

**Figure.** (A) Location of the epicenter of the Great East Japan Earthquake, the Fukushima-Daiichi nuclear power plants, and the study sites, and the proportions of patients with post-traumatic stress disorder (PTSD). (B) The questionnaire-based prevalence of PTSD in patients who experienced the Tsunami plus Earthquake, the Earthquake alone, or neither. (C) Kaplan-Meier survival curves for the primary endpoint. Adjusted hazard ratio (HR) was determined by a stepwise Cox proportional hazard model with the following variables: PTSD, disaster-related experience, age, sex, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, HF stage, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of cancer, stroke, HF hospitalization, ischemic heart disease, valvular heart disease, left ventricular ejection fraction, B-type natriuretic peptide level, and use of renin-angiotensin system inhibitors,  $\beta$ -blockers, loop diuretics and calcium-channel blockers.

The patients with PTSD were characterized by female sex, higher age, lower diastolic blood pressure, lower prevalence of ischemic heart disease, higher prevalence of stroke and, particularly, a higher frequency of a past or current history of insomnia medication use (Table). The prevalence of PTSD was highest in the hospitals in the area directly affected by the Tsunami or within close proximity (<30km) to the Fukushima-Daiichi nuclear power plant, and decreased in association with the reduction in seismic intensity (Figure A). The patients

who experienced the Tsunami had the highest prevalence of PTSD (Figure B). Multivariate logistic regression analysis revealed that PTSD was significantly associated with several factors, including female sex (adjusted odds ratio (adOR) 1.27; 95% confidence interval (CI) 1.02–1.57;  $P=0.02$ ), dyslipidemia (adOR 0.58; 95% CI 0.38–0.93;  $P=0.02$ ), past or current insomnia medication use (adOR 8.57; 95% CI 5.76–12.76;  $P<0.001$ ), experiencing the Tsunami (adOR 1.95; 95% CI 1.00–3.67;  $P=0.04$ ), major property loss (adOR 1.65; 95% CI



1.14–2.38;  $P < 0.01$ ) and economic poverty after the Earthquake (adOR 3.22; 95% CI 1.73–5.91;  $P < 0.001$ ). Interestingly, dyslipidemia (adOR 0.52; 95% CI 0.31–0.92;  $P = 0.02$ ), major property loss (adOR 1.78; 95% CI 1.15–2.72;  $P < 0.01$ ) and economic poverty (adOR 4.64; 95% CI 2.33–9.12;  $P < 0.001$ ) were more likely associated with PTSD in males, whereas experiencing the Tsunami (adOR 4.40; 95% CI 1.26–14.7;  $P = 0.02$ ) was in females. Past or current insomnia medication use had comparable effect between the sexes (adOR 8.80; 95% CI 5.30–14.1;  $P < 0.001$ , and adOR 10.00; 95% CI 5.00–20.4;  $P < 0.001$  for male and female, respectively). Importantly, during the median follow-up of 2 years, the patients with PTSD, as compared with those without it, more frequently experienced the primary endpoint (18.5% vs. 15.0%, adOR 1.26; 95% CI 1.02–1.57,  $P = 0.035$ ) (Figure C), regardless of age, sex, HF etiology or stage. Corporeal damages by the Tsunami and/or by the Earthquake did not influence the incidence of the primary endpoint (adOR 0.99; 95% CI 0.80–1.23,  $P = 0.93$ ) regardless of the presence or absence of PTSD.

## Discussion

To the best of our knowledge, this is the first study demonstrating the prevalence, predictors and adverse prognostic impact of psychological stress caused by a major earthquake. Although the overall prevalence of PTSD (11.4%) was comparable with that reported in the general population after major disasters,<sup>9,10</sup> the present study demonstrates for the first time that the intensity of the Earthquake, experiencing the Tsunami and proximity to the nuclear power plants were independently associated with the incidence of PTSD. PTSD was more frequently observed in females than in males,<sup>11</sup> and furthermore, sex differences were suggested in the mechanisms of PTSD after the Earthquake; dyslipidemia, major property loss and economic poverty were mainly associated with PTSD in males, whereas the Tsunami experience was the main factor for females. Thus, corporeal and spiritual losses differently influence mental disorders in males and females after a major natural disaster. In contrast, the prognostic effect of the Earthquake was comparable between the sexes in patients with PTSD.

In conclusion, PTSD was frequently noted in CVD patients at 6 months after the Great East Japan Earthquake and associated with subsequent adverse prognostic impact. Furthermore, the present study demonstrates the importance of a sex-based approach to preventing PTSD after major disasters when victims experience several types of stress.<sup>12</sup> Further studies are needed to generalize the present findings to other cohorts.

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## Conflict of Interest

H.S. received lecture fees from Bayer Yakuhin, Ltd (Osaka, Japan),

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## Supplementary Files

### Supplementary File 1

#### Appendix S1. The CHART-2 Study Investigators

Please find supplementary file(s);  
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## Prognostic Impact of Statin Use in Patients With Heart Failure and Preserved Ejection Fraction

– A Report From the CHART-2 Study –

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**Background:** The effectiveness of statins remains to be examined in patients with heart failure (HF) with preserved ejection fraction (EF).

**Methods and Results:** Among 4,544 consecutive HF patients registered in the Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2) between 2006 and 2010, 3,124 had EF  $\geq 50\%$  (HFpEF; mean age 69 years; male 65%) and 1,420 had EF  $< 50\%$  (HF with reduced EF (HFrEF); mean age 67 years; male 75%). The median follow-up was 3.4 years. The 3-year mortality in HFpEF patients was lower in patients receiving statins [8.7% vs. 14.5%, adjusted hazard ratio (HR) 0.74; 95% confidence interval (CI), 0.58–0.94;  $P < 0.001$ ], which was confirmed in the propensity score-matched cohort (HR, 0.72; 95% CI, 0.49–0.99;  $P = 0.044$ ). The inverse probability of treatment weighted further confirmed that statin use was associated with reduced incidence of all-cause death (HR, 0.71; 95% CI, 0.62–0.82,  $P < 0.001$ ) and noncardiovascular death (HR, 0.53; 95% CI, 0.43–0.66,  $P < 0.001$ ), specifically reduction of sudden death (HR, 0.59; 95% CI, 0.36–0.98,  $P = 0.041$ ) and infection death (HR, 0.53; 95% CI, 0.35–0.77,  $P = 0.001$ ) in HFpEF. In the HFrEF cohort, statin use was not associated with mortality (HR, 0.87; 95% CI, 0.73–1.04,  $P = 0.12$ ), suggesting a lack of statin benefit in HFrEF patients.

**Conclusions:** These results suggest that statin use is associated with improved mortality rates in HFpEF patients, mainly attributable to reductions in sudden death and noncardiovascular death. (*Circ J* 2015; **79**: 574–582)

**Key Words:** Heart failure; Lipids; Noncardiovascular death; Statins; Sudden death

Heart failure (HF) is a progressive disorder with high mortality and morbidity,<sup>1</sup> and its prevalence has been rapidly increasing worldwide.<sup>2</sup> Particularly, the obvious increase in the prevalence of HF with preserved ejection fraction (HFpEF) is now a serious healthcare problem all over the world.<sup>3</sup> To date, however, no pharmacological strategy has been established for the treatment of HFpEF patients.<sup>4–8</sup>

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Unlike in patients with HF with reduced ejection fraction (HFrEF), previous randomized clinical trials with cardioprotective drugs, including angiotensin-converting enzyme inhibitors (ACEIs),<sup>4</sup> angiotensin II receptor blockers (ARBs),<sup>5,6</sup> aldoste-

rone antagonists<sup>7</sup> and  $\beta$ -blockers,<sup>8</sup> have failed to show the effectiveness of these drugs in HFpEF patients, which could be at least in part explained by differences in the characteristics of HFrEF and HFpEF patients. Indeed, as compared with HFrEF, HFpEF is characterized by higher age, higher prevalence of female sex, hypertension, and left ventricular diastolic dysfunction associated with myocardial hypertrophy and fibrosis, and lower incidence of cardiovascular death, but comparable all-cause death.<sup>9–11</sup>

Statin [3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors] are cholesterol-lowering drugs with pleiotropic properties, such as antiinflammatory,<sup>12</sup> antihypertrophic,<sup>13</sup> antifibrotic and antioxidant effects,<sup>14,15</sup> all of which could be theoretically beneficial for the management of HF. However, previous

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clinical trials have failed to show beneficial effects of statins in HFrEF patients,<sup>16–18</sup> but the prognostic effect of statins in HFpEF patients remains to be elucidated. Therefore, in the present study, we aimed to examine whether statin use is associated with better clinical outcomes in HFpEF patients, using the database of the Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2), a multicenter prospective observational study of cardiovascular diseases (CVD) in Japan.<sup>19–22</sup>

### Methods

#### Data Sources

The CHART-2 Study is a registry of Japanese patients with CVD.<sup>19–22</sup> Between October 2006 and March 2010, 10,219 consecutive Japanese patients older than 20 years with ACC/AHA stages B–D of HF<sup>23</sup> or coronary artery disease (CAD) were enrolled in both in- and outpatient settings.<sup>19</sup> The ACC/AHA stages B–D of HF were defined as follows: Stage B, structural heart disease but without signs or symptoms of HF; Stage C, structural heart disease with prior or current symptoms of HF; Stage D, refractory HF requiring specialized interventions.<sup>23</sup> The diagnosis of HF was based on the Framingham criteria.<sup>24</sup> Written informed consent was provided by all patients before enrollment.<sup>19</sup> Information on medical history and baseline demographics, including medications and echo-

cardiographic data, was collected at the time of enrollment by the clinical research coordinators. Follow-up was at least twice yearly by review of medical records, surveys and telephone interviews conducted by clinical research coordinators. The CHART-2 Study was approved by the local ethics committees of the 24 participating hospitals (1 university hospital, 23 general hospitals) and registered in ClinicalTrials.gov (Identifier: NCT00418041).

#### Study Sample

Of 10,219 patients, 4,736 had a history of or current symptoms of HF (Stage C/D).<sup>19</sup> After exclusion of 192 patients lacking EF data, we enrolled 3,124 patients with HFpEF (EF ≥50%, mean [SD] age 69.4 [12.2] years; male 65%) and 1,420 patients with HFrEF (EF <50%, mean [SD] age 67.4 [12.4] years; male 75%) in the present study (Figure S1).

#### Study Outcomes and Definitions

The study endpoints were death, mode of death and hospitalization for worsening HF. All events and mode of death were reviewed and assigned by consensus of at least 2 independent physicians from the members of the Tohoku Heart Failure Association (Appendix S1) after reviewing case reports, death certificates, and hospital records provided by the investigators. Cardiovascular death was defined as death attributed to car-

**Table 1. Baseline Characteristics of the Total and Matched Cohorts of Patients With HFpEF**

	Total cohort (n=3,124)			Matched cohort (n=1,252)		
	Statin use		P value	Statin use		P value
	Yes (n=1,163)	No (n=1,961)		Yes (n=626)	No (n=626)	
Age, mean (SD), years	69.0 (11.0)	69.7 (12.9)	0.108	69.4 (11.2)	70.0 (11.9)	0.362
Male sex, n (%)	785 (67.5)	1,256 (64.0)	0.052	410 (65.5)	421 (67)	0.550
BP, mean (SD), mmHg						
Systolic	131 (18)	127 (19)	<0.001	129 (17)	130 (19)	0.360
Diastolic	74 (12)	72 (12)	<0.001	73 (12)	74 (12)	0.652
Heart rate, mean (SD), beats/min	71 (14)	72 (15)	0.008	72 (14)	71 (14)	0.163
Body mass index (SD), kg/m <sup>2</sup>	24.7 (3.6)	23.5 (3.8)	<0.001	24.2 (3.6)	24.2 (4.1)	0.884
NYHA classification, n (%)			<0.001			0.877
I	365 (30.4)	465 (23.7)		147 (23.5)	159 (35.4)	
II	723 (62.2)	1,286 (65.6)		422 (67.4)	409 (65.3)	
III	82 (7.1)	196 (10)		53 (8.5)	54 (8.6)	
IV	4 (0.3)	14 (0.7)		4 (0.6)	4 (0.6)	
Current or past smoker, n (%)	527 (45.3)	801 (40.8)	0.015	281 (44.9)	290 (46.3)	0.650
Medical history, n (%)						
Hospitalization for HF	488 (42.0)	994 (50.7)	<0.001	281 (44.9)	273 (43.6)	0.690
Hypertension	989 (85.0)	1,505 (76.7)	<0.001	518 (82.7)	505 (80.7)	0.380
Diabetes mellitus	393 (33.8)	409 (20.9)	<0.001	181 (28.9)	163 (26.0)	0.282
Dyslipidemia	1,158 (99.6)	1,073 (54.7)	<0.001	624 (99.7)	361 (57.7)	<0.001
Atrial fibrillation	243 (20.9)	848 (43.2)	<0.001	200 (31.9)	186 (29.7)	0.426
Stroke	217 (18.7)	338 (17.2)	0.033	113 (18.1)	119 (19.0)	0.716
Cancer	117 (10.1)	261 (13.3)	0.008	74 (11.6)	71 (11.3)	0.860
Previous MI	579 (49.8)	364 (18.6)	<0.001	212 (33.9)	211 (33.7)	1.000
Coronary artery disease	832 (71.5)	591 (30.8)	<0.001	344 (55.0)	307 (49.0)	0.042
Coronary artery angiography	505 (43.4)	360 (18.4)	<0.001	209 (33.4)	190 (30.4)	0.374
1-vessel disease	231 (19.9)	208 (10.6)	<0.001	110 (17.6)	106 (16.9)	0.764
2-vessel disease	174 (15.0)	103 (5.3)	<0.001	72 (11.5)	58 (9.3)	0.391
3-vessel disease	100 (8.6)	49 (2.5)	<0.001	27 (4.3)	26 (4.2)	1.000
Valvular dysfunction	212 (18.2)	673 (34.3)	<0.001	167 (26.7)	160 (25.6)	0.700
Hypertrophic cardiomyopathy	87 (7.5)	272 (13.9)	<0.001	67 (10.7)	77 (12.3)	0.425

(Table 1 continued the next page.)



	Total cohort (n=3,124)			Matched cohort (n=1,252)		
	Statin use		P value	Statin use		P value
	Yes (n=1,163)	No (n=1,961)		Yes (n=626)	No (n= 626)	
<b>Laboratory data</b>						
LDL-C, mg/dl	99 (27)	110 (31)	<0.001	101 (28)	113 (29)	<0.001
HDL-C, mg/dl	52 (15)	53 (16)	0.266	53 (15)	52 (15)	0.213
Triglyceride, mg/dl	134 (73)	124 (82)	0.001	136 (79)	128 (84)	0.109
Hemoglobin, g/dl	13.3 (2.1)	13.0 (2.0)	<0.001	13.2 (1.9)	13.2 (1.9)	0.937
BNP (IQR), pg/dl	76 (28–145)	116 (45–197)	<0.001	83 (32–155)	102 (37–159)	0.626
Potassium, mEq/L	4.4 (0.4)	4.4 (0.5)	0.036	4.3 (0.4)	4.4 (0.5)	0.829
eGFR, ml·min <sup>-1</sup> ·1.73m <sup>-2</sup>	61 (28)	62 (22)	0.310	61 (34)	62 (21)	0.752
CRP (IQR), mg/dl	0.2 (0.1–0.8)	0.3 (0.1–0.8)	0.018	0.2 (0.1–0.8)	0.3 (0.1–0.8)	0.098
LVEF, %	66 (9)	65 (9)	0.223	65 (9)	65 (9)	0.851
LAD, mm	41 (8)	43 (10)	<0.001	42 (9)	42 (9)	0.543
<b>Medications, n (%)</b>						
Loop diuretics	373 (32.1)	892 (45.5)	<0.001	246 (39.3)	221 (35.3)	0.161
ACEI or ARB	857 (73.7)	1,310 (66.8)	<0.001	440 (70.3)	454 (72.5)	0.416
β-blocker	533 (45.8)	772 (39.4)	<0.001	278 (44.4)	268 (42.8)	0.608
Aldosterone antagonist	174 (15.0)	426 (21.7)	<0.001	113 (18.1)	103 (16.5)	0.501
Calcium-channel blocker	590 (50.7)	810 (41.3)	<0.001	291 (46.5)	304 (48.6)	0.497
Antiplatelet or anticoagulant	1,048 (90.1)	1,437 (73.3)	<0.001	523 (83.5)	520 (83.1)	0.880
Other lipid-lowering medicine	43 (3.7)	78 (4.0)	0.774	28 (4.5)	21 (3.4)	0.382
<b>Intervention history, n (%)</b>						
PCI	625 (53.7)	360 (18.4)	<0.001	217 (34.7)	227 (36.3)	0.595
CABG	179 (15.4)	111 (5.7)	<0.001	61 (9.7)	47 (7.5)	0.190
ICD	11 (0.9)	27 (1.4)	0.316	6 (1.0)	6 (1.0)	1.000
CRTD	1 (0.1)	10 (0.5)	0.063	0	2 (0.3)	0.500

Values are expressed as n (%) unless otherwise indicated. The majority of variables were used for derivation of the propensity score. The following covariates were not included for derivation of the propensity score: diastolic BP; dyslipidemia; LDL-C, HDL-C, triglyceride and CRP levels; other lipid-lowering medicine, ICD, and CRTD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CRP, C-reactive protein; CRTD, cardiac resynchronization therapy defibrillator; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure and preserved ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation.

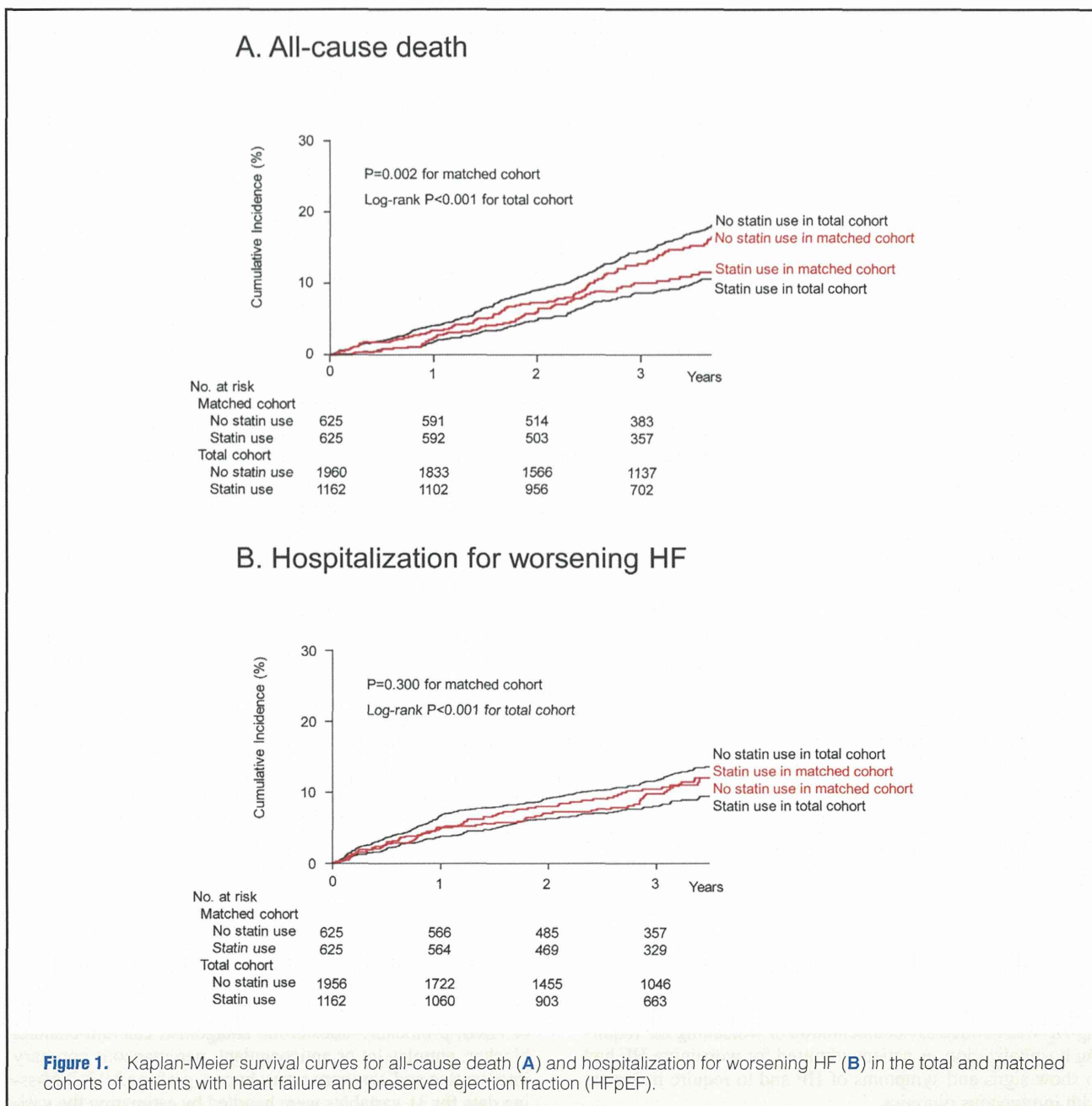
diovascular origins. Noncardiovascular death was defined as death from noncardiovascular causes. For the mode of death, only the main mode was recorded. Hospitalization for worsening HF was defined as documentation of worsening HF requiring hospitalization. A patient admitted for worsening HF had to show signs and symptoms of HF and to require treatment with intravenous diuretics.

### Statistical Analysis

Descriptive statistics, including mean±SD, median and frequencies for continuous and categorical data, are presented for all patients and by statin treatment category. The Wilcoxon rank sum and Pearson's chi-square test were used to compare the characteristics of patients with and without statin therapy.

To reduce confounding effects related to differences in the patient's background between those with and those without statin use, 3 propensity score (PS) methods were used in combination with Cox regression modeling. For the calculation of PS, we used a logistic regression model in which the treatment status of statins was regressed for the following 31 baseline characteristics: age, male sex, blood pressure, heart rate, body mass index, NYHA classification, smoking status (current and past smoker or nonsmoker), history of hospitalization for HF, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, stroke, cancer, previous myocardial infarction (MI), CAD

(3-vessel disease), hypertrophic cardiomyopathy, hemoglobin, B-type natriuretic peptide, potassium, estimated glomerular filtration rate, LVEF, left atrial dimension, loop diuretics, ACEI or ARB, β-blocker, aldosterone antagonist, calcium-channel blocker, antiplatelet or anticoagulant, percutaneous coronary intervention and coronary artery bypass grafting.<sup>9,11,25,26</sup> Missing data for 31 variables were handled by estimating the variables for each missing variable based on the pattern for all available observations. Area under the curve (AUC) to show the performance of the PS for statin use was 0.78 [95% confidence interval (CI), 0.77–0.80]. Using the PS, patients were matched for 1:1 optimal match with a <0.001 caliper and no replacement. The distribution of PS in the total and matched cohorts is shown in [Figure S2](#). Kaplan-Meier curves were plotted to evaluate the association between statin use and all-cause death or hospitalization for worsening HF in the total cohort using the log-rank test and PS-matched cohort using the PS-stratified Cox analysis. To reduce confounding in the time-to-event observational data, the inverse probability of treatment weighted (IPTW) method was used.<sup>27</sup> Using the same 31 variables for the PS calculation, case-weight estimation was done with a logistic regression model to predict the inverse probability of statin use. Finally, in order to examine the clinical effect of statins in the total cohort, we constructed 5 Cox proportional hazard models: unadjusted, age- and sex-adjusted, PS-



adjusted, PS-stratified and the IPTW analyses.<sup>27</sup> The assumption of proportional hazards was tested for the model, and no significant departure was found.

PS methods are used to eliminate the effect of treatment-selection bias in an observational study by estimating the probability of assignment to treatments or exposure on the outcomes. PS matching is a statistical matching technique aiming to estimate the effect of an intervention by accounting for the covariates that predict receiving the treatment. Our PS-stratified model enabled us to compare treated and untreated patients within each of the strata providing similar estimates of the PS, which can reduce the imbalance in observed covariates and thus can verify the results of PS matching. The IPTW method has recently been developed to utilize all sample information with assigned weights by making an unbiased estimation of

the true risk difference with the lowest standard error of the estimated risk difference, the lowest mean-squared error and approximately correct type I error rates. Although all 3 of these PS methods are useful to reduce selection bias in observational studies, we conferred the primary significance to the IPTW method in the present study, because it has been shown to have superior performance to other PS methods, including the PS-matching and PS-stratified methods.<sup>27</sup>

In the subgroup analysis, we examined interactions between selected baseline variables and statin use and reported the interaction P value. Baseline variables were selected from previous studies<sup>9,11,25,26</sup> and by using the Cox proportional hazard model with a stepwise method; we included variables with P<0.2.



**Table 2. Cox Regression Models for All-Cause Death and Hospitalization for Worsening HF by Statin Use in of Patients With HFpEF**

	No. of events/total (%)	HR	95% CI	P value
<b>All-cause death in the total cohort</b>				
Unadjusted	440/3,124 (14.1)	0.56	0.45–0.69	<0.001
Adjusted with age and sex	440/3,124 (14.1)	0.63	0.50–0.78	<0.001
Adjusted with propensity score	440/3,124 (14.1)	0.74	0.58–0.94	0.014
Adjusted with PS-stratified Cox model	440/3,124 (14.1)	0.67	0.53–0.86	0.002
Adjusted with IPTW	440/3,124 (14.1)	0.71	0.62–0.82	<0.001
<b>All-cause death in the matched cohort</b>				
	159/1,252 (12.7)	0.72	0.53–0.99	0.002
<b>Hospitalization for worsening HF in the total cohort</b>				
Unadjusted	351/3,124 (11.2)	0.63	0.50–0.79	<0.001
Adjusted with age and sex	351/3,124 (11.2)	0.67	0.53–0.85	0.001
Adjusted with propensity score	351/3,124 (11.2)	0.82	0.70–1.19	0.512
Adjusted with PS-stratified Cox model	351/3,124 (11.2)	0.87	0.67–1.13	0.300
Adjusted with IPTW	351/3,124 (11.2)	0.94	0.81–1.08	0.388
<b>Hospitalization for worsening HF in the matched cohort</b>				
	140/1,252 (11.2)	0.96	0.69–1.34	0.827

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighted; PS, propensity score. Other abbreviations as in Table 1.

**Table 3. Adjusted Risk for Each Mode of Death in the Cohort of Patients With HFpEF**

	Statin use in the total cohort			Adjusted HR	95% CI	P value
	Total (n=3,124)	Yes (n=1,163)	No (n=1,961)			
<b>All-cause death</b>	440	113	327	0.72	0.63–0.82	<0.001
Cardiovascular	210	64	146	1.01	0.83–1.22	0.960
Heart failure	97	28	69	1.16	0.88–1.53	0.288
Stroke	40	12	28	1.25	0.72–2.15	0.426
Sudden death	25	11	14	0.59	0.36–0.98	0.041
MI	11	3	8	0.61	0.27–1.38	0.234
Other cardiovascular	37	10	27	1.07	0.70–1.64	0.758
<b>Noncardiovascular</b>	206	47	159	0.53	0.43–0.66	<0.001
Cancer	75	22	53	0.74	0.53–1.03	0.078
Infection	67	14	53	0.53	0.36–0.77	0.001
Renal failure	18	5	13	0.73	0.36–1.47	0.371
Noninfectious respiratory conditions	5	1	4	0.65	0.07–6.28	0.713
Gastrointestinal bleeding	4	0	4	–	–	–
Other noncardiovascular	37	5	32	0.27	0.10–0.73	0.009
Unknown cause	24	2	22	0.17	0.01–0.42	<0.001

Other abbreviations as in Tables 1,2.

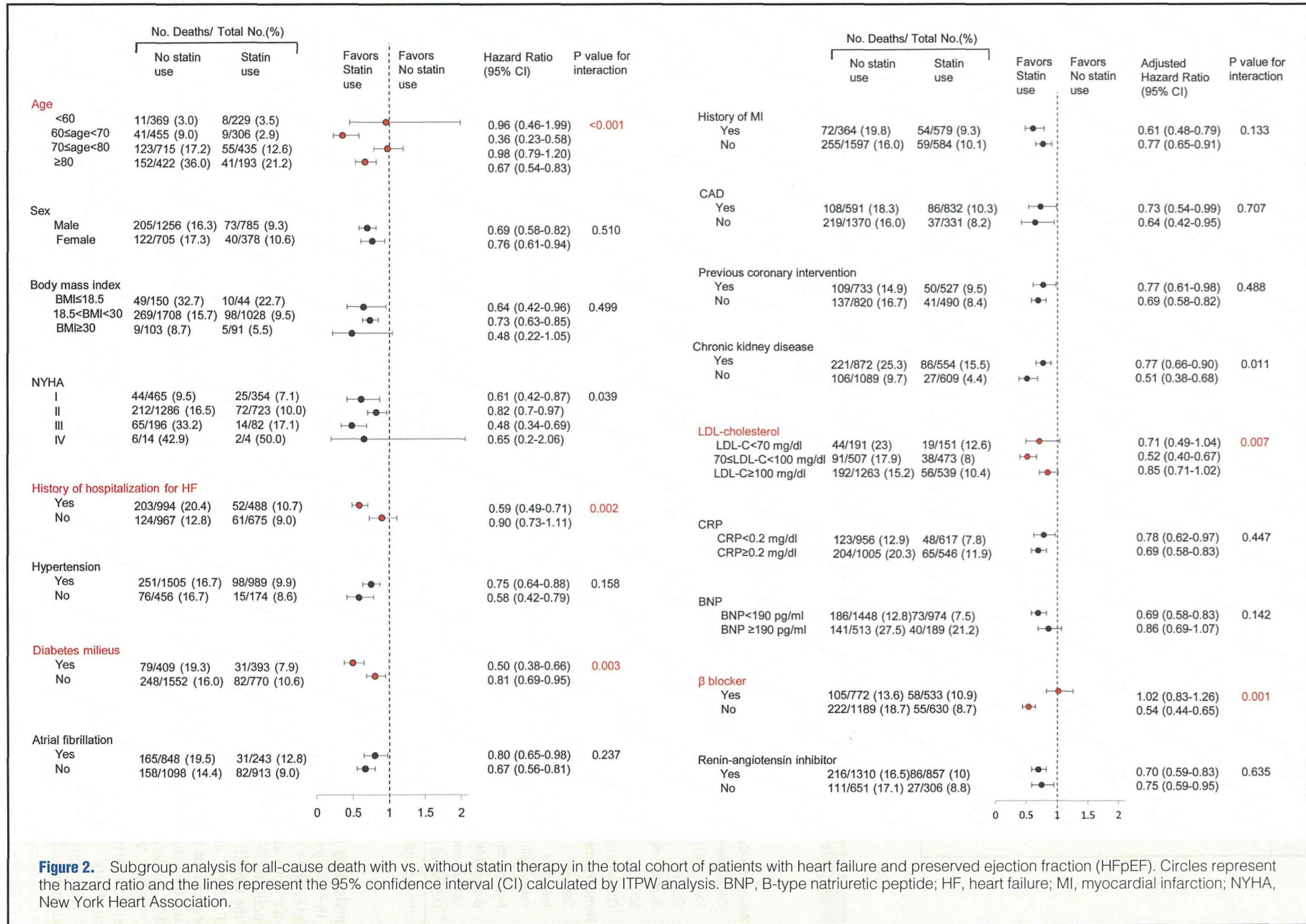
### Consistency Analysis

In the previous studies, statins did not reduce all-cause death in HFpEF.<sup>16–18</sup> Thus, in order to confirm consistency between those trials and the present study regarding the lack of stain benefit in HFpEF patients, we performed a statistical analysis of the HFpEF cohort derived from the same CHART-2 registry (EF <50%, n=1,420) and compared the results with those in the previous studies. In the HFpEF cohort, PS was calculated using the same 31 variables used in the HFpEF cohort and the IPTW models (Table S1). AUC for the PS was 0.80 (95% CI, 0.77–0.82). We performed all analyses using IBM SPSS Statistics 21.0 (IBM, Somers, NY, USA) and R 3.0.2. Two-sided probability values <0.05 and P<0.1 were considered to be statistically significant. All authors had a full access to the data and approved the manuscript as written.

### Results

#### Baseline Characteristics of HFpEF Patients (Table 1)

Among the 3,124 HFpEF patients, 1,163 (37.2%) received statins and 1,961 (62.8%) did not (specific agents and doses are listed in Table S2). In the total HFpEF cohort, there were several differences between the 2 groups. The patients taking statins were more likely to be male and less symptomatic, and had a higher prevalence of previous MI, medical treatment and a history of coronary intervention. Although the high-density lipoprotein cholesterol and triglyceride levels were comparable, low-density lipoprotein cholesterol (LDL-C) levels significantly differed between the patients with and without statin use (99 vs. 110 mg/dl). After PS matching, baseline characteristics became generally comparable between the 2 groups (Table 1). The patients excluded from the PS matching were younger and had a lower prevalence of smoking, hypertension, dyslip-



**Figure 2.** Subgroup analysis for all-cause death with vs. without statin therapy in the total cohort of patients with heart failure and preserved ejection fraction (HFpEF). Circles represent the hazard ratio and the lines represent the 95% confidence interval (CI) calculated by ITPW analysis. BNP, B-type natriuretic peptide; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association.



idemia and previous MI as compared with those included (Table S1).

### Reduced Incidence of All-Cause Death in HFpEF Patients Treated With Statins

During the median follow-up of 3.4 years, 440 (14.1%) patients died. In the total HFpEF cohort, crude 3-year mortality was 8.7% in patients treated with statins and 14.5% for those without statins (log-rank  $P < 0.001$ ) (Figure 1A). This difference in 3-year mortality remained after PS matching; 10.1% for patients with statins and 12.8% for those without statins with an adjusted hazard ratio (HR) of 0.72 (95% CI, 0.51–0.99,  $P = 0.002$ ) (Figure 1A, Table 2). Table 2 shows the HRs for the outcomes in the total and matched cohorts. In the PS-adjusted, PS-stratified and IPTW analyses of the total HFpEF cohort, statin use was significantly associated with reduced all-cause death, with HRs of 0.74 (95% CI, 0.58–0.94,  $P = 0.014$ ), 0.67 (95% CI, 0.53–0.86,  $P = 0.002$ ), and 0.71 (95% CI, 0.62–0.82,  $P < 0.001$ ), respectively (Table 2).

### Mode of Death in HFpEF Patients

Table 3 shows the association between statin use and mode of death. Of the 440 deaths in the total HFpEF cohort, 210 were cardiovascular deaths (48%), 206 were noncardiovascular deaths (47%) and 24 were of unknown cause (5%). Among the cardiovascular deaths, HF death was most common (97 deaths, 46% of cardiovascular deaths), followed by sudden death (40 deaths, 19% of cardiovascular deaths). Of the 206 noncardiovascular deaths, cancer death was most frequent (75 deaths, 36% of noncardiovascular deaths), followed by infection death (67 deaths, 33% of noncardiovascular deaths). The IPTW analysis revealed that statin use was significantly associated with reduced incidence of sudden death (HR, 0.59; 95% CI, 0.36–0.98,  $P = 0.041$ ), noncardiovascular death (HR, 0.53; 95% CI, 0.43–0.66,  $P < 0.001$ ) and infection death (HR, 0.53; 95% CI, 0.36–0.77,  $P = 0.001$ ) (Table 3).

### Hospitalization for Worsening HF in HFpEF Patients

Hospitalization for worsening HF was recorded for 351 (11.2%) patients in the total HFpEF cohort. Although the Kaplan-Meier estimates for hospitalization for worsening HF showed a significant difference between patients with and without statin use in the total cohort, the difference disappeared in the IPTW analysis (HR 0.94; 95% CI, 0.81–1.08,  $P = 0.388$ ). There also was no reduction in hospitalization for worsening of HF (HR 0.96; 95% CI, 0.69–1.34,  $P = 0.827$ ) in the matched cohort, confirming the result of the IPTW analysis (Figure 1B, Table 2).

### Subgroup Analysis

Figure 2 shows the results of subgroup analysis according to clinically relevant characteristics in the total HFpEF cohort by IPTW method. In the total HFpEF cohort, statin use significantly interacted with age, NYHA, history of hospitalization for worsening HF, diabetes mellitus, chronic kidney disease (CKD), LDL-C, and  $\beta$ -blocker therapy and did not interact with CAD or previous coronary intervention.

There was no interaction with C-reactive protein levels  $\geq 0.2$  mg/dl (HR, 0.69; 95% CI, 0.58–0.83) vs.  $< 0.2$  mg/dl (HR, 0.78; 95% CI, 0.62–0.97,  $P$  for interaction = 0.447).

### Analyses in the HFrEF Cohort

Table S3 shows the baseline characteristics of the total ( $n = 1,420$ ) and matched HFrEF cohorts ( $n = 416$ ). In the total HFrEF cohort, patients taking statins were younger, more likely to be male and had lower prevalence of hypertension and higher

prevalence of prior MI as compared with those without statins, whereas baseline characteristics became comparable in the matched cohort. Although statin use was associated with reduced mortality in the total HFrEF cohort, the difference became insignificant in both the matched and total cohort with the IPTW method (HR 0.87; 95% CI, 0.73–1.04,  $P = 0.118$ ) (Figure S3, Table S4).

## Discussion

To the best of our knowledge, this is the first study to examine whether statin use is associated with reduced mortality in a large-scale cohort of patients with HFpEF. Using state-of-the-art PS-based analyses, the present results clearly demonstrated that statin use was associated with reduced all-cause and noncardiovascular mortality rates, specifically with reduced incidence of sudden death and infection death. The findings for HFpEF patients were further strengthened by separate analysis of the HFrEF cohort in the same registry, in which no association between statin use and mortality was confirmed, as reported in previous studies.<sup>16–18</sup>

### Prognostic Effect of Statins in HFpEF Patients

The unadjusted survival curves showed a large separation between HFpEF patients with and without statin use. This beneficial association of statin use remained significant in the PS-matched, PS-adjusted, PS-stratified and IPTW models. Furthermore, statin use was significantly associated with reduced incidence of sudden death and noncardiovascular death, the latter being partly attributable a reduction in infection deaths. Because the prognosis of HFpEF patients is considerably poorer and the number of HFpEF patients has been rapidly increasing worldwide,<sup>1–3</sup> establishment of HFpEF management is currently an urgent matter. Thus, the present results have clinical significance, providing a clue to improving the management of HFpEF patients. In addition, the clinical significance of the present study is further emphasized by the fact that all previous clinical trials of cardiovascular drugs, including ACEIs, ARBs and  $\beta$ -blockers, have failed to show any benefits in HFpEF patients.<sup>4–8</sup>

### Mode of Death in HFpEF Patients Treated With Statins

Fukuta et al preliminarily reported that statin use was associated with lower mortality in HF patients with EF  $\geq 50\%$  (adjusted HR, 0.20; 95% CI, 0.06–0.62,  $P = 0.005$ ).<sup>28</sup> In their study, however, they did not investigate associations between mode of death and statin treatment, possibly because of the small sample size ( $n = 137$ ).<sup>28</sup> From this point of view, the present study clearly demonstrated that statin use was significantly associated with reduced all-cause and noncardiovascular mortality, specifically a reduced incidence of sudden death and infection death. Furthermore, the present study revealed that the beneficial effect of statin use was more evident in patients with a previous history of HF hospitalization, those with diabetes mellitus, those without CKD and those without  $\beta$ -blockers in the total HFpEF cohort. However, because the precise mechanisms for the interactions between statin use and those factors are unclear, we need to confirm these observations and to specify the characteristics of HFpEF patients who could most benefit from statin treatment in clinical practice.

### Statin Use and Cardiovascular Deaths in HFpEF

In the HFpEF cohort, statin use was not associated with the incidence of overall cardiovascular deaths, which was similar to the findings in the HFrEF cohorts in previous and present



studies.<sup>16–18</sup> In the present study, however, IPTW analysis revealed that statin use was associated with reduced incidence of sudden death. Despite the large amount of data showing the beneficial effect of statin therapy on reducing mortality, information regarding efficacy with regard to sudden cardiac death is limited. In a meta-analysis, Levantesi et al reported that statin treatment was associated with a 19% significant reduction in sudden death independent of patient characteristics or changes in lipid levels in patients with CVD.<sup>29</sup> Vrtovec et al reported that atorvastatin therapy increased heart rate variability, decreased QT variability, and shortened the QTc interval duration in patients with advanced chronic HF.<sup>30</sup> They further demonstrated in another study that atorvastatin therapy was associated with decreased incidence of sudden cardiac death in patients with advanced HF.<sup>31</sup> However, the effect on sudden cardiac death has never been reported in patients with HFpEF, regardless of study design or study sample size. Thus, our finding is clinically important in showing an association between statin use and reduced incidence of sudden death in HFpEF. It is conceivable that statin treatment was associated with a decrease in ventricular late potentials, resulting in a reduced incidence of fatal cardiac arrhythmia.<sup>29–31</sup> In addition, statin treatment has been reported to reduce acute coronary events possibly related to plaque stabilization, improvement of endothelial and platelet functions, and reduction of neutrophil infiltration.<sup>32</sup> Thus, there is a possibility that the reduced incidence of sudden death in HFpEF patients treated with statins might be attributed to fewer acute coronary events.

### Noncardiovascular Deaths and Statin Use in HFpEF

Another key finding of the present study was that statin use was associated with reduced incidence of noncardiovascular deaths in the HFpEF patients. In the present study, half of the deaths in the HFpEF cohort had noncardiovascular causes, with cancer and infection as the first and second reasons, respectively. Although the beneficial effect of statin on cancer death is controversial in a broad spectrum of patients,<sup>33,34</sup> beneficial effects of statins against infection in the general practice has been reported, including patients with vascular diseases,<sup>35</sup> CKD,<sup>36</sup> diabetes,<sup>37</sup> and intensive care unit-acquired infections,<sup>38</sup> and a meta-analysis confirmed the idea.<sup>39</sup> Statins have also been reported to suppress the inflammatory response to endotoxin *in vivo*<sup>40</sup> and decrease serum levels of tumor necrosis factor- $\alpha$  and interleukin-6 in patients with acute bacterial infection.<sup>41</sup> These lines of evidence suggest that antiinfective effects of statins were involved in the reduction of infection deaths in HFpEF patients in the present study. However, there have been no studies reporting the inhibitory effects of statins on infection death in patients with HF, regardless of HFrEF or HFpEF. Thus, our finding is clinically important because it is the first to suggest the efficacy of statin use for reduction of infection deaths as well.

### Consistency Analysis

In the previous randomized clinical trials, statin treatment failed to reduce mortality in HFrEF patients.<sup>16–18</sup> In the CORONA study, rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in a total of 5,011 patients aged 60 years or older with symptomatic and systolic HF of ischemic origin.<sup>16</sup> In the GISS-HF study, rosuvastatin also did not improve clinical outcomes in 4,574 patients aged 18 years or older with symptomatic HF irrespective of cause.<sup>17</sup> In the PEARL Study, no cardioprotective effects of pitavastatin were noted in a total of 574 Japanese HFrEF patients.<sup>18</sup> Also, in the present HFrEF cohort, statin use was not associated with lower

mortality, a consistent finding with the previous studies,<sup>16–18</sup> confirming that our CHART-2 registry is representative of other rigorous settings. Thus, our present findings could be generalized to other HFpEF cohorts, although caution is highly warranted.

### Study Limitations

First, the CHART-2 Study is an observational study in which prescription of statins was not randomized and thus the results could be affected by potential confounders. Even though we performed state-of-the-art statistical analyses using PS, the influence of baseline differences in LDL-C levels and unmeasured confounding factors might not have been completely excluded. Thus, although the present study has the strength of a broad spectrum of patients in real-world practice enrolled with a minimal selection bias, caution is needed when interpreting the results. Second, comparison of the prognostic effects of statins was based on medications at enrollment, and we did not include information on dose or type of statin or on adherence to statin treatment after registration or subsequent prescription of statins during the follow-up period. These factors might have modified the actual clinical effect of statin therapy on mortality. Third, the ratio of HFpEF to HFrEF in this study of consecutive patients was approximately 2:1, which represents the high proportion of HFpEF in real-world practice in Japan, and the relatively small number of HFrEF patients in the matched cohort (n=416) might have been underpowered to detect an effect on cardiovascular events in HFrEF patients.

### Conclusions

The present study demonstrates for the first time the beneficial effects of statin use in HFpEF patients. Our finding may have important clinical significance because no established pharmacological agents are yet available for HFpEF patients. Our findings need to be confirmed in future randomized clinical trials and other observational studies.

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### Conflicts of Interest

H.S. received lecture fees from Bayer Yakuhin, Ltd (Osaka, Japan), Daiichi Sankyo Co, Ltd (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan).

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