Differential Effects of Strong and Regular Statins on the Clinical Outcome of Patients With Chronic Kidney Disease Following Coronary Stent Implantation

– The Kumamoto Intervention Conference Study (KICS) Registry –

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Background: The aim of this study was to examine the effects of different statins on the clinical outcomes of Japanese patients with coronary stent implants.

Methods and Results: This study included 5,801 consecutive patients (males, 4,160; age, 69.7±11.1 years, mean±SD) who underwent stent implantation between April 2008 and March 2011. They were treated with a strong statin (n=3,042, 52%, atorvastatin, pitavastatin, or rosuvastatin), a regular statin (n=1,082, 19%, pravastatin, simvastatin, or fluvastatin) or no statin (n=1,677, 29%). The patients with chronic kidney disease (CKD) were divided into mild-to-moderate CKD (30≤eGFR<60, n=1,956) and severe CKD (eGFR <30, n=559). Primary endpoints included cardiovascular death and nonfatal myocardial infarction, including stent thrombosis and ischemic stroke. The clinical outcome for the primary endpoint in mild-to-moderate CKD patients treated with a strong statin (hazard ratio 0.50, 95% confidence interval 0.31–0.81; P=0.005) was significantly lower than in those on no statins, but that in the patients treated with a regular statin was not (P=0.160). The clinical outcome for the primary endpoint in severe CKD patients treated with a strong or regular statin was no different than not being on statin therapy (P=0.446, P=0.194, respectively).

Conclusions: In patients with mild-to-moderate CKD, only strong statins were associated with lower risk compared with no statin, but regular statins were not. It is possible that taking a strong statin from the early stage of CKD is useful for suppression of cardiovascular events. (*Circ J* 2015; **79**: 1115–1124)

Key Words: Cardiovascular events; Chronic kidney disease; Statins; Stents

HMG-CoA reductase inhibitors (statins) are used to prevent cardiovascular events because they are known to reduce the risk of cardiovascular and cerebrovas-

cular events, both directly and indirectly. The reduction in the risk of cardiovascular events is achieved by lowering low-density lipoprotein cholesterol (LDL-C) levels.^{1,2} Several stud-

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ies have reported that intensive treatment with lipid-lowering agents provides better protection against coronary artery plaque formation and prevents cardiovascular events compared with moderate treatment.^{3,4} For example, intensive statin treatment appears to improve clinical outcomes after acute coronary syndrome (ACS) and stable ischemic heart disease in Western countries, compared with standard statin treatment.^{3,5,6} In this regard, statins have other effects, in addition to their lipid-lowering effects, such as antiinflammatory and antioxidants effects.

Heart Association (ACC/AHA) Guidelines on the Assessment of Cardiovascular Risk recommend the use of intensive statin treatment for secondary prevention in high-risk patients with clinical atherosclerotic cardiovascular disease (ASCVD), regardless of the level of LDL-C.⁷ In Japan, statins tend to be used at low doses compared with Western countries, and the lipid management policy in Japan is to lower LDL-C to less than 100 mg/dl for secondary prevention in patients with ASCVD.⁸ Furthermore, a regular statin or low-dose strong statin is administered in Japan at the start of treatment of dyslipidemia as a strategy to protect against unwanted side effects. The use of strong statins is limited to high-risk patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI), but the “high” dose of statin used in Japan, even in such

Editorial p 976

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(A) Clinical characteristics	Strong statin (n=3,042)	Regular statin (n=1,082)	No statin (n=1,677)	P value
Male (%)	2,190 (72.0)	774 (71.5)	1,196 (71.3)	0.877
Age (years)	67.6±11.1***	70.9±10.5*	72.9±10.5	<0.001
Elderly (≥75 years)	901 (29.6)	446 (41.2)	838 (50.0)	<0.001†
BMI (kg/m ²)	24.4±3.4***	23.7±3.4*	23.1±3.4	<0.001
Obesity (BMI ≥25)	1,203 (39.7)	351 (32.5)	426 (25.9)	<0.001†
ACS (%)	1,701 (55.9)	532 (49.2)	818 (48.8)	<0.001†
Left main trunk lesion (%)	180 (5.9)	63 (5.8)	121 (7.2)	0.169
Current smoker (%)	871 (28.6)	245 (22.6)	319 (19.0)	<0.001†
Hypertension (%)	2,355 (77.4)	873 (80.7)	1,272 (75.8)	0.012
Dyslipidemia (%)	2,474 (81.3)	735 (67.9)	439 (26.2)	<0.001†
Previous MI (%)	621 (20.4)	254 (23.5)	317 (18.9)	0.014
Previous stroke (%)	398 (13.1)	146 (13.5)	236 (14.1)	0.634
PAD (%)	186 (6.1)	96 (8.9)	164 (9.8)	<0.001†
Diabetes (%)	1,356 (44.6)	451 (41.7)	654 (39.0)	0.001†
eGFR (ml/min/1.73m ²)	66.3±25.4*	65.9±97.7*	54.9±27.0	<0.001
CKD (eGFR <60)	1,134 (37.3)	473 (43.7)	908 (54.1)	<0.001†
Mild-to-moderate CKD (30≤eGFR<60)	970 (31.9)	380 (35.1)	606 (36.1)	0.007†
Severe CKD (eGFR<30)	164 (5.4)	93 (8.6)	302 (18.0)	<0.001†
Hemodialysis (%)	62 (2.0)	41 (3.8)	183 (10.9)	<0.001†
HbA1c (%)	6.2±1.4***	6.0±1.1	5.9±1.2	<0.001
LDL-C (mg/dl)	80.5±22.7	94.7±27.7	Not available	0.0056††
Thienopyridine derivative (%)	2,979 (97.9)	1,052 (97.2)	1,526 (91.0)	<0.001†
Ticlopidine (%)	1,266 (41.6)	415 (38.4)	573 (34.2)	<0.001†
Clopidogrel (%)	1,738 (57.1)	649 (60.0)	958 (57.1)	0.231
β-blocker (%)	1,342 (44.1)	431 (39.8)	447 (26.7)	<0.001†
ACEI or ARB (%)	2,297 (75.5)	815 (75.3)	972 (58.0)	<0.001†
ACEI (%)	1,076 (35.4)	355 (32.8)	382 (22.8)	<0.001†
ARB (%)	1,281 (42.1)	481 (44.5)	620 (37.0)	<0.001†
CCB (%)	1,325 (43.6)	513 (47.4)	727 (43.4)	0.063
Stent				
DES (%)	1,840 (60.5)	687 (63.5)	986 (58.8)	0.048
Bare metal stent (%)	1,202 (39.5)	395 (36.5)	691 (41.2)	0.048
(B) Clinical outcomes	Strong statin (n=3,042)	Regular statin (n=1,082)	No statin (n=1,677)	P value
Primary endpoint (%)	69 (2.3)	38 (3.5)	144 (8.6)	<0.001†
Cardiovascular death (%)	28 (0.9)	16 (1.5)	118 (7.0)	<0.001†
Nonfatal MI (%)	29 (1.0)	9 (0.8)	10 (0.6)	0.432
Ischemic stroke (%)	12 (0.4)	13 (1.2)	16 (1.0)	0.009†

(Table 1 continued the next page.)

(C) Results of univariate and multivariate cox proportional hazards analyses	Primary endpoint (n=251)				Cardiovascular death (n=162)			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Strong statin [†]	0.27 (0.20–0.36)	<0.001	0.46 (0.33–0.64)	<0.001	0.13 (0.08–0.19)	<0.001	0.32 (0.20–0.52)	<0.001
Regular statin [†]	0.42 (0.30–0.61)	<0.001	0.67 (0.46–0.98)	0.041	0.20 (0.12–0.34)	<0.001	0.48 (0.27–0.82)	0.008
Age ≥75 years	2.36 (1.84–3.04)	<0.001	1.54 (1.17–2.04)	0.002	2.96 (2.15–4.07)	<0.001	1.59 (1.11–2.28)	0.011
Obesity	0.67 (0.50–0.89)	0.006	1.05 (0.78–1.41)	0.757	0.60 (0.42–0.88)	0.008	1.07 (0.73–1.58)	0.721
Current smoker	1.06 (0.80–1.41)	0.679			0.87 (0.60–1.26)	0.451		
ACS	3.55 (2.62–4.81)	<0.001	2.73 (1.96–3.80)	<0.001	4.50 (2.99–6.76)	<0.001	2.66 (1.69–4.17)	<0.001
Previous MI	0.89 (0.64–1.22)	0.449			0.98 (0.67–1.44)	0.935		
PAD	1.46 (0.98–2.18)	0.062	1.45 (0.95–2.22)	0.089	1.80 (1.14–2.85)	0.012	1.96 (1.17–3.26)	0.010
Hypertension	0.88 (0.66–1.17)	0.363			0.75 (0.53–1.05)	0.095	1.07 (0.73–1.55)	0.743
Diabetes	0.90 (0.70–1.16)	0.415			0.76 (0.55–1.04)	0.087	0.97 (0.69–1.37)	0.871
CKD	2.63 (2.02–3.41)	<0.001	1.96 (1.47–2.59)	<0.001	3.71 (2.61–5.25)	<0.001	2.32 (1.59–3.40)	<0.001
Thienopyridine	0.08 (0.06–0.11)	<0.001	0.15 (0.11–0.21)	<0.001	0.04 (0.03–0.06)	<0.001	0.12 (0.08–0.17)	<0.001
β-blocker	0.63 (0.48–0.83)	0.001	0.85 (0.63–1.14)	0.272	0.41 (0.28–0.60)	<0.001	0.73 (0.48–1.11)	0.148
ACEI or ARB	0.43 (0.34–0.55)	<0.001	0.66 (0.50–0.88)	0.005	0.24 (0.18–0.33)	<0.001	0.53 (0.36–0.78)	0.001
CCB	0.36 (0.26–0.48)	<0.001	0.49 (0.36–0.67)	<0.001	0.17 (0.11–0.27)	<0.001	0.28 (0.17–0.45)	<0.001
DES	0.39 (0.30–0.51)	<0.001	0.71 (0.54–0.94)	0.017	0.27 (0.20–0.38)	<0.001	0.58 (0.40–0.83)	0.003

(A) *P<0.05 vs. No statin, post-hoc multiple comparison by Bonferroni method; **P<0.05 vs. Regular statin, post-hoc multiple comparison by Bonferroni method; †P<0.05, chi-square test for trend was used to assess a linear trend in proportions across the categories; ††statistical significance of differences in mean values between the strong and regular statin groups assessed by Student's t-test. (B) †P<0.05, chi-square test for trend was used to assess a linear trend in proportions across the categories. (C) †vs. No statin.

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin-receptor blocker; BMI, body mass index; CCB, calcium-channel blocker; CI, confidence interval; CKD, chronic kidney disease; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KICS, Kumamoto Intervention Conference Study; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease.

patients, is lower than that used in Western countries. In this regard, the incidence of cardiovascular events is low in Japan compared with Western countries, and the protective effects of statins on ASCVD have also been reported in Japanese patients. At this stage, however, there is no solid information on whether strong statins are more effective than regular statins in Japan. This report describes the findings of a prospective nationwide study designed to determine the difference in clinical effect between strong statins (atorvastatin, pitavastatin or rosuvastatin) and regular statins (pravastatin, simvastatin or fluvastatin) in patients with CAD after PCI.

Methods

Study Population

The Kumamoto Intervention Conference Study (KICS) is a physician-initiated non-company-sponsored multicenter registry of consecutive patients undergoing PCI in 16 centers across Japan.⁹ Between April 2008 and March 2011, 6,219 consecutive procedures were recorded on the PCI list. All consecutive patients who gave written informed consent were enrolled in this study. The exclusion criteria were: no coronary stenting or

unsuccessful coronary stenting procedure, which was defined as residual stenosis ≥50% or major complications during hospitalization, including death, myocardial infarction (MI), subacute thrombosis and emergency coronary artery bypass graft surgery. Finally, 5,801 patients with implanted stents were enrolled in this prospective multicenter study with 12-month follow-up. They included 4,124 patients treated with statins and 1,677 without statins. Furthermore, the statin group was divided into strong statins (atorvastatin, pitavastatin or rosuvastatin; n=3,042) and regular statins (pravastatin, simvastatin or fluvastatin; n=1,082). The selection of treatment was left to the discretion of the attending physician at each hospital, and treatment was mostly tailored to reduce LDL-C to <100 mg/dl for secondary prevention.⁸ Compliance with treatment was checked regularly throughout the study. The compliance of patients with the medication was confirmed at hospital discharge by the attending physician of each facility.

The study protocol followed the guidelines of the ethics committee of each institution and written informed consent was provided by each patient or the family of the subject.

Clinical Outcomes and Definitions

The primary endpoint was defined as cardiovascular death or nonfatal MI, including stent thrombosis and ischemic stroke. Cardiovascular death was defined as death from MI, stent thrombosis, congestive heart failure, or documented sudden cardiac death. The universal definition of MI was used.¹⁰ Diagnosis of ischemic stroke was based on clinical and radiological evidence of stroke without intracranial hemorrhage. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m². For subjects experiencing more than 2 acute events, only the first event was considered in the analysis. The patients were followed up for 12 months or the endpoint.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD, and categorical variables are expressed as frequencies and percentages. Continuous variables were compared among the 3 groups (strong statin, regular statin and no statin) by one-way ANOVA. In the case of $P<0.05$, post-hoc multiple comparisons were made with the Bonferroni method. For categorical variables, a chi-square test for trend was used to assess a linear trend in proportions across the categories. The data for the level of LDL-C were obtained at 6–9 months after coronary stenting in a single center. The statistical significance of differences in mean values between groups was assessed with Student's t-test. Estimates of the cumulative event rates were calculated by the

Kaplan-Meier method, and differences among the groups were compared by the log-rank test. Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CI) as estimates for each endpoint. The HRs were adjusted for clinical characteristics according to the univariate analysis for each event. All variables with $P < 0.10$ in the univariate analysis were considered in the multivariate model. In the Cox proportional hazards regression, we evaluated HRs and 95% CI of the groups of strong and regular statins, with the no statin group as the reference. $P < 0.05$ denoted the presence of a statistically significant difference. All statistical analyses were performed using SPSS software version 21 (SPSS, Chicago, IL, USA).

Results

Of the 5,801 patients, 4,124 were on statins (statin group) and 1,677 patients were not treated with statins. The clinical features of these patients are summarized in **Table 1A**. Patients in the strong statin group were the youngest and had the highest body mass index (BMI), with a higher proportions of ACS, current smokers, dyslipidemia, and diabetes, among the 3 groups. Interestingly, the propensity of patients with CKD was higher in the no statin group among the 3 groups. The mean level of LDL-C measured at 6–9 months after coronary stenting was significantly lower in the strong statin group (80.5 ± 22.7 mg/dl) than in the regular statin group (94.7 ± 27.7 , $P = 0.0056$). As shown in **Table 1B**, the use of a strong statin was associated with a low frequency of the primary endpoint (cardiovascular death and ischemic stroke) among the groups. The rate of nonfatal MI was not significantly different among the groups. **Figure 1** shows the results of Kaplan-Meier analysis and the cumulative rate of clinical outcomes. The rate of the primary endpoint in the strong statin group was the lowest among the groups.

Table 1C shows the results of Cox proportional hazard analysis for the primary endpoint and cardiovascular death. As compared with the no statin group, rate of the primary endpoint was significantly lower in the strong statin group (adjusted HR, 0.46, 95% CI 0.33–0.64; $P < 0.001$) and in the regular statin group (adjusted HR, 0.67, 95% CI 0.46–0.98; $P = 0.041$).

We also performed subgroup analysis of the CKD patients divided into mild-to-moderate ($30 \leq \text{eGFR} < 60$) and severe CKD ($\text{eGFR} < 30$). Analysis of the mild-to-moderate CKD patients showed no significant differences in the baseline characteristics, except for age, BMI, ACS, hypertension, dyslipidemia, previous MI, diabetes, medication and stent type, among the strong, regular and no statin groups (**Table 2A**). Also in the severe CKD patients, there were no significant differences in baseline characteristics, except for BMI, ACS, hypertension, dyslipidemia, diabetes and medication. **Figure 2** shows the results of Kaplan-Meier analysis and the cumulative rate of the primary endpoint in the mild-to-moderate and severe CKD patients. The primary endpoint of cardiovascular death, nonfatal MI and ischemic stroke in the mild-to-moderate CKD patients occurred in 29 patients (3.0%) in the strong statin group, 15 (3.9%) in the regular statin group and 65 (10.7%) in the no statin group (**Table 2B**). As compared with the no statin group, rate of the primary endpoint was significantly lower in the strong statin group (adjusted HR, 0.50, 95% CI 0.31–0.81; $P = 0.005$), but not in the regular statin group (adjusted HR, 0.65, 95% CI 0.36–1.18; $P = 0.160$) (**Table 2C**). In the severe CKD patients, the primary endpoint occurred in 9 patients (5.5%) in the strong statin group, 4 (4.3%) in the regular statin group and 44 (14.6%) in the no statin group (**Table 2B**). As compared with the no statin group, the rate of the primary

endpoint was not significantly different in the strong statin group (adjusted HR, 0.73, 95% CI 0.33–1.64; $P = 0.446$), and regular statin group (adjusted HR, 0.49, 95% CI 0.17–1.43; $P = 0.194$) (**Table 2C**). **Table 3** showed hazard risks of strong and regular statin use for cardiovascular events in all patients, mild to moderate CKD patients, and severe CKD patients.

Discussion

The main finding of this study was that both strong and regular statins were associated with a lower rate of the primary endpoint and cardiovascular death compared with no statin therapy. Although there was no difference among the 3 groups for nonfatal MI in all patients, a strong statin was associated with a lower rate of ischemic stroke compared with a regular or no statin. Several studies have shown that lipid-lowering therapy with statins reduces the risk of ischemic stroke,^{11,12} and we consider that the beneficial effect of strong statins on the incidence of ischemic stroke rate is mediated through a reduction of the LDL-C level. Unlike the significant difference in the rate of ischemic stroke, there were no differences in the rate of nonfatal MI among the groups. The reason for this finding is unknown, but we speculate that it is related to the higher incidence of ischemic stroke in Japanese compared with the rate of cardiac events in Western countries, thus showing a larger reduction in stroke incidence.

CKD is an important risk factor for cardiovascular events, similar to dyslipidemia. The risks of cardiovascular mortality and morbidity are increased with progression of CKD.^{13,14} Renal function is considered to be impaired in patients with CAD, and CAD patients with renal dysfunction have poor clinical outcome after revascularization therapy.^{14–16} Furthermore, previous studies reported beneficial effects of statins on the clinical outcome of cardiovascular events in mild-to-moderate CKD patients.^{17,18} The SHARP trial showed that reduction of LDL-C significantly reduced the incidence of cardiovascular events not only in patients with mild-to-moderate but also in those with severe CKD ($15 \leq \text{eGFR} < 30$, not on dialysis).¹⁹ However, LDL-C lowering therapy in patients with end-stage kidney disease on hemodialysis did not reduce cardiovascular events, similar to the results of 4D and AURORA studies.^{20,21} Meta-analysis demonstrated that statin therapy reduced the risk of cardiovascular events in patients with CKD on hemodialysis; however, progression of CKD resulted in a significant decreased in the effect of statin therapy on cardiovascular events.²²

Results of our subgroup analysis of severe CKD patients showed that strong and regular statins were not associated with a lower risk for cardiovascular events compared with no statin. A Japanese registry study by Natsuaki et al showed the use of statins was associated with a significantly lower incidence of cardiovascular events in patients who underwent revascularization, especially patients with mild CKD.²³ In the EVENT registry, study focused on patients undergoing only PCI for CAD and showed favorable outcomes after PCI.²⁴ These registry studies failed to prove beneficial effects of statins in patients with severe CKD or on dialysis, as in the present study. Future studies should clarify the effect of statins in patients with severe CKD or on dialysis who undergo coronary stent implantation.

Our other important analysis of the patients with mild-to-moderate CKD showed that the use of a strong statin was associated with a significantly lower rate of cardiovascular events compared with no statin. And there was no significant difference in the rate of cardiovascular events between the use of a regular statin and no statin. Previous studies^{17–19,23,24} demonstrated beneficial effects of statins on clinical outcome of

Table 2. Clinical Characteristics, Clinical Outcomes and Results of Univariate and Multivariate Cox Proportional Hazards Analyses of Mild-to-Moderate and Severe CKD Patients Included in the KICS Registry

(A) Clinical characteristics	Mild-to-moderate CKD			
	Strong statin (n=970)	Regular statin (n=380)	No statin (n=606)	P value
Male (%)	651 (67.1)	265 (69.7)	411 (67.8)	0.650
Age (years)	72.7±9.3***	74.7±8.5*	76.8±8.6	<0.001
Elderly (≥75 years)	453 (46.7)	206 (54.2)	396 (65.3)	<0.001†
BMI (kg/m ²)	24.3±3.5***	23.7±3.4*	23.1±3.2	<0.001
Obesity (BMI ≥25)	363 (37.4)	117 (30.8)	139 (22.9)	<0.001†
ACS (%)	505 (52.1)	172 (45.3)	319 (52.6)	0.048
Left main trunk lesion (%)	63 (6.5)	30 (7.9)	60 (9.9)	0.050†
Current smoker (%)	182 (18.8)	66 (17.4)	92 (15.2)	0.189
Hypertension (%)	820 (84.5)	322 (84.7)	470 (77.6)	0.001†
Dyslipidemia (%)	793 (81.8)	259 (68.2)	171 (28.2)	<0.001†
Previous MI (%)	238 (24.5)	109 (28.7)	125 (20.6)	0.015
Previous stroke (%)	172 (17.7)	55 (14.5)	100 (16.5)	0.348
PAD (%)	80 (8.2)	40 (10.5)	59 (9.7)	0.356
Diabetes (%)	438 (45.2)	163 (42.9)	202 (33.3)	<0.001†
HbA1c (%)	6.2±1.2*	6.0±1.1	5.8±1.1	<0.001
Thienopyridine derivative	950 (97.9)	367 (96.6)	542 (89.4)	<0.001†
Ticlopidine (%)	439 (45.3)	140 (36.8)	207 (34.2)	<0.001†
Clopidogrel (%)	518 (53.4)	233 (61.3)	335 (55.3)	0.031
β-blocker (%)	431 (44.4)	139 (36.6)	159 (26.2)	<0.001†
ACEI or ARB (%)	776 (80.0)	308 (81.1)	362 (59.7)	<0.001†
ACEI (%)	330 (34.0)	121 (31.8)	148 (24.4)	<0.001†
ARB (%)	470 (48.5)	191 (50.3)	226 (37.3)	<0.001†
CCB (%)	467 (48.1)	199 (52.4)	249 (41.1)	0.001†
Stent				
DES (%)	607 (62.6)	256 (67.4)	348 (57.4)	0.006
Bare metal stent (%)	363 (37.4)	124 (32.6)	258 (42.6)	0.006
(B) Clinical outcomes	Mild-to-moderate CKD			
	Strong statin (n=970)	Regular statin (n=380)	No statin (n=606)	P value
Primary endpoint (%)	29 (3.0)	15 (3.9)	65 (10.7)	<0.001†
Cardiovascular death (%)	13 (1.3)	8 (2.1)	55 (9.1)	<0.001†
Nonfatal MI (%)	11 (1.1)	1 (0.3)	1 (0.2)	0.040†
Ischemic stroke (%)	5 (0.5)	6 (1.6)	9 (1.5)	0.086†
(C) Results of univariate and multivariate cox proportional hazards analyses	Mild-to-moderate CKD			
	Primary endpoint (n=109)			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Strong statin†	0.27 (0.17–0.41)	<0.001	0.50 (0.31–0.81)	0.005
Regular statin†	0.35 (0.20–0.62)	<0.001	0.65 (0.36–1.18)	0.160
Age ≥75 years	1.93 (1.29–2.89)	0.001	1.63 (1.08–2.47)	0.020
Obesity	0.74 (0.47–1.16)	0.185		
ACS	4.90 (2.99–8.04)	<0.001	3.13 (1.84–5.33)	<0.001
LMT lesion	2.48 (1.50–4.11)	<0.001	1.48 (0.87–2.51)	0.150
Hypertension	0.66 (0.43–1.03)	0.068	1.06 (0.67–1.66)	0.812
Diabetes	0.80 (0.54–1.18)	0.250		
Thienopyridine	0.07 (0.05–0.11)	<0.001	0.13 (0.08–0.20)	<0.001
β-blocker	0.49 (0.32–0.77)	0.002	0.68 (0.42–1.10)	0.119
ACEI or ARB	0.41 (0.28–0.60)	<0.001	0.89 (0.57–1.40)	0.616
CCB	0.34 (0.22–0.53)	<0.001	0.54 (0.34–0.85)	0.008
DES	0.37 (0.25–0.54)	<0.001	0.73 (0.49–1.11)	0.143

(Table 2 continued the next page.)

Severe CKD				
(A) Clinical characteristics	Strong statin (n=164)	Regular statin (n=93)	No statin (n=302)	P value
Male (%)	106 (64.6)	60 (64.5)	203 (67.2)	0.808
Age (years)	71.3±10.7	70.9±11.8	72.9±10.6	0.144
Elderly (≥75 years)	73 (44.5)	38 (40.9)	150 (49.7)	0.265
BMI (kg/m ²)	23.6±3.7*	23.6±4.3*	22.5±3.4	0.002
Obesity (BMI ≥25)	52 (31.7)	31 (33.3)	64 (21.2)	0.015†
ACS (%)	93 (56.7)	47 (50.5)	128 (42.4)	0.011†
Left main trunk lesion (%)	19 (11.6)	7 (7.5)	29 (9.6)	0.565
Current smoker (%)	28 (17.1)	16 (17.2)	46 (15.2)	0.832
Hypertension (%)	152 (92.7)	87 (93.5)	250 (82.8)	0.001†
Dyslipidemia (%)	135 (82.3)	60 (64.5)	66 (21.9)	<0.001†
Previous MI (%)	47 (28.7)	17 (18.3)	72 (23.8)	0.169
Previous stroke (%)	34 (20.7)	21 (22.6)	58 (19.2)	0.763
PAD (%)	28 (17.1)	19 (20.4)	60 (19.9)	0.720
Diabetes (%)	111 (67.7)	59 (63.4)	160 (53.0)	0.006†
HbA1c (%)	6.2±1.4	6.1±1.0	5.8±1.4	0.039
Thienopyridine derivative	161 (98.2)	92 (98.9)	271 (89.7)	<0.001†
Ticlopidine (%)	72 (43.9)	40 (43.0)	101 (33.4)	0.048†
Clopidogrel (%)	90 (54.9)	53 (57.0)	173 (57.3)	0.878
β-blocker (%)	85 (51.8)	46 (49.5)	94 (31.1)	<0.001†
ACEI or ARB (%)	121 (73.8)	64 (68.8)	148 (49.0)	<0.001†
ACEI (%)	51 (31.1)	25 (26.9)	41 (13.6)	<0.001†
ARB (%)	79 (48.2)	46 (49.5)	117 (38.7)	0.061†
CCB (%)	98 (59.8)	53 (57.0)	157 (52.0)	0.252
Stent				
DES (%)	104 (63.4)	62 (66.7)	177 (58.6)	0.307
Bare metal stent (%)	60 (36.6)	31 (33.3)	125 (41.4)	0.307
Severe CKD				
(B) Clinical outcomes	Strong statin (n=164)	Regular statin (n=93)	No statin (n=302)	P value
Primary endpoint (%)	9 (5.5)	4 (4.3)	44 (14.6)	0.001†
Cardiovascular death (%)	4 (2.4)	3 (3.2)	36 (11.9)	<0.001†
Nonfatal MI (%)	2 (1.2)	0 (0.0)	5 (1.7)	0.454
Ischemic stroke (%)	3 (1.8)	1 (1.1)	3 (1.0)	0.730
Severe CKD				
(C) Results of univariate and multivariate cox proportional hazards analyses	Primary endpoint (n=57)			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Strong statin [‡]	0.35 (0.17–0.72)	0.004	0.73 (0.33–1.64)	0.446
Regular statin [‡]	0.27 (0.10–0.76)	0.013	0.49 (0.17–1.43)	0.194
Obesity	0.46 (0.22–0.98)	0.044	0.56 (0.26–1.19)	0.132
ACS	2.34 (1.35–4.07)	0.002	2.05 (1.14–3.69)	0.016
Hypertension	0.63 (0.32–1.25)	0.189		
Diabetes	0.58 (0.34–0.97)	0.037	0.59 (0.34–1.02)	0.059
Thienopyridine	0.08 (0.04–0.14)	<0.001	0.11 (0.06–0.21)	<0.001
β-blocker	0.41 (0.22–0.76)	0.004	0.56 (0.29–1.08)	0.084
ACEI or ARB	0.30 (0.17–0.52)	<0.001	0.43 (0.24–0.80)	0.007

(A) *P<0.05 vs. No statin, post-hoc multiple comparison with Bonferroni method; **P<0.05 vs. Regular statin, post-hoc multiple comparison with Bonferroni method; †P<0.05, chi-square test for trend was used to assess a linear trend in proportions across the categories. (B) †P<0.05, chi-square test for trend was used to assess a linear trend in proportions across the categories. (C) ‡vs. No statin. Abbreviations as in Table 1.

cardiovascular events in mild-to-moderate CKD patients, but, to our knowledge, this study is the first to evaluate the effect of statins on cardiovascular events in CKD patients who underwent coronary stent implantation, by comparing the statin group separately. The other study from the CREDO-Kyoto Registry Cohort-2 by Natsuaki et al showed that the use of strong statins was associated with a significantly lower incidence of cardiovascular events in patients who underwent revascularization compared with those on a regular statin,²⁵ but they did not investigate the effect of strong and regular statins in CKD patients, so it is unclear whether was a difference between strong and regular statins in CKD patients. The present study demonstrated a beneficial effect only of strong statins in mild-to-moderate CKD patients, but not regular statins, suggesting that the effect of statins on cardiovascular events is CKD stage-dependent, and that the earlier the CKD stage, the better the effects of a strong statin on cardiovascular events.

These findings probably relate to the plaque characteristics in patients with CKD. Compared with non-CKD patients, coronary plaques in CKD patients have a large lipid volume, calcification, cholesterol crystals, and plaque disruption.²⁶ Kono et al reported that advancement of CKD is associated with a gradual increase in the volumes of necrotic core and dense calcium, a gradual decrease in the necrotic core/dense calcium ratio in coronary plaque, and gradual calcification of the plaque.²⁷

We speculate that statins are not efficacious in patients with severe CKD and on hemodialysis because at that stage of the disease process, atherosclerosis of the coronary artery and of the entire body is at an advanced stage. Future studies should clarify the difference between the effects of strong and regular statins in patients with mild-to-moderate CKD.

Study Limitations

First, our data were registered prospectively, but this study was a post-hoc analysis. Our major problem was the presence of unmeasured confounding factors that affect the risk for cardiovascular events, such as blood pressure and lipid profile (high-density lipoprotein cholesterol,²⁸ remnant lipoprotein,²⁹ etc). Second, because the absolute number of events of interest was low in this study, the precision of the estimate of effect on the statin group might have been limited, especially in the group with CKD. Third, because we did not check for side effects, the strong statins might not have been tolerated by some patients with regular statin and no statin. So confounding by indication might have occurred in this study. Fourth, we had low power and small sample size to evaluate patients with severe CKD and on dialysis compared with patients with mild-to-moderate CKD. Fifth, we were able to investigate the levels of LDL-C at 6–9 months after coronary stenting in a single center, but we did not obtain the data in all centers. So referral filter bias was considered in this study. Sixth, compliance was only assessed at hospital discharge, so we did not consider the patients whose medication was changed. Finally, we did not collect information on the dose of the statin, and could not confirm dose-dependent effects of statins. Because the dose of statin in Japan is different from that used in Western countries, we should design a randomized controlled study to investigate whether intensive statin therapy is useful and safety in Japanese patients, especially CKD patients.

Conclusions

The present study demonstrated that strong and regular statins were associated with a lower risk for cardiovascular events in patients with CAD who underwent PCI compared with those on no statin therapy. In patients with mild-to-moderate CKD,

Table 3. Unadjusted and Adjusted Risks of Strong and Regular Statin Use for Primary Endpoint (Composite of Cardiovascular Death, Nonfatal MI, and Ischemic Stroke) in All Patients, Mild-to-Moderate CKD and Severe CKD Patients in the KICS Registry

	Primary endpoint			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All patients				
Strong statin (vs. no statin)	0.27 (0.20–0.36)	<0.001	0.46 (0.33–0.64)	<0.001
Regular statin (vs. no statin)	0.42 (0.30–0.61)	<0.001	0.67 (0.46–0.98)	0.041
Mild-to-moderate CKD				
Strong statin (vs. no statin)	0.27 (0.17–0.41)	<0.001	0.50 (0.31–0.81)	0.005
Regular statin (vs. no statin)	0.35 (0.20–0.62)	<0.001	0.65 (0.36–1.18)	0.160
Severe CKD				
Strong statin (vs. no statin)	0.35 (0.17–0.72)	0.004	0.73 (0.33–1.64)	0.446
Regular statin (vs. no statin)	0.27 (0.10–0.76)	0.013	0.49 (0.17–1.43)	0.194

Abbreviations as in Table 1.

only a strong statin was associated with lower risk compared with no statin, but regular statin therapy was not. In Japanese patients with severe CKD, the statins were not associated with lower risk. It is possible that taking a strong statin from the early stage of CKD is useful for suppression of cardiovascular events.

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Disclosures

None.

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Appendix

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