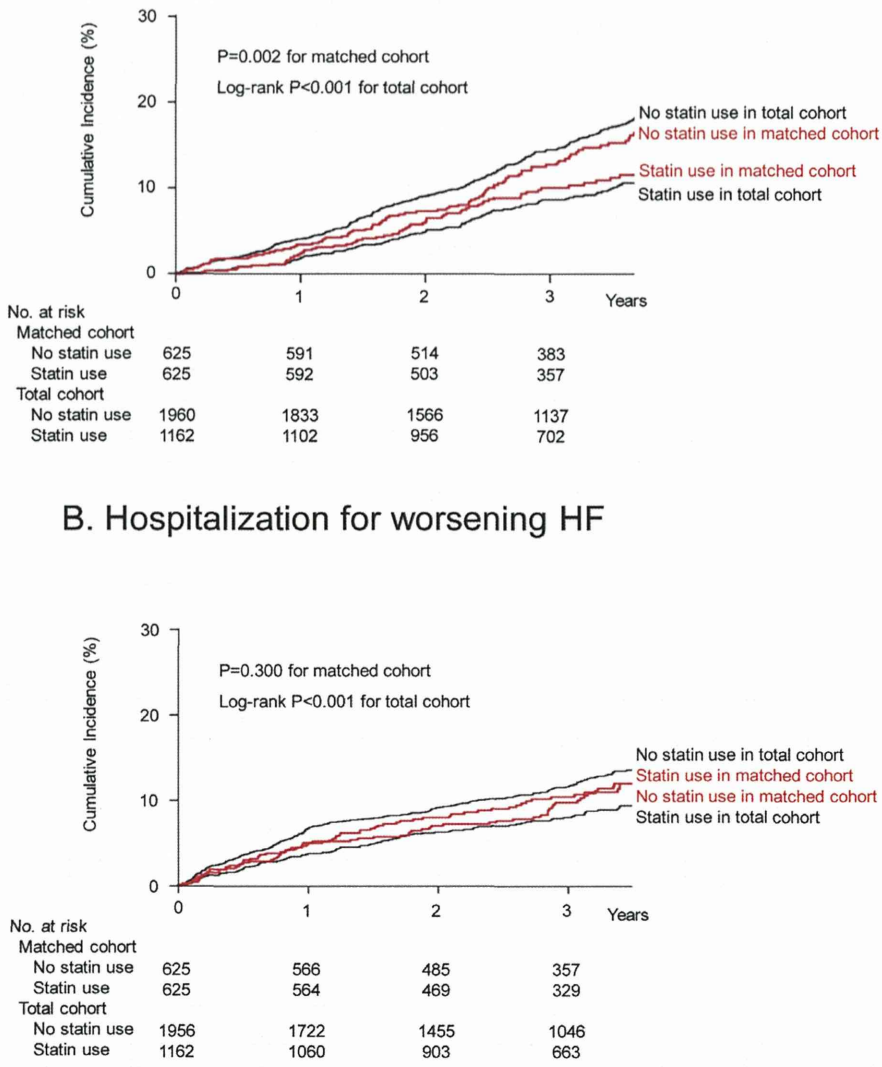

Figure 1. Kaplan-Meier survival curves for all-cause death (**A**) and hospitalization for worsening HF (**B**) in the total and matched cohorts of patients with heart failure and preserved ejection fraction (HFpEF).

adjusted, PS-stratified and the IPTW analyses.[27] 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 ITPW 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.[27]

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[9,11,25,26] 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
All-cause death in the total cohort				
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
All-cause death in the matched cohort	159/1,252 (12.7)	0.72	0.53–0.99	0.002
Hospitalization for worsening HF in the total cohort				
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
Hospitalization for worsening HF in the matched cohort	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					
	Total (n=3,124)	Yes (n=1,163)	No (n=1,961)	Adjusted HR	95% CI	P value
All-cause death	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
Noncardiovascular	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 HFrEF.[16–18] Thus, in order to confirm consistency between those trials and the present study regarding the lack of stain benefit in HFrEF patients, we performed a statistical analysis of the HFrEF 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 HFrEF cohort, PS was calculated using the same 31 variables used in the HFpEF cohort and the ITPW 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-

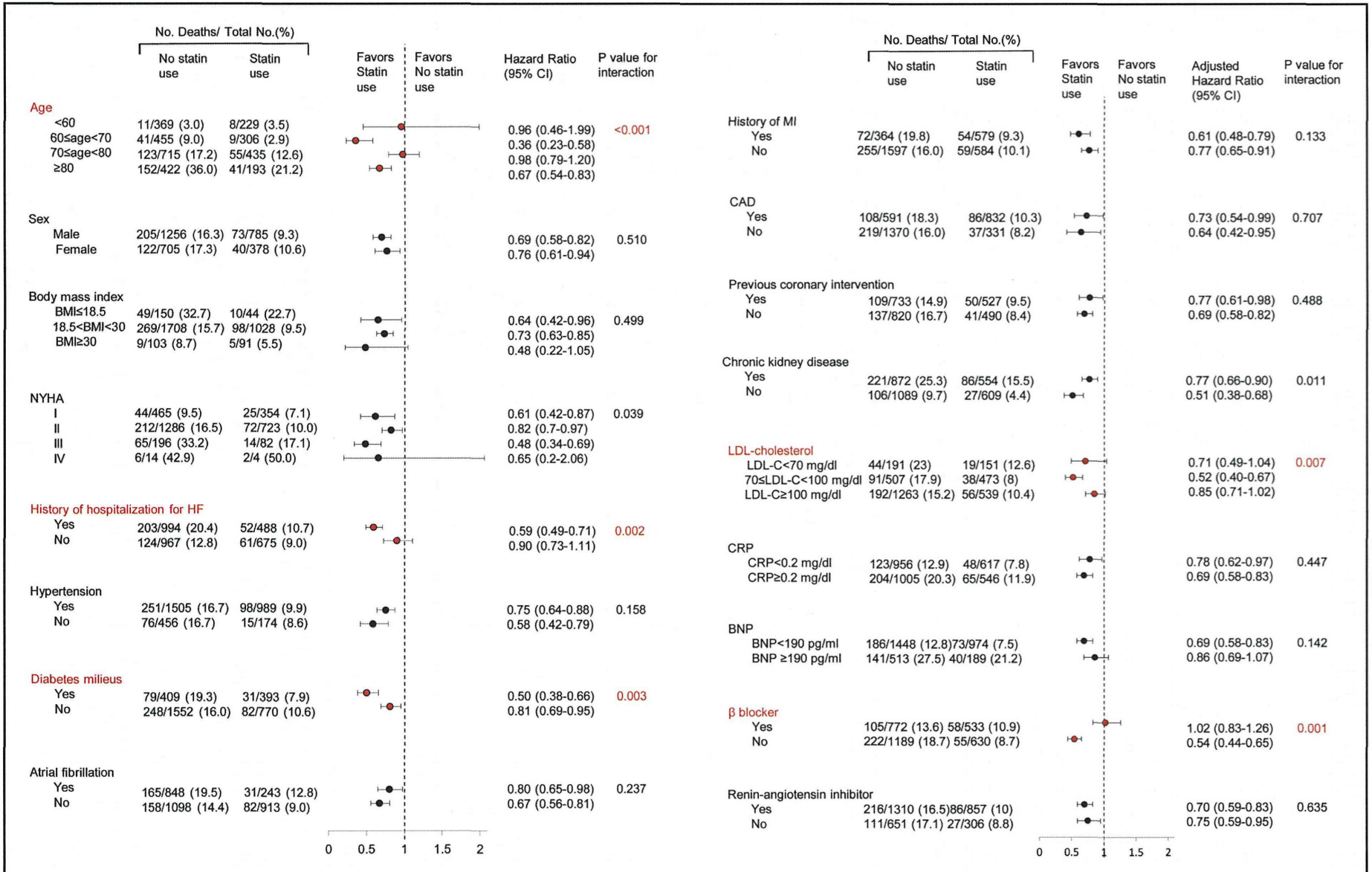

Figure 2. Subgroup analysis for all-cause death with vs. without statin therapy in the total cohort of patients with heart failure and preserved ejection fraction (HFpEF). Circles represent the hazard ratio and the lines represent the 95% confidence interval (CI) calculated by ITPW analysis. BNP, B-type 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 ITPW 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 ITPW 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 ITPW 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 ITPW 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 β-blocker therapy and did not interact with CAD or previous coronary intervention.

There was no interaction with C-reactive protein levels ≥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.[16–18]

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 ITPW 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,[1–3] 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 β-blockers, have failed to show any benefits in HFpEF patients.[4–8]

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 ≥50% (adjusted HR, 0.20; 95% CI, 0.06–0.62, P=0.005).[28] 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).[28] 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 β-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.[16–18] 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.[29] 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.[30] They further demonstrated in another study that atorvastatin therapy was associated with decreased incidence of sudden cardiac death in patients with advanced HF.[31] 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 stain 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.[29–31] 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.[32] 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,[33,34] beneficial effects of statins against infection in the general practice has been reported, including patients with vascular diseases,[35] CKD,[36] diabetes,[37] and intensive care unit-acquired infections,[38] and a meta-analysis confirmed the idea.[39] Statins have also been reported to suppress the inflammatory response to endotoxin in vivo[40] and decrease serum levels of tumor necrosis factor-α and interleukin-6 in patients with acute bacterial infection.[41] 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.[16–18] 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.[16] 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.[17] In the PEARL Study, no cardioprotective effects of pitavastatin were noted in a total of 574 Japanese HFrEF patients.[18] Also, in the present HFrEF cohort, statin use was not associated with lower mortality, a consistent finding with the previous studies,[16–18] 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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Supplementary Files

Supplementary File 1

Figure S1. Allocation of patients to cohorts.

Figure S2. Distribution of propensity scores (PS) in the total and matched cohorts of patients with heart failure and preserved ejection fraction (HFpEF).

Figure S3. Kaplan-Meier survival curves for all-cause death in the total and matched cohorts of patients with reduced ejection fraction (HFrEF).

Table S1. Characteristics of HFpEF patients included or excluded from PS-matched analysis

Table S2. Specific agents and doses of statins in the cohort of patients with HFpEF

Table S3. Baseline characteristics of patients with HFrEF in total and matched cohorts

Table S4. Prognostic effect of statins in the cohort of patients with HFrEF

Appendix S1. The CHART-2 Study Investigators

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0865

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ORIGINAL ARTICLE
Heart Failure

Prognostic Impact of Subclinical Microalbuminuria in Patients With Chronic Heart Failure

– Report From the CHART-2 Study –

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Background: Microalbuminuria, traditionally defined as urinary albumin/creatinine ratio (UACR) ≥30 mg/g, is a risk factor for mortality even in patients with preserved glomerular filtration rate (GFR). The prognostic impact of subclinical microalbuminuria, however, remains unknown in patients with chronic heart failure (CHF).

Methods and Results: In the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 Study, we enrolled 2,039 consecutive symptomatic CHF patients (median age, 67.4 years; 68.9% male) after excluding those on hemodialysis. On classification and regression tree analysis, UACR=10.2 mg/g and 27.4 mg/g were identified as the first and second discriminating points to stratify the risk for composite of death, acute myocardial infarction, HF admission and stroke, therefore subclinical microalbuminuria was defined as UACR ≥10.2 and <27.4 mg/g. There were 506 composite endpoints (24.8%) during the median follow-up of 2.69 years. On Kaplan-Meier analysis and multivariate Cox modeling, subclinical microalbuminuria was significantly associated with increased composite endpoints with hazard ratios of 1.90 (P<0.001) and 2.29 (P<0.001) in patients with preserved (>60 ml·min^{-1}·1.73 m^{-2}, n=1,129) or mildly reduced eGFR (30–59.9 ml·min^{-1}·1.73 m^{-2}, n=789), respectively. In patients with severely reduced GFR (eGFR <30 ml·min^{-1}·1.73 m^{-2}, n=121), >80% had microalbuminuria or macroalbuminuria, and only 9.1% were free from any composite endpoints.

Conclusions: Subclinical microalbuminuria was associated with increased risk of cardiovascular events in CHF patients with mildly reduced or preserved renal function. (*Circ J* 2014; **78:** 2890–2898)

Key Words: Chronic heart failure; Chronic kidney disease; Prognosis; Subclinical microalbuminuria

Microalbuminuria, traditionally defined as between 30 and 300 mg/g urinary albumin/creatinine ratio (UACR),[1] is an independent risk for mortality in the general population and in patients with hypertension or diabetes mellitus.[2–4] The latest classification of chronic kidney disease (CKD) has defined microalbuminuria as a risk for adverse outcome even in patients with preserved glomerular filtration rate (GFR; ml·min^{-1}·1.73 m^{-2}).[1] Recently, however, several large population studies suggested that the normal albuminuria level is much lower than 30 mg/g.[5–7] For example, the Prevention of Renal and Vascular End/stage Disease (PREVEND) Trial in the Netherlands reported that the median UACR was 6.1 mg/g (95% confidence interval [95% CI]: 2.3–28.7 mg/g),[5] and the most recent evaluation of the National Health and Nutrition Examination Survey (NHANES) Data noted a mean UACR of 12.3 mg/g in young healthy participants.[6] Moreover, subclinical microalbuminuria was significantly associated with the development of heart failure (HF) in the general population.[8,9] Thus, it is now considered that even subclinical microalbuminuria, usually <30 mg/g UACR, is likely to have a prognostic impact.[8–14]

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In patients with chronic heart failure (CHF), it has been reported that microalbuminuria is also associated with poorer

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Table 1. Baseline Patient Characteristics

UACR (mg/g)	All patients (n=2,039)	Normoalbuminuria <10.2 (n=614)	Subclinical microalbuminuria 10.2–27.3 (n=534)	Microalbuminuria 27.4–300 (n=684)	Macroalbuminuria >300 (n=207)	P-value
Age (years)	67.5±12.4	64.5±12.5	67.7±12.1	69.7±11.8	68.5±12.5	<0.001
Male (%)	68.9	74.3	65.9	65.6	71.0	0.003
History of admission for HF (%)	53.6	52.4	50.4	55.3	59.4	0.21
Ischemic heart disease (%)	46.2	44.3	49.1	42.5	56.5	0.002
Comorbidity (%)						
Hypertension	82.5	76.1	82.0	86.4	89.9	<0.001
Diabetes	40.3	31.3	34.6	45.2	66.0	<0.001
Hyperlipidemia	76.0	76.9	76.4	73.4	81.2	0.12
Hyperuricemia	46.8	44.8	42.7	46.6	63.8	<0.001
Atrial fibrillation	32.2	28.3	31.4	37.6	28.4	<0.001
Cerebrovascular disease	16.7	12.1	16.7	19.9	19.8	0.001
Clinical status						
NYHA class 3 and 4 (%)	11.2	9.0	10.8	12.4	15.0	0.03
BMI (kg/m^2)	23.7±4.6	23.8±4.2	23.6±4.4	23.7±4.8	23.5±5.2	0.81
SBP (mmHg)	127.0±18.7	123.2±16.7	126.0±17.4	128.8±19.5	134.3±21.7	<0.001
DBP (mmHg)	72.7±12.0	72.1±11.5	72.8±11.2	73.3±12.6	73.8±15.0	0.40
Heart rate (beats/min)	72.3±14.9	70.6±14.2	72.3±14.7	73.5±15.5	73.8±15.0	0.002
Laboratory data						
LVEF (%)	55.3±15.7	54.1±16.2	55.8±15.7	55.7±15.6	55.7±14.8	0.20
LVEF ≥50% (%)	64.6	62.8	63.3	66.7	66.5	0.41
LVDd (mm)	52.5±9.4	53.4±9.9	52.4±9.3	52.1±9.4	52.0±8.6	0.08
Hemoglobin (g/dl)	13.3±2.2	13.7±2.1	13.4±2.2	13.2±2.1	12.3±2.6	<0.001
BUN (mg/dl)	19.3±10.4	17.0±6.2	17.7±6.5	20.2±11.8	26.7±17.4	<0.001
Serum sodium (mEq/L)	141.0±2.8	141.2±2.5	140.8±2.7	140.8±3.0	141.1±3.2	0.02
Serum potassium (mEq/L)	4.4±0.4	4.4±0.4	4.3±0.4	4.3±0.4	4.4±0.5	0.02
GFR (ml·min^{-1}·1.73 m^{-2})	62.8±20.9	66.9±18.4	66.1±19.1	60.8±21.5	48.7±23.0	<0.001
UACR (mg/g)	21.5 (8.3–74.4)	5.8 (3.9–7.5)	16.5 (13.0–21.4)	64.0 (39.6–121)	679.0 (407–1,283)	<0.001
BNP (pg/ml)	99.3 (39.0–229)	67.8 (27.2–148)	96.0 (37.9–213)	130.5 (54.2–264)	180.1 (64.4–373)	<0.001
Medication (%)						
RAS inhibitor	73.2	70.4	71.3	74.9	80.7	0.02
β-blocker	52.2	52.5	51.5	52.7	53.6	0.90
CCB	37.3	27.5	33.9	43.6	54.6	<0.001
Loop diuretic	44.6	43.3	42.9	44.4	53.6	0.049
Aldosterone antagonists	25.9	29.2	24.7	26.6	17.4	0.008
Statins	40.5	39.1	41.6	37.9	50.7	0.008
Outcome						
Composite endpoints	24.8	13.4	23.4	31.6	40.1	<0.001

Data given as mean±SD, %, or median (IQR). BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blocker; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HF, heart failure; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

prognosis regardless of the presence of diabetes, hypertension or renal dysfunction.[15–17] Indeed, we recently found that urinary albumin excretion has a significant prognostic impact in CHF patients with preserved ejection fraction.[17] In contrast, only a few studies previously examined the clinical impact of subclinical microalbuminuria in CHF patients, and furthermore they did not examine that of subclinical albuminuria in detail.[18,19] Thus, it remains to be clarified whether subclinical microalbuminuria also has a significant prognostic impact in CHF patients, particularly with a reference to renal function. Thus, in the present study, we examined microalbuminuria level to determine mortality or cardiovascular events in CHF patients according to renal function status, in the Chronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study.[17,20–23]

Methods

Subjects and Inclusion Criteria

Details of the design, purpose and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[17,21–23] Briefly, the CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients in stages B/C/D HF according to the ACCF/AHA guideline.[24] The study protocol was approved by the local ethics committee in the 24 participating hospitals and written informed consent was obtained from all

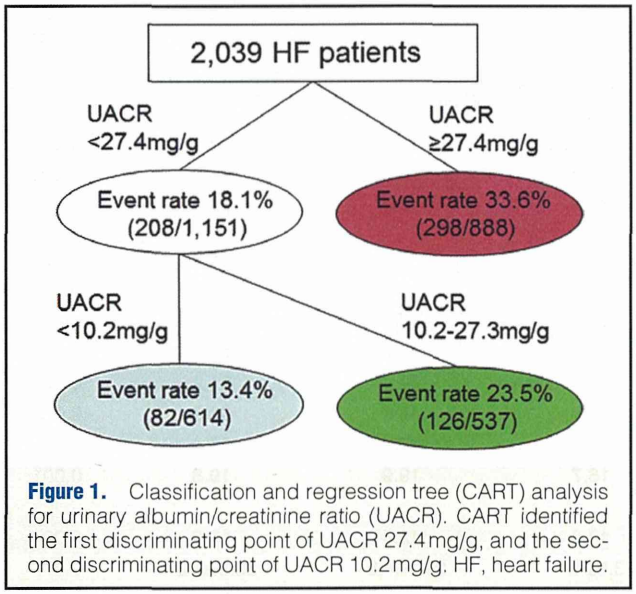

Figure 1. Classification and regression tree (CART) analysis for urinary albumin/creatinine ratio (UACR). CART identified the first discriminating point of UACR 27.4 mg/g, and the second discriminating point of UACR 10.2 mg/g. HF, heart failure.

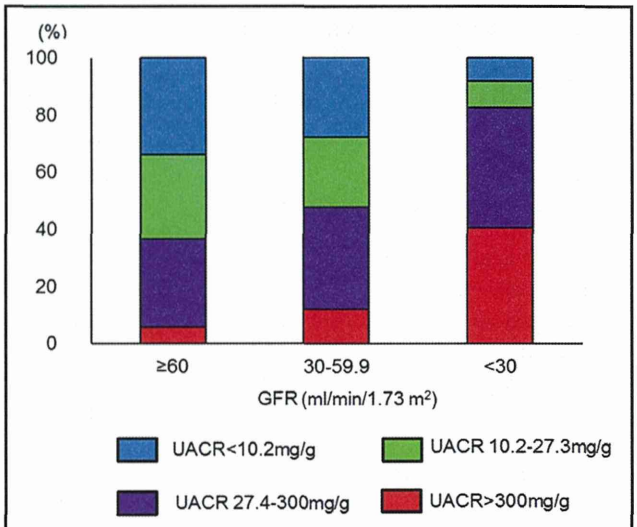

Figure 2. Distribution of urinary albumin/creatinine ratio (UACR) according to estimated glomerular filtration rate (eGFR). More than 80% of the patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} had clinical albuminuria.

patients. Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[25] All data and events will be surveyed at least once a year until March 2018.[17,21–23]

Among the 10,219 patients, we enrolled 4,735 consecutive patients with stage C/D CHF in the present study. We excluded 63 patients on hemodialysis, 2,591 without UACR measurement, and 42 without appropriate follow-up. Finally, 2,039 patients with stage C/D CHF were included in the present study.

UACR and GFR Measurement

Albuminuria was quantitatively evaluated using UACR. Urine samples were collected in outpatient clinics or before discharge, and urine albumin was measured in a central laboratory (SRL, Tokyo, Japan) to calculate UACR. Estimated GFR (eGFR; ml·min^{-1}·1.73 m^{-2}) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient[26] at the time of enrollment. We defined preserved eGFR as ≥60 ml·min^{-1}·1.73 m^{-2}, mildly reduced eGFR as 30–59.9 ml·min^{-1}·1.73 m^{-2}, and severely reduced eGFR as <30 ml·min^{-1}·1.73 m^{-2} according to the guidelines.[1]

Study Outcomes

The outcomes of the present study included composite of death, acute myocardial infarction, HF admission and stroke. Mode of death was determined by the attending physician and was confirmed by 1 independent physician who was a member of the Tohoku Heart Failure Association.[20]

Statistical Analysis

Classification and regression tree (CART) analysis[27] was done in order to identify the cut-off points of UACR to classify CHF patients for the composite endpoints. CART analysis is an empirical and statistical technique based on recursive partitioning of the data space to predict response.[28] The models are obtained by binary discrimination of the data by predictors, and the discrimination variable and discriminating point are automatically selected from possible predictor values to achieve the best fit. Then, one or both "child nodes" are discriminated into 2 or more regions recursively, and the process continues until some stopping rule is applied.[28] Finally, the result of this process is represented as a binary decision tree. We divided the patients into 4 groups according to UACR cut-offs obtained 1 CART analysis as follows: normoalbuminuria, subclinical microalbuminuria, microalbuminuria, and macroalbuminuria.

Kaplan-Meier curves and Cox proportional hazard models were used to compare the risk for composite endpoints among the 4 groups. Cox proportional hazard models were adjusted for the following covariates that could potentially influence outcome: age, sex, New York Heart Association (NYHA) class, history of HF admission and malignant tumor, ischemic etiology of HF, systolic blood pressure, heart rate, left ventricular ejection fraction (LVEF), body mass index, hemoglobin, serum sodium, serum potassium, blood urea nitrogen (BUN), brain natriuretic peptide (BNP), eGFR, comorbidities (atrial fibrillation, diabetes mellitus, hyperlipidemia, hyperuricemia and cerebrovascular disease), and medications (β-blockers, renin-angiotensin system [RAS] inhibitors, loop diuretics, aldosterone antagonists, calcium channel blockers and statins). We also performed subgroup analyses based on sex, age (<median or ≥median), LVEF (<50% or ≥50%), history of hypertension and diabetes mellitus, and medications (β-blockers, RAS inhibitors and statins). In addition, CART analysis was done using both UACR and eGFR to evaluate the importance of subclinical microalbuminuria on renal function. Comparisons among the 4 groups were done using chi-squared test. Continuous data are described as mean±SD and discrete data as %. UACR and BNP are described as median.

SPSS Statistics 21.0 (SPSS, Chicago, IL, USA) and R 2.15.2 were used for statistical analysis.[27] The statistical significance was defined as 2-sided $P<0.05$. Comparison of the baseline characteristics among the 4 groups was performed using ANOVA for continuous variables and chi-squared test for categorical variables. Comparison of BNP and UACR among the 4 groups was done using Kruskal-Wallis test.

Results

Baseline Characteristics

Table 1 lists patient baseline characteristics. Median age was

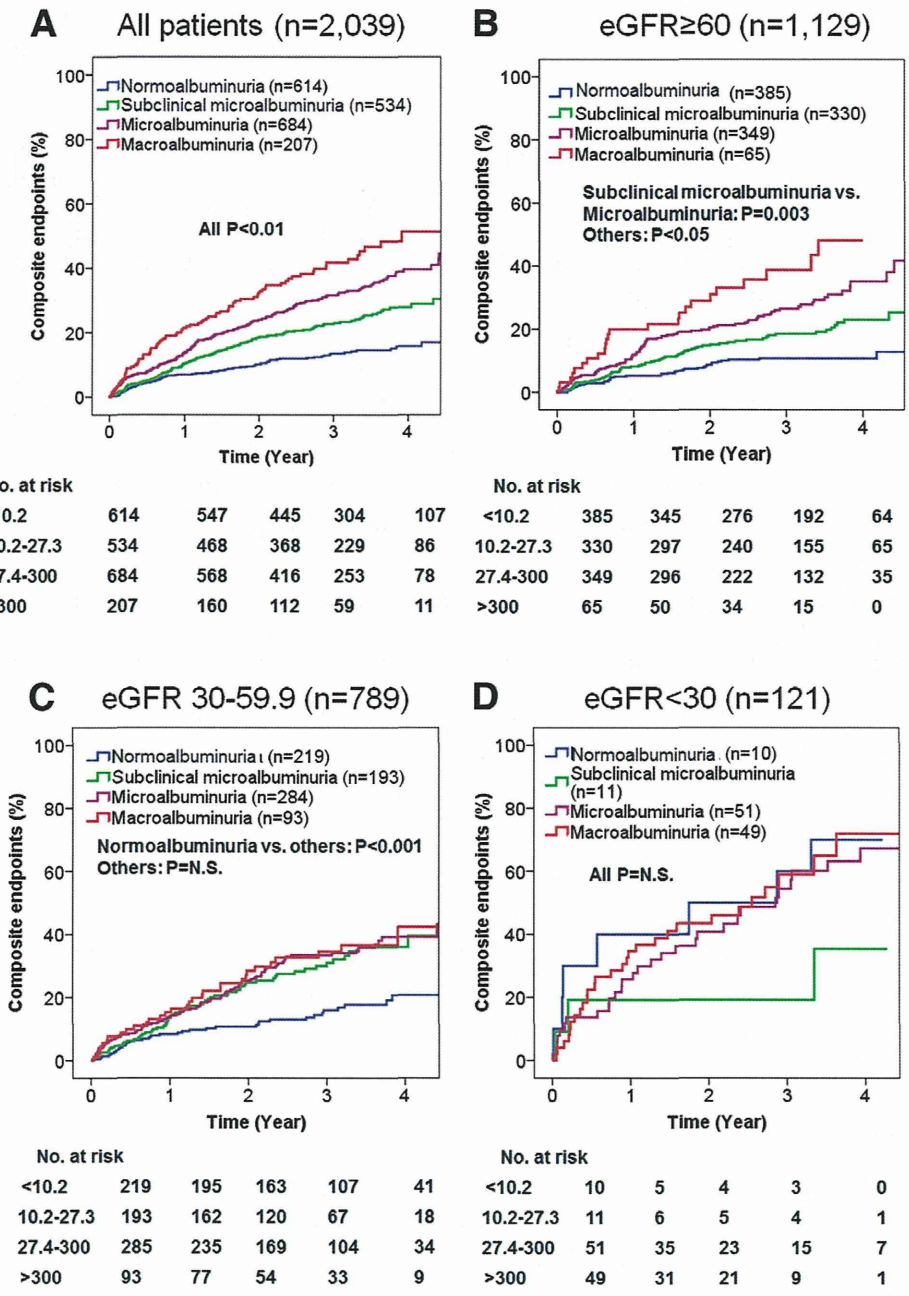

Figure 3. Kaplan-Meier curves for composite endpoints. (**A**) All patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min^{-1}·1.73 m^{-2}; (**C**) eGFR 30–59.9 ml·min^{-1}·1.73 m^{-2}; (**D**) eGFR <30 ml·min^{-1}·1.73 m^{-2}.

67.4 years and male patients accounted for 68.9%. History of ischemic heart disease was noted in 46.2% and mean LVEF and eGFR were 55.3±15.7% and 62.8±20.9 ml·min^{-1}·1.73 m^{-2}, respectively. The prevalence of eGFR <60 ml·min^{-1}·1.73 m^{-2} was 44.6% (n=910), and median UACR was 21.5 mg/g. On CART analysis UACR=27.4 mg/g and 10.2 mg/g were identified as the first and the second discriminating points to stratify risk for composite endpoints, respectively (**Figure 1**). Thus, normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria were defined as UACR (mg/g) <10.2, 10.2–27.3, 27.4–300, and >300, respectively. The prevalence of normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria was 30.1%, 26.2%, 33.5%, and 10.2%, respectively. As shown in **Figure 2**, the prevalence of normoalbuminuria was decreased along with a decrease in eGFR categories. It was noted that, even in patients with preserved eGFR and mildly reduced eGFR, the prevalence of subclinical microalbuminuria was 29.2% and 24.5%, respectively. The characteristics of the patients with subclinical microalbuminuria or microalbuminuria were generally intermediate between those with normoalbuminuria and those with macroalbuminuria, in terms of age, comorbidity, NYHA class,