (36.2)	NA
ICD/CRTD	16 (1.6)	103 (2.8)	0.031

Data given as mean±SE, median (IQR) or n (%). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CCB, calcium channel blockers; CRTD, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RASI, renin angiotensin system inhibitors.

statistically significant. All calculations were performed using SPSS 22.0 for Windows and R version 3.0.2.

Results

Temporal Trend in Baseline Characteristics of Symptomatic HF

There were no significant differences in age, sex or blood pressure between the CHART-1 and the CHART-2 patients, whereas BNP was significantly lower in the CHART-2 patients (Table 1). In the echocardiography data, prevalence of preserved LVEF was higher and LV dimensions were smaller in the CHART-2 patients. The prevalences of HFpEF, hypertension, dyslipidemia and DM were all increased from CHART-1 to CHART-2. The prevalence of ischemic HF was significantly increased from CHART-1 to CHART-2 (26.7 vs. 47.6%, P<0.001), whereas the prevalence of HF due to CM was significantly decreased (33.2 vs. 17.5%, P<0.001). Interestingly, the prevalence of ischemic HF with preserved EF (≥50%) was dramatically increased from CHART-1 to CHART-2 (8.7 vs. 28.5%, P<0.001), but that of ischemic HF with reduced LVEF (<50%) remained unchanged. The use of β-blockers, renin-angiotensin system inhibitors (RASI) and aldosterone antagonists was increased, whereas that of loop diuretics and digitalis

Table 2. (A) Baseline Characteristics of Patients With Non-Ischemic HF and Those With Ischemic HF, (B) Baseline Characteristics of Patients With HFrEF and Those With HFpEF

A	Non-ischemic HF (n=2,664)			Ischemic HF (n=2,018)		
	CHART-1 (n=737)	CHART-2 (n=1,927)	P-value	CHART-1 (n=269)	CHART-2 (n=1,749)	P-value
Age (years)	68.2±0.5	68.4±0.3	0.685	71.0±0.7	71.1±0.3	0.866
Male	447 (60.7)	1,102 (57.2)	0.114	195 (72.5)	1,310 (74.9)	0.408
BP (mmHg)						
Systolic	125.6±0.8	124.1±0.5	0.104	125.9±1.3	126.8±0.5	0.537
Diastolic	71.6±0.5	71.5±0.3	0.852	70.8±0.7	71.5±0.3	0.342
Heart rate (beats/min)	75.0±0.7	73.8±0.4	0.130	75.7±0.9	71.2±0.3	<0.001
BMI (kg/m²)	22.9±0.2	23.0±0.1	0.864	22.8±0.2	23.5±0.1	0.034
NYHA classification			<0.001			<0.001
II	584 (79.2)	1,645 (85.4)		202 (75.1)	1,497 (85.6)	
III	146 (19.8)	262 (13.6)		64 (23.8)	233 (13.3)	
IV	7 (0.9)	20 (0.7)		3 (1.1)	19 (1.1)	
Laboratory data						
Hb (g/dl)	13.0±0.1	13.1±0.1	0.201	12.9±0.1	13.0±0.1	0.419
Anemia	279 (37.9)	690 (35.8)	0.345	116 (43.1)	685 (39.2)	0.228
BUN (mg/dl)	21.7±0.5	20.5±0.3	0.025	22.2±1.0	20.8±0.3	0.093
Cre (mg/dl)	1.07±0.04	1.00±0.02	0.053	1.15±0.05	1.17±0.02	0.782
eGFR (ml/min/1.73 m²)	61.5±0.9	61.6±0.5	0.880	55. 9±1.4	57.0±0.5	0.449
BNP (pg/ml)	150.0 (64.5–309.0)	134.0 (56.3–218.0)	0.020	181.4 (85.3–413.2)	107.0 (44.6–253.3)	<0.001
Echocardiography						
LVEF (%)	51.5±0.6	56.6±0.4	<0.001	45.2±0.9	54.6±0.4	<0.001
LVEF ≥50%	375 (50.9)	1,268 (65.8)	<0.001	88 (32.7)	1,048 (59.9)	<0.001
LVDd (mm)	56.5±0.4	52.0±0.2	<0.001	57.4±0.6	52.8±0.2	<0.001
LVDs (mm)	42.3±0.4	36.6±0.3	<0.001	45.1±0.6	37.7±0.3	<0.001
Comorbidity			<0.001			
Hypertension	339 (46.0)	1,623 (84.2)	<0.001	129 (48.0)	1,580 (90.4)	<0.001
Dyslipidemia	78 (10.6)	1,381 (71.7)	<0.001	85 (31.6)	1,498 (85.6)	<0.001
Diabetes mellitus	106 (14.4)	502 (26.1)	<0.001	88 (32.7)	778 (44.5)	<0.001
Atrial fibrillation	359 (48.7)	1,068 (55.5)	0.002	64 (23.8)	461 (26.4)	0.412
Ventricular tachycardia	155 (21.0)	249 (12.9)	<0.001	61 (22.7)	171 (9.8)	<0.001
Medication						
β-blockers	206 (28.0)	1,001 (51.9)	<0.001	82 (30.5)	887 (50.7)	<0.001
RASI	505 (68.5)	1,425 (73.9)	0.006	184 (68.4)	1,255 (71.8)	0.277
ACEI	417 (56.6)	932 (48.4)	<0.001	158 (58.7)	789 (45.1)	<0.001
ARB	96 (13.0)	576 (29.9)	<0.001	29 (10.8)	531 (30.4)	<0.001
Aldosterone antagonists	127 (17.8)	637 (33.1)	<0.001	55 (21.0)	347 (19.8)	0.679
Loop diuretics	543 (78.1)	1,226 (63.6)	<0.001	186 (72.9)	815 (46.6)	<0.001
Digitalis	402 (55.7)	679 (35.2)	<0.001	76 (28.9)	242 (13.8)	<0.001
CCB	187 (25.9)	622 (32.3)	0.002	101 (38.1)	766 (43.8)	0.084
Statins	NA	366 (19.0)	NA	NA	966 (55.2)	NA
ICD/CRTD	9 (1.2)	69 (3.6)	0.001	7 (2.6)	34 (1.9)	0.484

(Table 2 continued the next page.)

B	HFrEF (n=1,903)			HFpEF (n=2,779)		
	CHART-1 (n=543)	CHART-2 (n=1,360)	P-value	CHART-1 (n=463)	CHART-2 (n=2,316)	P-value
Age (years)	67.3±0.6	68.3±0.3	0.114	70.9±0.6	70.5±0.3	0.547
Male	381 (70.2)	999 (73.5)	0.155	261 (56.4)	1,413 (61.0)	0.069
BP (mmHg)						
Systolic	123.7±0.9	121.3±0.5	0.027	127.9±1.0	127.8±0.4	0.916
Diastolic	71.2±0.5	70.6±0.3	0.324	71.5±0.6	72.0±0.3	0.407
Heart rate (beats/min)	75.8±0.8	73.3±0.4	0.005	74.4±0.8	72.1±0.3	0.006
BMI (kg/m^2)	22.7±0.2	22.8±0.1	0.616	23.2±0.2	23.5±0.1	0.193
NYHA classification			<0.001			<0.001
II	413 (76.1)	1,124 (82.6)		373 (80.6)	2,018 (87.1)	
III	125 (23.0)	215 (15.8)		85 (18.4)	280 (12.1)	
IV	5 (0.9)	21 (1.5)		5 (1.1)	18 (0.8)	
Laboratory data						
Hb (g/dl)	13.2±0.1	13.2±0.1	0.492	12.6±0.1	13.0±0.0	0.001
Anemia	180 (33.1)	498 (36.6)	0.168	215 (46.4)	877 (37.9)	0.001
BUN (mg/dl)	22.1±0.8	21.6±0.3	0.493	21.5±0.5	20.1±0.2	0.007
Cre (mg/dl)	1.08±0.04	1.17±0.03	0.087	1.10±0.04	1.03±0.02	0.088
eGFR (ml/min/1.73 m^2)	61.5±1.0	57.8±0.6	0.002	58.2±1.1	60.3±0.5	0.064
BNP (pg/ml)	178.2 (83.7–393.2)	172.0 (71.6–374.0)	0.342	138.0 (58.7–282.0)	96.6 (40.9–218.0)	<0.001
Echocardiography						
LVEF (%)	37.8±0.4	37.9±0.3	0.925	63.4±0.5	65.1±0.2	<0.001
LVDd (mm)	60.6±0.4	58.9±0.3	<0.001	52.4±0.4	48.9±0.2	<0.001
LVDs (mm)	50.0±0.4	47.9±0.3	<0.001	35.1±0.4	31.5±0.2	<0.001
Comorbidity						
Hypertension	235 (43.3)	1,157 (85.1)	<0.001	233 (50.3)	2,046 (88.4)	<0.001
Dyslipidemia	102 (18.8)	1,100 (80.9)	<0.001	61 (13.2)	1,779 (76.8)	<0.001
Diabetes mellitus	108 (19.9)	497 (36.5)	<0.001	86 (18.6)	783 (33.8)	<0.001
Atrial fibrillation	194 (35.7)	502 (36.9)	0.636	229 (49.5)	1,027 (44.4)	0.046
Ventricular tachycardia	151 (27.8)	259 (19.1)	<0.001	65 (14.0)	161 (7.0)	<0.001
Etiology						
Ischemic heart disease	181 (33.3)	701 (51.5)	<0.001	88 (19.0)	1,048 (45.3)	<0.001
Cardiomyopathy	222 (40.9)	369 (27.1)	<0.001	112 (24.2)	275 (11.9)	<0.001
DCM	195 (35.9)	343 (25.2)		72 (15.6)	162 (7.0)	
HCM	6 (1.1)	20 (1.5)		29 (6.3)	95 (4.1)	
Other cardiomyopathy	21 (3.9)	6 (0.4)		11 (2.4)	18 (0.8)	
Medication						
β-blockers	184 (33.9)	870 (64.0)	<0.001	104 (22.5)	1,018 (44.0)	<0.001
RASI	385 (70.9)	1,061 (78.0)	0.001	304 (65.7)	1,619 (69.9)	0.078
ACEI	327 (60.2)	707 (52.0)	0.001	248 (53.6)	1,014 (43.8)	<0.001
ARB	61 (11.2)	399 (29.3)	<0.001	64 (13.8)	708 (30.6)	<0.001
Aldosterone antagonists	116 (22.4)	493 (36.2)	<0.001	66 (14.5)	491 (21.2)	0.001
Loop diuretics	729 (76.7)	2,038 (55.5)	<0.001	401 (78.6)	903 (66.4)	<0.001
Digitalis	478 (48.5)	920 (25.0)	<0.001	249 (47.2)	335 (24.6)	<0.001
CCB	126 (23.9)	356 (26.2)	0.318	162 (35.4)	1,032 (44.6)	<0.001
Statins	NA	515 (37.9)	NA	NA	817 (35.3)	NA
ICD/CRTD	6 (1.1)	72 (5.3)	<0.001	10 (2.2)	31 (1.3)	0.202

Data given as mean±SE, median (IQR) or n (%). HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction. Other abbreviations as in Table 1.

was decreased in the CHART-2 Study. Implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy defibrillator (CRTD) were more frequently used in CHART-2. Similar trends from CHART-1 to CHART-2 were noted in both ischemic and non-ischemic HF (Table 2A), and also in both HFrEF and HFpEF (Table 2B).

Temporal Trend in Long-Term Prognosis of Symptomatic HF

During the 3-year follow-up, a total of 771 patients died (236 and 535 in the CHART-1 and the CHART-2 Studies, respectively) and 923 were hospitalized for HF (302 and 621 in the CHART-1 and the CHART-2 Studies, respectively). Crude 3-year mortality was significantly decreased from 23.5% in CHART-1 to 14.6% in CHART-2 (hazard ratio [HR], 0.59; 95% CI: 0.50–0.69; P<0.001; Figure 1A). Three-year cardiovascular death rate was also improved from 17.4% (n=175) in CHART-1 to 7.5% (n=275) in CHART-2 (HR, 0.41; 95% CI: 0.34–0.50; P<0.001; Figure 1B). Also, 3-year HF admission

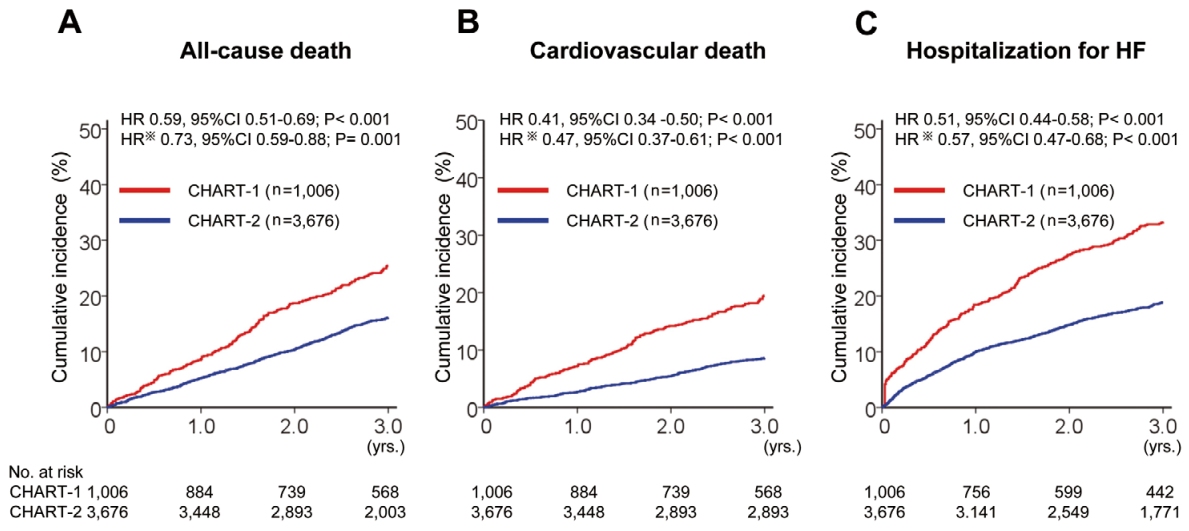

Figure 1. Temporal trend in long-term prognosis of symptomatic heart failure (HF). Kaplan-Meier curves for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening HF. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and ventricular tachycardia.

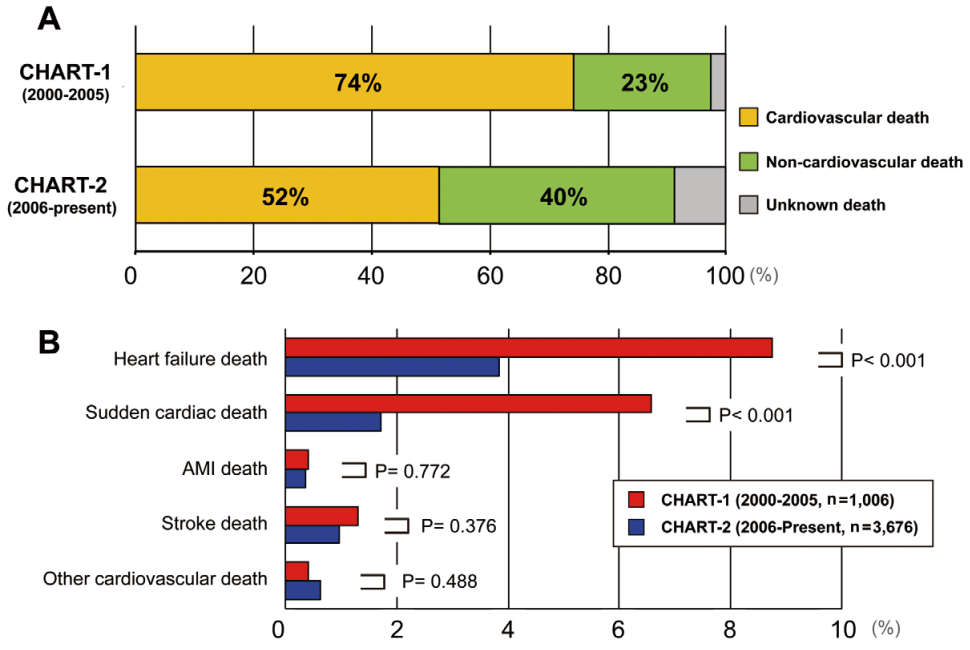

Figure 2. Temporal trends in mode of death in symptomatic heart failure patients. AMI, acute myocardial infarction.

rate was significantly decreased from 30.0% (n=302) in CHART-1 to 16.9% (n=621) in CHART-2 (HR, 0.51; 95% CI: 0.44–0.58; P<0.001; Figure 1C). After adjustment for clinical background, the CHART-2 patients still had improved prognosis compared with the CHART-1 patients for all-cause death (Figure 1A), cardiovascular death (Figure 1B) and HF admission (Figure 1C).

Temporal Trend in Mode of Death in Symptomatic HF

Among the 236 deaths in the CHART-1 Study, there were 175 cardiovascular deaths (74.1%) and 55 non-cardiovascular deaths (23.3%). The cause of the remaining 6 deaths was unknown (Figure 2A). Among the 535 deaths in the CHART-2 patients, 275 (51.4%) were cardiovascular deaths and 213 (39.8%) were non-cardiovascular deaths, while the cause of

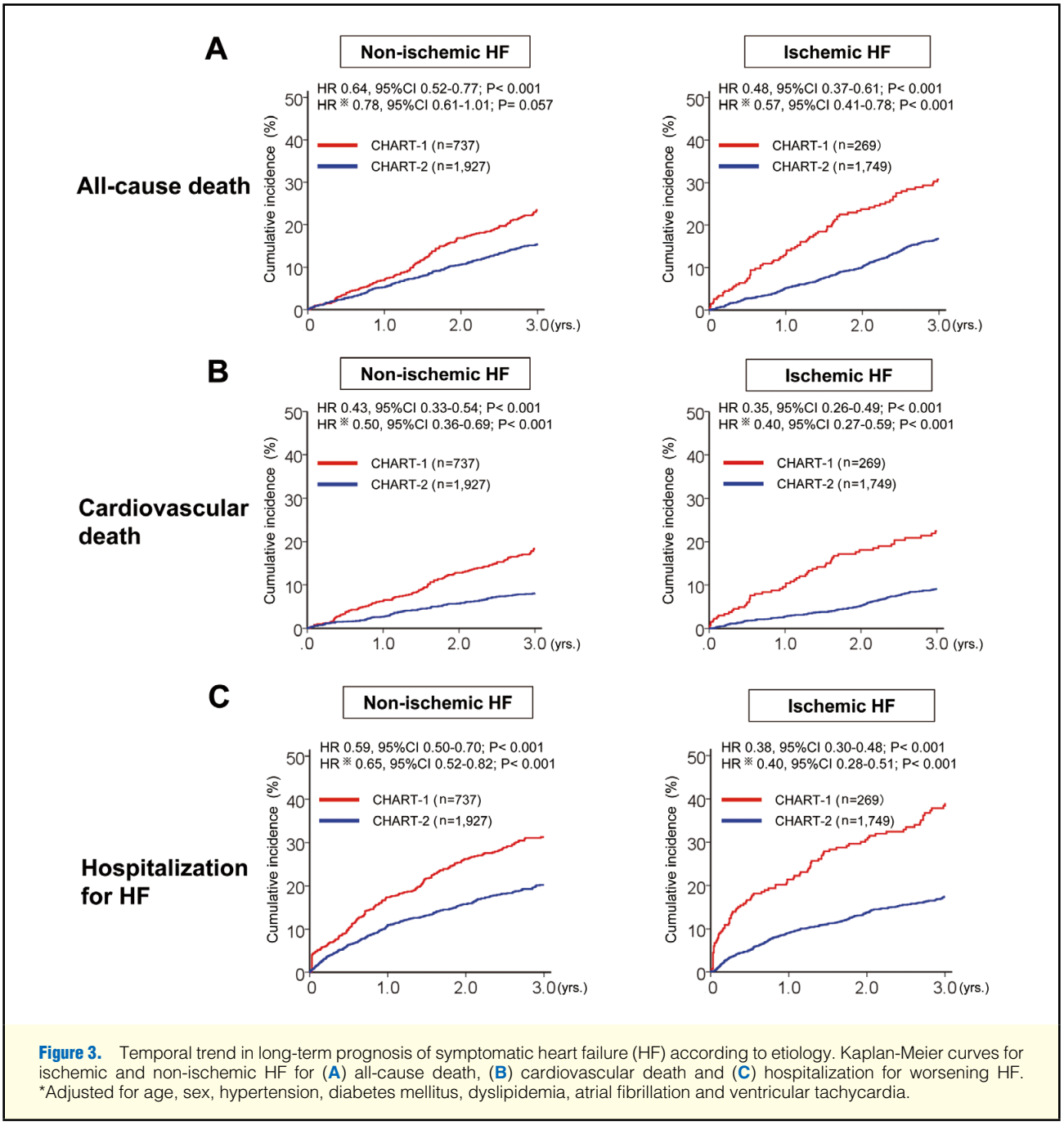

Figure 3. Temporal trend in long-term prognosis of symptomatic heart failure (HF) according to etiology. Kaplan-Meier curves for ischemic and non-ischemic HF for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening HF. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and ventricular tachycardia.

the remaining 47 deaths was unknown (Figure 2A). Among the cardiovascular deaths, the incidence of death due to HF (from 8.7 to 3.8%, P<0.001) and sudden cardiac death (from 6.6 to 1.7%, P<0.001) were markedly and significantly decreased, whereas the incidence of death due to acute myocardial infarction (from 0.4 to 0.4%, P=0.772) or stroke (from 1.3 to 1.0%, P=0.376) was unchanged (Figure 2B).

Difference in Long-Term Prognosis Between Non-Ischemic and Ischemic HF

We further examined the differences in 3-year mortality between the CHART-1 and the CHART-2 Studies in the subgroups of non-ischemic and ischemic HF patients. In both the non-ischemic and ischemic groups, the long-term prognosis of HF was improved from CHART-1 to CHART-2, including all-cause death (22 vs. 14%, and 29 vs. 15%; Figure 3A), cardiovascular death (16 vs. 7% and 20 vs. 8%; Figure 3B) and HF admission (28 vs. 18% and 35 vs. 16%; all P<0.001; Figure 3C). These trends of improved prognosis in non-ischemic and ischemic HF were generally unchanged after adjustment for clinical background (Figure 3).

Difference in Long-Term Prognosis Between HFpEF and HFrEF

The prevalence of HFpEF was increased from 46% in CHART-1 to 63% in CHART-2 (Table 1). In both the HFpEF and HFrEF

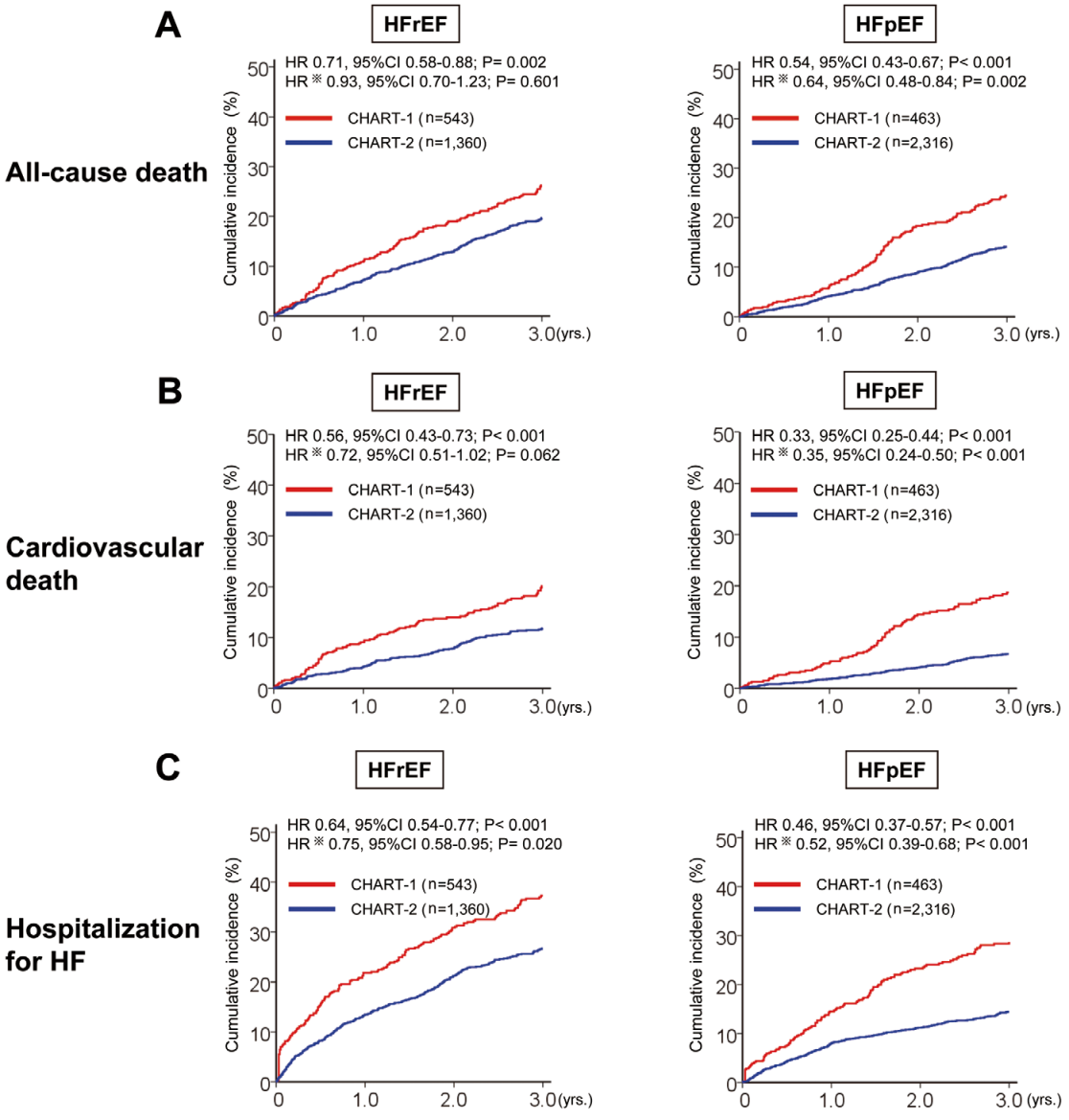

Figure 4. Temporal trend in long-term prognosis of symptomatic heart failure (HF) according to left ventricular ejection fraction (LVEF). Kaplan-Meier curves for HF with preserved EF (HFpEF; LVEF ≥50%) and HF with reduced EF (HRrEF; LVEF <50%) for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening HF. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and ventricular tachycardia.

subgroups, long-term prognosis of symptomatic HF was improved from CHART-1 to CHART-2, including all-cause death (HFrEF, 24 vs. 18%, P=0.002; HFpEF, 23 vs. 13%, P<0.001; **Figure 4A**), cardiovascular death (HFrEF, 18 vs. 10%, P<0.001; HFpEF, 17 vs. 6%, P<0.001; **Figure 4B**) and HF admission (HFrEF, 34 vs. 23%, P<0.001; HFpEF, 26 vs. 13%, P<0.001; **Figure 4C**). After adjustment for clinical background, however, the decrease in the incidence of all-cause death from CHART-1 to CHART-2 (adjusted HR [adjHR], 0.93; P=0.601) was no longer significant in the HFrEF group, whereas it remained significant in the HFpEF group (adjHR, 0.64, P=0.002). Similarly, the difference in the incidence of cardiovascular death between CHART-1 and CHART-2 became insignificant in the HFrEF groups after adjustment for clinical background (adjHR, 0.72; P=0.062), while there remained a significant difference in the HFpEF groups (adjHR, 0.35, P<0.001; **Figures 4A,B**).

Prognostic Factors in Symptomatic HF

Factors associated with all-cause death in the total population (n=4,682) selected using the stepwise multivariable Cox model are shown in **Table 3**. Age, BMI, heart rate, NYHA, SBP, DM, dyslipidemia, LVDd, BNP and eGFR were significantly associated with all-cause mortality. Using these factors as variables and adjusting for clinical background, the prognostic impact of each medication in the CHART-1 and the

Table 3. Multivariate Cox Predictors of All-Cause Death

	HR	95% CI	P-value
Age (per 10 years)	1.42	1.30–1.54	<0.001
BMI	0.97	0.95–0.98	<0.001
Heart rate	1.01	1.00–1.01	0.001
Systolic BP (per 10 mmHg)	0.93	0.89–0.96	<0.001
NYHA III/IV	1.62	1.34–1.95	<0.001
Diabetes mellitus	1.37	1.15–1.64	<0.001
Dyslipidemia	0.70	0.59–0.84	<0.001
LVDd	1.01	1.00–1.02	0.012
BNP (per 100 pg/ml)	1.08	1.06–1.10	<0.001
eGFR (per 10 ml/min/1.73 m^2)	0.93	0.89–0.96	<0.001

HR, hazard ratio. Other abbreviations as in Table 1.

CHART-2 patients (Figure 5) was determined on the multivariate Cox modeling. Given that β-blockers and statins tended to improve the prognosis of the CHART-2 patients (Figure 5A), we further examined their prognostic impact in the HFpEF and HFrEF subgroups. In the HFrEF group, use of β-blockers was associated with decreased incidence of all-cause death in CHART-2 (Figure 5B), whereas, in the HFpEF group, statin use was associated better prognosis in CHART-2 but not in CHART-1 (Figure 5C). Use of RASI, aldosterone antagonists, loop diuretics, digitalis or calcium channel blockers was not associated with all-cause mortality in CHART-1 or CHART-2 (Figure 5).

Discussion

The novel findings of the present study are that in symptomatic HF patients in Japan: (1) the prevalence of IHD and lifestyle-related diseases (eg, hypertension, hyperlipidemia and DM) has increased; (2) the prevalence of HFpEF has increased in both ischemic and non-ischemic HF; (3) evidence-based medications have been implemented more often; and (4) the 3-year incidence of all-cause death, cardiovascular death and admission for HF has decreased. To the best of our knowledge, this is the first study on the temporal trend of symptomatic HF in Japan.

Increased Prevalence of Ischemic HF

We have previously reported a trend in the westernization of HF etiologies and implementation of evidence-based medications in the CHART Studies, in which a broad spectrum of HF patients in Japan was enrolled.[3,6] In the present study, in order to obtain further insights into the temporal trends in HF management in Japan, we examined a total of 4,682 symptomatic HF patients from the CHART-1 (n=1,006) and the CHART-2 (n=3,676) Studies with the same inclusion criteria. In the present study, we not only confirmed the trend in westernization of HF etiology and better implementation of evidence-based medications in symptomatic HF patients, as we previously reported,[3,6] but also obtained several new findings.

One of the most important findings was the marked increase in prevalence of ischemic HF: it had increased from 27% in CHART-1 to 48% in CHART-2. In Japan, Tsutsui et al reported that the prevalence of IHD was 30% in 2004,[15] which is similar to that (27%) in the CHART-1 Study, in which patients were enrolled between 2000 and 2004. In contrast, the prevalence of IHD in the CHART-2 Study, in which patients were enrolled between 2006 and 2010, was markedly increased to 48%. Thus, the prevalence of IHD in Japanese patients with symptomatic HF has already reached the same level as in Western countries (44–59%).[16–20]

Increased Prevalence of HFpEF

Another important finding of the present study was the increase in the prevalence of HFpEF in Japan. Although recent studies reported that the prevalence of HFpEF has increased worldwide, the increase from 46% to 63% in the CHART Studies is remarkable. For example, in the Framingham Heart Study, the prevalence of HF with LVEF ≥50% had increased from 33% in 2000 to 39% in 2010.[21] Thus, the present study demonstrated that the higher prevalence of HFpEF in the Japanese population has recently become more evident. In addition, it should be noted that the prevalence of IHD with LVEF ≥50%, but not with LVEF <50%, dramatically increased in the CHART-2 Study, indicating the rapid increase in HFpEF in ischemic HF, along with the westernization of clinical characteristics of symptomatic HF in Japan. It is possible that the recent changes in lifestyle and advances in coronary intervention for acute myocardial infarction have caused the increase in HFpEF in IHD.[22–25] Interestingly, however, the prevalence of HFpEF was also increased in patients without IHD, possibly reflecting a trend in HF in the aged populations as well.[1–3]

Temporal Trend in HF According to Etiology and LV Function

Although we have previously reported the increased prevalence of lifestyle-related disease and implementation of evidence-based medications in Japanese HF patients,[3,6] it has been unclear whether these trends were related to HF etiology (ischemic vs. non-ischemic) or LV function (HFrEF vs. HFpEF). In the present study, we found a similar trend in westernization of the prevalence of comorbidities and better implementation of evidence-based medications, regardless of HF etiology or LV function. Thus, it should be underlined that prevention of future ischemic events is an emerging issue in symptomatic HF patients regardless of HF etiology or LV function. In particular, patients with HFpEF and those with non-ischemic HF should be given more attention, given that the use of evidence-based medications was lower in these patients, even in the CHART-2 Study.

Improved Long-Term Prognosis of Japanese Symptomatic HF Patients

We recently reported that long-term prognosis of DCM patients has been improved, along with the implementation of evidence-based medications in Japan.[26] There have been few reports, however, that examined the temporal trends in clinical outcome of Japanese patients with symptomatic HF in general. In

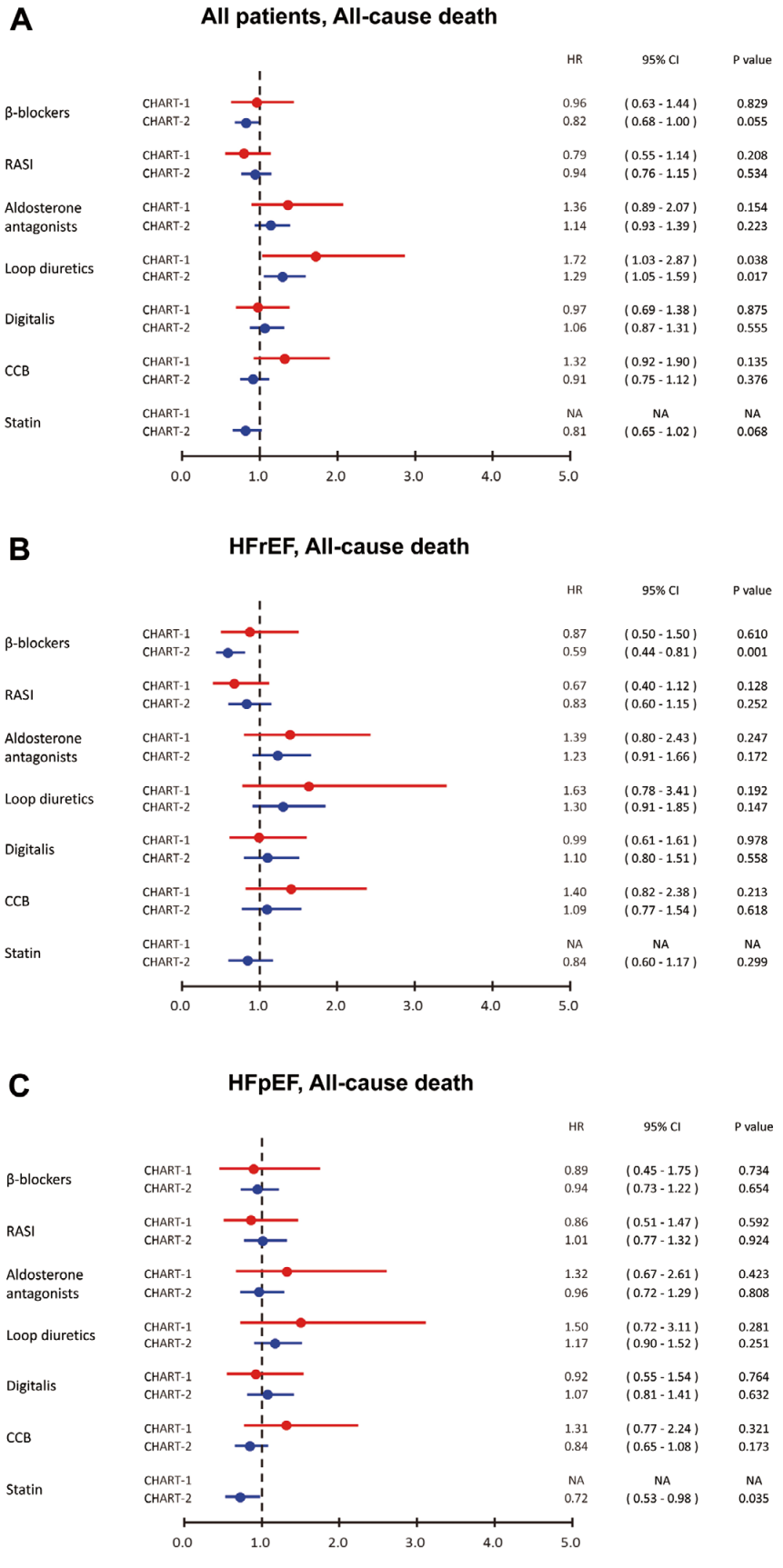

Figure 5. Effects of medications on long-term prognosis of symptomatic heart failure (HF). Forest plots for effect of each medicine for all-cause death in (**A**) all patients, (**B**) HF with reduced ejection fraction (HFrEF), and (**C**) HF with preserved ejection fraction (HFpEF). Multivariate Cox proportional hazard model. *Adjusted for age, body mass index, heart rate, systolic blood pressure, left ventricular end-diastolic diameter, brain natriuretic peptide, estimated glomerular filtration rate, New York Heart Association, diabetes mellitus, dyslipidemia. CCB, calcium channel blockers; RASI, renin-angiotensin system inhibitors.

the present study, we examined the temporal trend in long-term prognosis along with the changes in clinical characteristics and management of Japanese patients with symptomatic HF. Indeed, the present study has shown that 3-year incidences of all-cause death, cardiovascular death and admission for HF were all significantly decreased from CHART-1 to CHART-2. Importantly, the decreased incidence of the 3 events remained significant in the overall population, even after adjustment for clinical background, suggesting that implementation of evidence-based medicine played a major role independently of westernization of patient clinical characteristics.

Many previous studies examined the prognosis of HF,[27–30] but most of the studies focused on prognosis after hospitalization for acute HF, and there have been few reports on the prognosis of CHF. In the Framingham cohort, it was reported that the 5-year mortality rate was 65% (13%/year) in male HF patients surviving at least 90 days after the diagnosis of HF,[16] and that 5-year mortality was decreased from 70% (14%/year) in 1950–1969 to 59% (12%/year) in 1990–1999.[31] There are few reports, however, regarding the improvement of prognosis in HF patients after 2000, namely, in the era of evidence-based medicine. In this sense, the present study has provided important evidence that the prognosis of HF has been improved after 2000: the 3-year mortality was improved from 24% (8%/year) in CHART-1 to 15% (5%/year) in CHART-2 in the present study. It should be noted, however, that in the HFrEF subgroup, improvement of all-cause mortality from CHART-1 to CHART-2 became insignificant after adjustment for clinical background. Thus, further implementation of evidence-based management including use of newer drugs such as ivabradine;[32] ICD/CRTD and exploration of better management are required for HFrEF patients.[33–34]

Temporal Trend in Mode of Death

The present study demonstrated that the prevalence of cardiovascular death was decreased, whereas that of non-cardiovascular death was increased from CHART-1 to CHART-2. One of the explanations for this observation is that implementation of evidence-based medicine has mainly reduced cardiovascular death. Another explanation is the increase in the prevalence of HFpEF in symptomatic HF from CHART-1 to CHART-2, given that, in HFpEF patients, the prevalence of sudden death was lower and that of non-cardiovascular death higher as compared with HFrEF patients.[35]

In the present study, it was also noted that the rate of sudden cardiac death was significantly decreased from CHART-1 to CHART-2. Implementation of evidence-based medications might have played a significant role in decreasing the rate of sudden cardiac death.[27–30] In addition, it is conceivable that ICD/CRTD treatment prevented sudden cardiac death in the CHART-2 Study, because the prevalence of patients with ICD/CRTD was increased. The underuse of ICD/CRTD for HF, however, remains an important problem worldwide.[33,36,37] Thus, more effort is needed to achieve appropriate use of ICD/CRTD in order to further reduce sudden death in patients with symptomatic HF.

Medications Contributing to Improvement of Long-Term Prognosis

The CHART-2 patients had better clinical characteristics compared with the CHART-1 patients, which might have contributed in part to the improved prognosis of the CHART-2 patients. Given that the CHART Studies are observational, the patients had already been treated with pharmacologic medications at the time of registration. Thus, reduced BNP, lower NYHA class and higher prevalence of preserved LVEF in the CHART-2 Study were likely, at least in part, due to more frequent implementation of evidence-based medication. The prescription rates of β-blockers, RASI and aldosterone antagonists were all increased in the CHART-2 Study as compared with the CHART-1 Study. Along with these changes, 3-year prognosis, particularly 3-year cardiovascular mortality, was decreased. Previous studies reported that the use of β-blockers, RASI and aldosterone antagonists significantly reduced the risk of cardiovascular death and sudden cardiac death in patients with HF, particularly in those with HFrEF.[27–30] In the present study, however, the prognostic impacts of RASI and aldosterone antagonists were not significant in the CHART-1 or the CHART-2 Study. In contrast, β-blockers tended to improve all-cause mortality in the overall population in CHART-2 but not in CHART-1. Furthermore, on subgroup analysis the use of β-blockers was associated with improved mortality in HFrEF patients, but not in HFpEF patients, in the CHART-2 Study. Thus, in the present study, the reduced mortality in the HFrEF patients could be, at least in part, attributable to better implementation of β-blockers in the CHART-2 Study. In contrast, the use of statins may have improved the mortality from CHART-1 to CHART-2 in HFpEF patients, although no data on statin use were available in the CHART-1 Study. In the present study, the use of statins was significantly associated with reduced mortality in the CHART-2 patients. Given that statin use is associated with decreased incidence of all-cause death, mainly that in sudden death and non-cardiovascular death in HFpEF patients,[14] the decrease in sudden death and non-cardiovascular death in HFpEF patients could be attributable to an increase in statin use from CHART-1 to CHART-2. Although we have no data on the use of statin in the CHART-1 Study, it is likely that the prevalence of HF treated with statins increased from CHART-1 to CHART-2 along with the increase in the prevalence of IHD.

Study Limitations

Several limitations should be mentioned for the present study. First, given that both the CHART-1 and the CHART-2 Studies are prospective observational studies in the Tohoku district of Japan, we need to be cautious when extrapolating the present findings to other cohorts, particularly to those in other countries. Second, the prognostic impact of medications was analyzed based on the initial data at enrollment, and we did not include information on the dose and adherence of these drugs during the follow-up period.

Conclusions

The long-term prognosis of symptomatic HF patients has been significantly improved along with the implementation of evidence-based medications in Japan. Also, the prevalence of ischemic HF and that of HFpEF have markedly increased in Japan.

Acknowledgments

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Conflict of Interest

The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by 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). H.S. has received lecture fees from Bayer Yakuhin (Osaka, Japan), Daiichi Sankyo (Tokyo, Japan) and Novartis Pharma (Tokyo, Japan).

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Supplementary Files

Supplementary File 1

Appendix S1. CHART-2 Study Investigators

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0514