Effect of Statins on Mortality in Heart Failure With Preserved Ejection Fraction Without Coronary Artery Disease

— Report From the JASPER Study —

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Background: Statins might be associated with improved survival in patients with heart failure with preserved ejection fraction (HFpEF). The effect of statins in HFpEF without coronary artery disease (CAD), however, remains unclear.

Methods and Results: From the JASPER registry, a multicenter, observational, prospective cohort with Japanese patients aged ≥ 20 years requiring hospitalization with acute HF and LVEF $\geq 50\%$, 414 patients without CAD were selected for outcome analysis. Based on prescription of statins at admission, we divided patients into the statin group ($n=81$) or no statin group ($n=333$). We followed them for 25 months. The association between statin use and primary (all-cause mortality) and secondary (non-cardiac death, cardiac death, or rehospitalization for HF) endpoints was assessed in the entire cohort and in a propensity score-matched cohort. In the propensity score-matched cohort, 3-year mortality was lower in the statin group (HR, 0.21; 95% CI: 0.06–0.72; $P=0.014$). The statin group had a significantly lower incidence of non-cardiac death ($P=0.028$) and rehospitalization for HF ($P<0.001$), but not cardiac death ($P=0.593$). The beneficial effect of statins on mortality did not have any significant interaction with cholesterol level or HF severity.

Conclusions: Statin use has a beneficial effect on mortality in HFpEF without CAD. The present findings should be tested in an adequately powered randomized clinical trial.

Key Words: All-cause death; Heart failure with preserved ejection fraction; Non-ischemic heart failure; Statin

Nearly half of community-based patients with heart failure (HF) have preserved left ventricular ejection fraction (LVEF), and the number of patients with HF with preserved EF (HFpEF) has been rapidly increasing worldwide.^{1–3} Moreover, patients with HFpEF have high mortality and morbidity,^{3–5} making it a major health problem. Unlike in HF with reduced ejection fraction, however, previous randomized clinical trials with cardio-protective drugs, including angiotensin-converting enzyme inhibitors (ACEI),⁶ angiotensin II receptor blockers (ARB),^{7,8} aldosterone antagonists,⁹ and β -blockers,¹⁰ showed that they are not effective with regard to mortality in HFpEF. Therefore, establishing how to manage HFpEF is currently an urgent matter.

The effect of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) on clinical outcomes in HFpEF has

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been reported in prospective and retrospective observational studies.^{11–18} These previous studies included patients with and without coronary artery disease (CAD). Although the beneficial effects of statins in patients with CAD has been established,^{19–23} the effects of statins in HF patients without CAD remains unknown.

In addition to lipid-lowering effects, statins have pleiotropic effects,^{24–31} such as prevention of LV fibrosis and hypertrophy, improvement of endothelial dysfunction and arterial stiffness, and an anti-inflammatory effect, all of which can contribute to the pathophysiology of HFpEF without CAD.^{32,33} No study, however, has assessed the effects of statins in HFpEF patients without CAD in detail.

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We conducted this study to elucidate the efficacy of statins with regard to mortality in HFpEF patients without CAD.

Methods

Data Sources

The Japanese heart failure Syndrome with Preserved Ejection fraction (JASPER) registry is a multicenter, observational, prospective cohort of 535 patients aged ≥ 20 years who required hospitalization between July 2012 and March 2015 with a diagnosis of acute HF according to the Framingham criteria,³⁴ by at least 2 experienced cardiologists. Patients in the registry had preserved LV systolic function, defined as LVEF $\geq 50\%$ with the modified Simpson method, or LV fractional shortening $\geq 25\%$ on echocardiography. Echocardiography was performed using commercially available ultrasound equipment. The median duration between echocardiography and admission was 0 days (IQR, 0–1 days). Patients with acute coronary syndrome (ACS), receiving hemodialysis, or with a history of heart transplantation were excluded.³⁵

Patient demographic data including comorbidity, clinical signs, laboratory and echocardiographic data, in-hospital treatment including oral and i.v. medication, and length of hospital stay, were obtained. Follow-up was performed at hospital discharge and at 12 and 24 months after discharge through direct contact with patients or their physicians in the hospital or outpatient clinic setting, or via patient interview by telephone and mail by dedicated coordinators and investigators. If patients were deceased, their family members were contacted. In this study, because patient information was anonymized and de-identified prior to analysis, written informed consent was not obtained from each patient. We publicized the study, however, by posting an easy-to-understand summary of the protocol on the website of the National Cerebral and Cardiovascular Center. This notice clearly informed patients of their right

to refuse enrollment. This study, including the procedure for enrollment, conformed to the principles of the Declaration of Helsinki and has been approved by the institutional review board of each participating site. It was registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601).

Subjects

Absence of CAD was defined as no history of CAD at the beginning of the study.³⁶ A history of CAD included a history of myocardial infarction (MI) or coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). After excluding patients with a history of CAD, the remaining patients were included in the outcome analysis.

Follow-up and Endpoints

The primary endpoint of the present study was all-cause death. The principal secondary endpoints were non-cardiac death and cardiac death, which included sudden cardiac death (SCD) and HF death. Rehospitalization for HF was an additional secondary endpoint. The duration of the follow-up period was calculated from the day of admission until an endpoint occurred or the last patient contact. SCD was defined as unexpected death either ≤ 1 h after cardiac symptoms in the absence of progressive cardiac deterioration, during sleep, or ≤ 24 h after last being seen alive.³⁷ HF death was defined as death associated with unstable, progressive deterioration of pump function despite active therapy. Rehospitalization for HF was defined as unexpected hospitalization for HF.

Statistical Analysis

All continuous variables are presented as mean $\pm$ SD. Unpaired t-test was used to compare groups. Non-normally distributed variables are presented as median (IQR). Non-continuous and categorical variables are presented as

Table 1. Baseline Clinical Characteristics vs. Statin Use and Propensity Score Matching

	Entire cohort (n=414)				PSM cohort (n=112)		
	All patients (n=414)	No statin use (n=333)	Statin use (n=81)	P-value	No statin use (n=56)	Statin use (n=56)	P-value
Age (years)	77±11	77±11	78±10	0.584	76±10	78±9	0.298
Male	198 (48)	172 (52)	26 (32)	0.002	22 (39)	19 (34)	0.421
BMI (kg/m ²)	23.8±4.9	23.4±4.8	25.3±5.0	0.003	24.6±5.3	24.6±4.4	0.961
Hypertension	305 (74)	231 (69)	74 (91)	<0.001	48 (86)	50 (89)	0.568
Dyslipidemia	147 (36)	79 (24)	68 (84)	<0.001	15 (27)	44 (79)	<0.001
Diabetes mellitus	123 (30)	95 (29)	28 (35)	0.270	20 (36)	20 (36)	1.000
Atrial fibrillation	270 (65)	219 (66)	51 (63)	0.869	44 (79)	34 (61)	0.054
Current smoker	43 (10)	37 (11)	6 (7.4)	0.444	3 (5.4)	6 (11)	0.427
History of hospitalization for HF	134 (32)	103 (31)	31 (38)	0.258	22 (39)	22 (39)	1.000
NYHA functional class (n=396)				0.693			0.502
I	4 (1.0)	3 (0.9)	1 (1.4)		0	1 (1.9)	
II	93 (23)	75 (23)	18 (24)		9 (17)	9 (17)	
III	164 (41)	130 (40)	34 (46)		20 (38)	26 (48)	
IV	135 (34)	114 (35)	21 (28)		23 (44)	18 (33)	
SBP (mmHg)	119±21	119±21	121±20	0.552	119±19	123±20	0.312
DBP (mmHg)	63±13	63±13	65±13	0.257	64±12	64±13	0.879
BNP (pg/mL)	324 (176–586)	324 (165–586)	332 (207–608)	0.436	287 (104–597)	359 (207–638)	0.059
Creatinine (mg/dL)	1.18±0.79	1.17±0.79	1.23±0.81	0.518	1.05±0.44	1.30±0.88	0.052
eGFR (mL/min/1.73m ²)	53±26	54±27	48±22	0.087	53±22	47±23	0.130
Albumin (g/dL)	3.6±0.5	3.6±0.5	3.7±0.5	0.027	3.8±0.4	3.7±0.5	0.142
Serum sodium (mEq/L)	140±4	140±4	141±4	0.090	141±3	141±4	0.980
Hemoglobin (g/dL)	11.4±2.2	11.4±2.3	11.5±2.0	0.840	11.8±2.2	11.2±2.0	0.118
HDL-C (mg/mL)	49±14	48±14	52±14	0.033	52±14	52±14	0.838
LDL-C (mg/mL)	91±30	92±31	87±26	0.263	97±35	85±27	0.053
Triglycerides (mg/mL)	97±129	93±138	115±78	0.206	99±52	112±74	0.302
Total cholesterol (mg/mL)	160±39	160±40	160±32	0.935	171±47	156±33	0.062
CRP (mg/dL)	0.27 (0.10–0.89)	0.35 (0.11–0.90)	0.31 (0.20–0.69)	0.817	0.40 (0.11–1.09)	0.23 (0.08–0.64)	0.780
ECG variables							
Heart rate (beats/min)	74±17	74±18	73±16	0.668	75±18	71±15	0.286
CLBBB	19 (4.6)	14 (4.2)	5 (6.2)	0.668	5 (8.9)	5 (8.9)	1.000
Echocardiographic variables							
Septal wall thickness (mm)	11±3	11±3	11±3	0.327	11±3	10±2	0.428
LV posterior wall thickness (mm)	11±2	11±2	11±2	0.622	11±2	10±1	0.326
Diastolic LV diameter (mm)	46±7	46±7	46±6	0.552	46±8	46±6	0.809
LVEF (%)	60±8	60±9	60±9	0.894	60±8	61±8	0.851
LAD (mm)	45±10	46±7	46±6	0.776	46±10	45±6	0.667
E peak (cm/s)	100±35	100±36	101±33	0.942	103±35	100±35	0.694
A peak (cm/s)	80±34	79±34	86±30	0.332	76±36	85±28	0.367
E/A	1.29±0.83	1.31±0.79	1.21±1.03	0.608	1.43±0.97	1.26±1.15	0.634
E-wave deceleration time (ms)	194±69	193±69	196±71	0.771	197±64	199±65	0.942
E/e'	18.6±9.2	18.4±9.1	19.5±9.9	0.501	20.5±9.5	18.3±7.5	0.341
TRPG (mmHg)	37±13	37±13	36±12	0.794	35±11	38±12	0.181
Medications at baseline							
β-blocker	155 (37)	120 (36)	35 (43)	0.232	28 (50)	26 (46)	0.705
ACEI or ARB	227 (55)	174 (52)	53 (65)	0.033	34 (61)	34 (61)	1.000
Aldosterone antagonist	88 (21)	76 (23)	12 (15)	0.114	18 (32)	9 (16)	0.047
Diuretic	206 (50)	164 (49)	42 (52)	0.674	32 (57)	31 (55)	0.849
Digoxin	49 (12)	37 (11)	12 (15)	0.335	8 (14)	9 (16)	0.792
Anticoagulant	193 (47)	154 (46)	39 (48)	0.758	34 (61)	24 (43)	0.059

Data given as mean±SD, median (IQR) or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CLBBB, complete left bundle branch block; CRP, C-reactive protein; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LAD, left atrium diameter; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PSM, propensity score-matched; SBP, systolic blood pressure; TRPG, tricuspid regurgitation peak gradient.

Figure 2. Kaplan-Meier all-cause death (A,C) event-free survival rate and (B,D) 3-year event rate in the (A,B) entire and (C,D) propensity score-matched cohorts according to statin use.

frequency or percentage. They were compared using the chi-squared test. Cumulative event-free survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression models were used to calculate hazard ratios (HR) and 95% CI for each endpoint. Multivariable Cox regression was performed using covariates that were significantly associated with each endpoint on univariable analysis. Stepwise selection with $P<0.1$ for backward elimination was used to select the best predictive model. For subgroup analyses of statin use, a Cox proportional hazards model was used to calculate the HR for statin use and P -values for the interaction between statin use and selected baseline variables. We used median B-type natriuretic peptide (BNP; 324 pg/mL) as the cut-off for creating a binary explanatory variable. In addition, to reduce the effect of treatment selection bias and possible confounders, we performed adjustment for significant differences in patient baseline characteristics using propensity score matching. The propensity score adjusted for baseline covariates that were significantly different between the 2 groups: gender; prevalence of hypertension; body mass index (BMI); albumin level, and high-density lipoprotein cholesterol (HDL-C) level; and use of ACEI or ARB. Each patient treated with a statin was matched to 1 patient not treated with a statin using nearest-neighbor matching using a caliper width of 0.01 without replacement. All statistical tests were 2-sided and $P<0.05$ was regarded as statistically significant. Statistical analysis was performed using SPSS version 24.0 (IBM, Armonk, NY, USA).

Results

Baseline Clinical Characteristics

After excluding 121 patients with a history of MI ($n=66$), CABG ($n=10$), or PCI ($n=45$) from 535 HFpEF patients, 414 patients met the inclusion criteria. All 414 patients were included in the outcome analysis (Figure 1). Mean LVEF was 60%. We divided the patients into 2 groups according to statin use at admission: the statin group ($n=81$) and the no statin group ($n=333$). Table 1 compares the baseline clinical characteristics of the 2 groups. Patients in the statin group were less likely to be male (32% vs. 52%; $P=0.002$). They had higher BMI (25.3 ± 5.0 kg/m² vs. 23.4 ± 4.8 kg/m²; $P=0.003$) and albumin (3.7 ± 0.5 g/dL vs. 3.6 ± 0.5 g/dL; $P=0.027$) and a higher prevalence of hypertension (91% vs. 69%; $P<0.001$). The statin group used ACEI or ARB more frequently than the no statin group (65% vs. 52%; $P=0.033$). As expected, patients taking statins had a higher prevalence of dyslipidemia (84% vs. 24%; $P<0.001$) and higher HDL-C (52 ± 14 mg/mL vs. 48 ± 14 mg/mL; $P=0.039$) than the no statin group. There were no significant differences in BNP or low-density lipoprotein cholesterol (LDL-C), LV systolic function, E/A ratio, or left atrial size.

Hospitalization for Acute HF

Duration of hospitalization was similar between the statin group (median, 15 days; IQR, 11–23 days) and the no statin group (median, 15 days; IQR, 12–21 days). The statin and no statin groups had similar rates of i.v. treatment (86% vs. 89%; $P=0.534$) and mechanical ventilation (19%

Table 2. Risk Factors for All-Cause Death in HFpEF Without CAD

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (per 10-year increment)	1.59	1.21–2.08	0.001	1.47	1.01–2.15	0.046
Male	1.17	0.74–1.89	0.505			
BMI (per 1-kg/m ² increment)	0.90	0.85–0.96	0.001		Not selected	
Hypertension	0.76	0.46–1.27	0.302			
Dyslipidemia	0.47	0.28–0.82	0.008		VIF	
Diabetes mellitus	0.84	0.50–1.42	0.512			
Atrial fibrillation	1.13	0.68–1.91	0.637			
Current smoker	0.64	0.35–1.18	0.156			
History of hospitalization for HF	1.61	0.99–2.62	0.053			
NYHA class ≥III	2.72	1.24–5.95	0.012		Not selected	
SBP (per 10-mmHg increment)	0.91	0.81–1.03	0.150			
DBP (per 10-mmHg increment)	0.88	0.73–1.07	0.195			
Log (BNP) (per 1-pg/mL increment)	2.33	1.27–4.26	0.006		Not selected	
eGFR (per 1-mL/min/1.73 m ² decrement)	1.01	1.01–1.02	0.006		Not selected	
Albumin (per 1-g/dL decrement)	4.67	2.86–4.67	<0.001	7.75	3.82–15.63	<0.001
Serum sodium (per 1-mEq/L decrement)	1.07	1.02–1.12	0.004		Not selected	
Hemoglobin (per 1-g/dL decrement)	1.24	1.12–1.39	<0.001		Not selected	
HDL-C (per 1-mg/mL increment)	0.98	0.96–1.00	0.053			
LDL-C (per 1-mg/mL increment)	0.99	0.99–1.00	0.170			
Triglycerides (per 1-mg/mL increment)	0.99	0.99–1.00	0.301			
Total cholesterol (per 1-mg/mL increment)	0.99	0.99–1.00	0.171			
Log (CRP) (per 1-mg/dL increment)	1.45	1.05–2.07	0.023		Not selected	
ECG parameters						
Heart rate (per 10-beats/min increment)	0.96	0.89–1.04	0.335			
Presence of CLBBB	0.89	0.44–1.80	0.750			
Echocardiographic variables						
Septal wall thickness (per 1-mm increment)	0.99	0.90–1.10	0.881			
LV posterior wall thickness (per 1-mm increment)	0.95	0.84–1.08	0.441			
Diastolic LV diameter (per 1-mm increment)	1.02	0.98–1.05	0.416			
LVEF (per 10% increment)	1.34	0.99–1.81	0.053			
LAD (per 5-mm increment)	1.04	0.93–1.18	0.488			
E peak (per 1-cm/s increment)	1.00	0.99–1.01	0.999			
A peak (per 1-cm/s increment)	0.99	0.98–1.00	0.160			
E-wave deceleration time (per 10-ms increment)	1.00	0.96–1.04	0.990			
E/e' (per unit increment)	1.01	0.98–1.04	0.629			
TRPG (per 5-mmHg increment)	1.13	1.04–1.23	0.005	1.11	1.01–1.24	0.041
Medication at baseline						
β-blocker	1.53	0.96–2.44	0.075			
ACEI or ARB	0.95	0.60–1.50	0.820			
Aldosterone antagonist	2.80	1.75–4.48	<0.001	2.67	1.39–5.19	0.003
Diuretic	2.50	1.51–4.12	<0.001	1.88	0.89–3.97	0.098
Digoxin	0.80	0.37–1.74	0.572			
Anticoagulant	1.34	0.84–2.12	0.219			
Statin	0.34	0.15–0.78	0.011	0.33	0.11–0.97	0.045

CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; VIF, variance inflation factor. Other abbreviations as in Table 1.

vs. 18%; $P=0.916$). During hospitalization, 6 deaths occurred in the no statin group, consisting of 1 cardiac and 5 non-cardiac deaths. In contrast, no patients in the statin group died ($P=0.224$).

Primary Endpoint: All-Cause Death

Table S1 lists the primary and secondary endpoints. During a median follow-up period of 25 months (IQR, 18–28

months), 71 patients (17%) died. The statin group had a lower incidence of all-cause death than the no statin group ($P=0.007$; **Figure 2A**). The estimated 3-year rate for the primary endpoint was lower in the statin group than in the no statin group (12.9% vs. 25.3%; $P=0.007$; **Figure 2B**). **Table 2** shows univariable and multivariable Cox regression analyses of risk factors for all-cause death. In a stepwise multivariable Cox model that adjusted for factors that

Figure 3. Kaplan-Meier non-cardiac death (A,C) event-free survival rate and (B,D) 3-year event rate in the (A,B) entire and (C,D) propensity score-matched cohorts according to statin use.

were significant on univariable analysis, statin use was significantly associated with future mortality reduction (HR, 0.33; 95% CI: 0.11–0.97; $P=0.045$). A propensity score-matched cohort consisting of 56 patients with and without statin use was constructed (Table 1). In this model that matched for gender; BMI; history of hypertension; levels of albumin and HDL-C; and ACEI or ARB use, all-cause death occurred less frequently in the statin group than in the no statin group (8.9% vs. 23%; $P=0.040$, Table S1; $P=0.032$, Figure 2C). The estimated 3-year rate for the primary endpoint was also lower in the statin group than in the no statin group on propensity score matching (15.4% vs. 30%; $P=0.032$; Figure 2D). On multivariable Cox proportional hazard modeling, statin use was also significantly associated with future mortality reduction (HR, 0.21; 95% CI: 0.06–0.72; $P=0.014$; Table S2).

Principal Secondary Endpoints: Non-Cardiac Death and Cardiac Death

During the follow-up period, non-cardiac death occurred in 53 patients (13%). Cardiac death occurred in 18 patients (4.3%); 2 patients (0.5%) died suddenly, and 16 (3.9%) had HF death. Fewer non-cardiac deaths occurred in the statin group ($P=0.018$, Table S1; $P=0.013$, Figure 3A,B). These differences remained after propensity score matching (Figure 3C,D). There were no significant differences, however, in the incidence of cardiac death by statin use (Figure 4A,B). In the propensity score-matched cohort, there were no significant differences in the incidence of cardiac death by statin use (Table S1; Figure 4C,D).

Additional Secondary Endpoint: Rehospitalization for HF

Rehospitalization for HF occurred in 91 patients (22%). There were no significant differences in the incidence ($P=0.255$, Table S1; $P=0.186$, Figure 5A) or estimated 3-year event rate ($P=0.202$, Figure 5B) of this endpoint between the 2 groups. After propensity score matching, however, the statin group had a lower incidence ($P=0.001$, Table S1; $P<0.001$, Figure 5C) and estimated 3-year rate ($P<0.001$, Figure 5D) of rehospitalization for HF than the no statin group.

Primary and Secondary Endpoints After Discharge

To evaluate the effect of statins after discharge, we constructed a new cohort with 387 patients who could be followed after discharge. They were divided into 2 groups based on whether statins were prescribed at discharge: the statin use group ($n=97$) and the no statin group ($n=290$). Statin therapy had a beneficial effect on all-cause death ($P=0.023$), in particular non-cardiac death ($P=0.015$), but not on cardiac death ($P=0.669$; Figure S1).

Subgroup Analysis

Figure 6 shows the results of subgroup analyses according to clinically relevant factors in the entire cohort. There were no significant interactions between statin use and other factors such as gender, age, and BNP and LDL-C levels.

Discussion

In the JASPER study, prescription of statins at admission was associated with a substantial mortality reduction in

Figure 4. Kaplan-Meier cardiac death (A,C) event-free survival rate and (B,D) 3-year event rate in the (A,B) entire and (C,D) propensity score-matched cohorts according to statin use.

HFpEF patients without CAD during a median follow-up of 25 months. After propensity score matching, the benefit of statin use was confirmed, and, on multivariable Cox modeling, statin prescription at admission was associated with a 79% reduction in mortality risk. Decreased mortality was not associated with gender, age, or BNP and LDL-C. To the best of our knowledge, this is the first nationwide study analyzing a cohort of hospitalized HFpEF patients without CAD that has demonstrated the beneficial effects of statins.

Prognostic Effect of Statins in HFpEF

Some previous studies have shown that statins had a beneficial effect in patients with HFpEF. Preliminary results from Fukuta et al showed 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; $P=0.005$).¹¹ In a recent observational study of 9,140 Swedish patients with HFpEF, statin use was associated with reduced all-cause mortality, cardiovascular mortality, and combined all-cause mortality or cardiovascular hospitalization.¹⁶ In addition, the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study, a multicenter prospective observational study of cardiovascular disease in Japan, showed that statin use was associated with decreased mortality in patients with HFpEF, which was mainly attributable to reductions in sudden and non-cardiovascular death.¹⁷ According to a meta-analysis of 4 studies with 5,526 propensity score-matched patients, statin therapy was associated with reduced mortality (OR,

0.690; 95% CI: 0.493–0.965; $P=0.030$).¹⁸ All of these studies, however, included patients with and without CAD.

Prognostic Effect of Statin in HFpEF Without CAD

The benefits of statins in patients with CAD are already known.^{19–23} Statin therapy has been reported to reduce acute coronary events, possibly through plaque stabilization, improvement of endothelial and platelet function, and reduction of neutrophil infiltration.³⁸ Meanwhile, a substantial number of patients with HF and sudden death have been documented to have ACS precipitated by plaque rupture on autopsy.³⁹ Thus, the efficacy of statin therapy in HF patients with CAD could be primarily related to plaque stabilization and prevention of anti-thrombotic events. The CHART-2 study therefore showed that statin use reduced the risk for sudden death in HFpEF patients, including those with CAD.¹⁷

The effects of statins in HF patients without CAD, however, remain unknown. A few small randomized trials limited to HF patients with systolic dysfunction showed that statin use had no significant effect on mortality and hospitalization in patients without CAD.^{40–43} In an observational study on HFpEF from the Swedish Heart Failure Registry, there was a strong interaction between the effect of statin use and presence of CAD (interaction $P=0.001$).⁴⁴ That study showed that statin use had a beneficial effect on mortality in HFpEF patients with CAD (HR, 0.76; 95% CI: 0.70–0.82; $P<0.001$), but not in those without CAD (HR, 0.95; 95% CI: 0.85–1.07; $P=0.43$).⁴⁴ In contrast, subgroup analyses in the aforementioned Swedish and

Figure 5. Kaplan-Meier re-hospitalization for heart failure (HF) (A,C) event-free survival rate and (B,D) 3-year event rate in the (A,B) entire and (C,D) propensity score-matched cohorts according to statin use.

Japanese studies showed that statin use was associated with reduced mortality in HFpEF patients without CAD.^{16,17} Nevertheless, these studies lacked detailed analyses focusing on HFpEF patients without CAD. Thus, we conducted the present study to assess the effect of statins in HFpEF patients without CAD.

We divided HFpEF patients without CAD into 2 groups by statin use. On survival curve analysis, the statin group had a significantly lower incidence of death, especially non-cardiac death, and rehospitalization for HF than the no statin group (Figures 2–5). Although the causes of non-cardiac death in the present study were unclear, the CHART-2 study investigated the cause of death in detail. In that study, 206 of 3,124 patients with HFpEF (6.6%) had non-cardiovascular death during a follow-up period of 3.4 years.¹⁷ Cancer ($n=75$, 36%) was the most common non-cardiac cause of death, followed by infection ($n=67$, 33%) and renal failure ($n=18$, 24%).¹⁷ In particular, the incidence of death due to infection was significantly lower ($P=0.001$) and cancer-related mortality tended to be lower ($P=0.078$) in the statin use group than in the no statin use group.¹⁷ In addition, in previous studies statin use was associated with reduced cancer-related mortality⁴⁵ and with a small reduction in the rate of kidney function loss in patients with cardiovascular disease.⁴⁶ Thus, statin therapy might reduce mortality from infection, cancer, and renal failure. Furthermore, despite the lack of significant interactions, the subgroup analyses indicated that statin therapy might be reasonable for patients with a history of hospital-

ization for HF; atrial fibrillation; use of β -blocker, ACEI or ARB; reduced estimated glomerular filtration rate; or increased BNP. Thus, statin therapy is presumed to be effective in patients with advanced HFpEF in addition to β -blocker, ACEI, or ARB therapy. Although further studies are needed, the present results suggest that statin therapy is effective for patients with HFpEF, even if they do not have CAD.

Possible Mechanisms for Benefits of Statins in HFpEF Without CAD

The mechanisms by which statins benefit HFpEF patients without CAD are still unknown, but there are some hypotheses. First, patients without CAD might benefit from the pleiotropic effects of statin therapy, including regression of LV hypertrophy and fibrosis,^{24–26} a mild anti-hypertensive effect,²⁸ improved endothelial and autonomic function,²⁷ increased arterial distensibility,^{28,29} and LV remodeling.⁴⁷ Of the 107 patients in the present study who underwent 1-year follow-up echocardiography, LV diastolic diameter of the no statin group showed a non-significant increase (from 45.4 mm to 46.9 mm, $P=0.210$). In contrast, the statin group had a non-significant decrease (from 44.9 mm to 44.3 mm, $P=0.573$), which suggests that statins could affect LV remodeling. There is limited evidence, however, that these pleiotropic effects can translate into improved outcomes in patients with non-ischemic cardiomyopathy.⁴⁸ Second, other potential beneficial actions of statins that are not limited to effects for HF, such as

Figure 6. Subgroup analysis of all-cause death by statin use in the entire cohort. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association.

anti-inflammatory and antioxidant effects,^{30,31} might also confer beneficial effects in patients with HFpEF. The CHART-2 study showed that statins were associated with a reduction in the number of infectious deaths among patients HFpEF.¹⁷ Third, the beneficial effects of statins are likely related to their effects on diabetes⁴⁹ and impaired renal function,⁵⁰ which are common comorbidities in patients with HFpEF. These factors might explain some of the benefit of statins observed in HFpEF patients without CAD.

Study Limitations

First, the JASPER study is an observational study in which the prescription of statins was not randomized. Even though we performed propensity score matching, the influence of baseline differences in the prevalence of dyslipidemia and unmeasured confounders might not have been completely excluded. Second, lipid profiles at baseline and during treatment were not available for all patients. Furthermore, we do not have complete data on compliance with statin use or subsequent initiation of statin therapy. These factors might have modified the actual clinical effect of statin therapy on mortality. Third, we excluded patients with a history of CAD, but there might be undiagnosed CAD. Only 66 patients (16%) underwent evaluation of the coronary arteries on coronary angiography at the beginning of this study, because coronary angiography was based on physician judgment. Moreover, during the follow-up period,

some patients might have developed asymptomatic CAD. Future studies should evaluate the coronary arteries in all patient to exclude those with hidden CAD, and assess the effect of statins on endpoints in patients without CAD. Fourth, we could not investigate all causes of death. There was a significant difference in the incidence of non-cardiac death between the statin and no statin groups, but we were not able to assess non-cardiac deaths in detail. Further study should assess this cause of death in detail. Fifth, the number of subjects in this study was relatively smaller than in previous studies. We had well-defined inclusion criteria, however, for hospitalized patients with HF. Therefore, despite the relatively small number of subjects, we believe that the diagnosis of HFpEF was adequately confirmed in the present study. Finally, the results from the stepwise selection process are potentially biased due to overfitting of the derivation data set.

Conclusions

Statin use has a beneficial effect on mortality in HFpEF patients without CAD. The underlying mechanisms need further investigation. The present findings should be tested in an adequately powered randomized clinical trial.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier curves for (A) all-cause death, (B) non-cardiac death, (C) cardiac death and (D) rehospitalization for heart failure (HF) according to statin use at discharge.

Table S1. Primary and secondary endpoints during follow-up

Table S2. Risk factors for all-cause death in HFpEF without CAD in the propensity score-matched cohort

Please find supplementary file(s);
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