Preventive Effect of Statin Pretreatment on Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Angioplasty: Propensity Score Analysis from a Multicenter Registry

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Short title: Statin Preteatment for Contrast-induced Nephropathy

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Abstract (250 words)

Background: The prophylactic benefit of statins in reducing the incidence of contrast-induced acute kidney injury (CI-AKI) has been investigated in several studies with conflicting results. We sought to investigate whether statin pretreatment prevents CI-AKI in coronary artery disease (CAD) patients undergoing percutaneous coronary intervention (PCI).

Methods: A total of 2198 CAD patients who underwent PCI, except for those undergoing dialysis or who died within 7 days after angioplasty, were analyzed from the ICAS (Ibaraki Cardiovascular Assessment Study) multicenter registry. Analyzed subjects were divided into 2 groups according to statin pretreatment: statin pretreatment (n=839) and non-statin pretreatment (n=1359). Selection bias of statin pretreatment was adjusted by propensity score-matching method: pretreatment statin (n=565) and non-statin pretreatment (n=565). CI-AKI was defined as an increase in serum creatinine of ≥ 25% or 0.5 mg/dl from baseline within 1 week of contrast medium exposure.

Results: A total of 192 (8.7%) patients developed CI-AKI. No significant differences were observed in baseline patient characteristics between the statin and non-statin pretreatment groups after propensity score matching. In the propensity score-matched groups, the incidence of CI-AKI was significantly lower in patients with statin pretreatment than in those without statin pretreatment (3.5% vs.10.6%, odds ratio [OR]: 0.31, 95% confidence interval [CI]: 0.18-0.52, $P<0.001$). Multivariate logistic regression analysis showed that statin pretreatment remained an independent negative

predictor of CI-AKI (OR: 0.31, 95%CI: 0.18-0.53, *P*<0.001) among propensity score-matched subjects.

Conclusions: Statin pretreatment was associated with significant decrease in the risk of CI-AKI in CAD patients undergoing PCI in the ICAS registry.

1. Introduction

Contrast-induced acute kidney injury (CI-AKI), an important complication that can occur after percutaneous coronary intervention (PCI) [1-3], has been associated with both short- and long-term adverse outcomes, including the need for renal replacement therapy, major cardiac adverse events, and mortality [4]. Previous reports showed that approximately 10% of patients develop CI-AKI following PCI [4]. Several prophylactic strategies, including periprocedural hydration with normal saline, limiting the amount of contrast medium, and using iso- or low-osmolar contrast are well established measures for the prevention of CI-AKI [2,3,5-7].

Statins are a class of drug that improves the lipid profile of patients and has been reported to have pleiotropic effects in the vasculature. A few studies focusing on statin treatment as a specific prophylactic agent against CI-AKI have been published with conflicting results [8-12]. Moreover, the supposed pleiotropic effects of preventing post-procedural AKI represent a wide-spread range of effects that they have been reported in aortic valve surgery as well, not only in coronary artery disease (CAD) patients [13]. The aim of this study was to investigate whether statin pretreatment prevents CI-AKI in CAD patients undergoing PCI. To address this issue, we analyzed consecutive CAD patients undergoing PCI who were enrolled in the Ibaraki Cardiovascular Assessment Study (ICAS) registry.

2. Methods

2.1. Study Design

The ICAS registry was designed as a retrospective multicenter observational study of CAD in Ibaraki prefecture in Japan. All consecutive CAD patients who underwent

PCI at 12 cooperating centers were enrolled in this registry. Study subjects are summarized in Figure 1. A total of 2657 patients were enrolled from April 2007 to April 2010. We excluded the patients on dialysis (n=83) and those who died within 7- days of PCI (n=56). Patients with no information regarding serial measurements of serum creatinine were also excluded (n=320). The study population thus comprised 2198 patients who were divided into 2 groups according to statin pretreatment: statin pretreatment group (n=839) and non-pretreatment group (n=1359). This study was approved by the institutional review boards or ethics committees of all participating institutions.

2.2. Clinical Data Collection

Patient demographic information, cardiovascular risk factors, laboratory findings, angiographic findings, and percutaneous procedural characteristics were recorded according to information on medical charts at initial enrollment in the registry. Oral medications prescribed before the PCI procedure were also assessed. Statin pretreatment was defined as taking a statin prior to contrast exposure. The serum concentration of creatinine was measured serially, before contrast exposure and at 24-, 48-, and 72- hour after PCI. When it was not available at 48- or 72- hour post PCI, we used data obtained within 1 week after contrast exposure. Estimated glomerular filtration rate (GFR) was calculated with the Modification of Diet in Renal Disease study equation modified for the Japanese population [14] and estimated GFR of <60ml/min/1.73m^2 was defined as chronic kidney disease. Contrast volume (CV) used during each PCI was collected, and the CV/GFR ratio was calculated by dividing CV by the baseline estimated GFR. The Mehran risk score was calculated on the basis of information collected before the

procedure. Briefly, this is a scoring system based on comorbidities and procedural risk factors, including hypotension, intra-aortic balloon pump use, heart failure, age >75 years, anemia, diabetes mellitus, volume of contrast, and renal function. Predicted incidences of CI-AKI are reported to be 7.5%, 14%, 26.1%, and 57.3% for scores of ≤5 (low risk), 6-10 (moderate risk), 11-15 (high risk), and ≥16 (very high risk), respectively [15]. Based on the baseline diagnostic angiogram, SYNTAX score was calculated using the algorithm which is available on the SYNTAX website [16].

2.3. Follow-up Survey and Study Endpoint

All follow-up data and clinical events were surveyed once a year during the study period. Data for patients who were lost to follow-up were censored at the time of the last contact. The primary endpoint for the present analysis was the development of CI-AKI defined as an increase in serum creatinine of ≥25% or 0.5 mg/dl from the baseline within 1 week after contrast exposure [6]. The serum creatinine concentration was not available at 48- or 72- hour in 25% of the patients; therefore, we used the data obtained within 1 week after contrast exposure. Secondary endpoints assessed included the composite and individual endpoint of requiring dialysis and/or all-cause death within 30, 180, and 360 days. All deaths were confirmed by medical charts or by contacting the referring physician and/or patient's family, and all events were registered by the attending physicians.

2.4. Statistical Analysis

Continuous variables are reported as mean ± SD or median and interquartile ranges, as appropriate. The Student *t*-test and nonparametric Mann-Whitney test were used to

determine differences between mean values for parametrically and non-parametrically distributed variables, respectively. Categorical variables are reported as absolute values and percentages and were analyzed by either chi-square or Fisher exact test, as appropriate. Stratified analysis based on Mehran risk score was performed with the Breslow-Day test of homogeneity and Cochran-Mantel-Haenszel test. Kaplan-Meier curves were constructed to assess event-free survival rates, and the log-rank test was used to identify significant differences in unadjusted survival rate among each groups. Because use of a statin was decided by individual physicians, a propensity score was calculated to adjust for potential selection bias of statin pretreatment. For each patient, a propensity score indicating the probability of being on a pretreatment statin was calculated by binary logistic regression analysis with forced simultaneous entry method. We included 24 covariates to calculate propensity score: demographic data such as age, male sex; baseline characteristics such as hypertension, diabetes, current smoking, estimated GFR, body mass index, family history of cardiovascular disease, prior history of myocardial infarction, PCI, bypass grafting, heart failure, stroke, and peripheral artery disease; other risk factors such as ejection fraction, syntax score, culprit lesion in the left anterior descending artery, and emergency procedure; and concomitant medications of aspirin, clopidogrel, beta-blocker, angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker, calcium channel blocker, and nitrate. Goodness of fit of the propensity score was evaluated by the Hosmer-Lemeshow test and the *c* statistic. The propensity score was used in the following two ways. First, the derived propensity scores were used to match 565 statin pretreatment patients with non-pretreatment patients at a 1:1 ratio (Figure 1). The maximum difference in the propensity score allowed for a match was 0.015 [17]. Second, propensity scores were

used for adjustment for multivariate analysis [17]. Multivariate logistic analysis was performed to determine the independent effect of statin pretreatment for the primary endpoint with stepwise backward elimination method according to a selection-stay criterion of P <0.05. Covariates included age, male sex, statin pretreatment, acute coronary syndrome, ejection fraction ≤45%, multivessel disease, and Mehran risk score. When all subjects were analyzed, propensity scores were also incorporated into a subsequent multivariate model [17]. A two-sided P value of <0.05 was considered to be statistically significant throughout the analysis. Data were analyzed with IBM SPSS Statistics 18.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline Patient Characteristics and Statin Use

We analyzed a total of 2198 consecutive CAD patients who underwent PCI in this study. Mean age was 69.5±10.7 years and 77% of patients were men. Before undergoing PCI, the prescription rate of statin was 38% among all patients. Of these, 82% of patients had been taking a statin ≥4 weeks before contrast exposure. The statins used were included; rosuvastatin 329, atorvastatin 172, pitavastatin 97, pravastatin 79, simvastatin 22, fluvastatin 16, and unknown 124. The propensity score derivation model was reliable (Hosmer-Lemeshow test, χ^2=4.99, p=0.76) and discriminative (*c* statistic, 0.80). Baseline characteristics of all patients and propensity score-matched patients are listed in Table 1. After propensity score matching, well-balanced distribution of the covariates was confirmed between with and without statin pretreatment groups.

3.2. Laboratory Data, Contrast Medium, and Mehran Risk Score

Laboratory data, contrast volume, and Mehran risk score are shown in Table 2. The concentrations of total cholesterol and LDL cholesterol remained significantly different between the 2 groups even after propensity score matching. There were no significant differences in the CV/GFR ratio between the 2 groups. All procedures were performed with use of low-osmolar contrast medium. There was a significant difference in Mehran risk score between the 2 groups; however, this difference disappeared after propensity score matching.

3.3. Primary and Secondary Endpoints

Of the 2198 patients, 192 (8.7%) patients developed CI-AKI following PCI. In all patients, the incidence of CI-AKI was observed less frequently in those with statin pretreatment than in those without statin pretreatment (3.9% vs. 11.7%, respectively, odds ratio [OR]: 0.31, 95% confidence interval [CI]: 0.21-0.45, $P<0.001$). Even after propensity score matching, similar benefit was confirmed in patients with statin pretreatment (OR: 0.31, 95% CI: 0.18-0.52, $P<0.001$) (Table 3). When the patients were divided into 4 groups according to Mehran risk score, the incidence of CI-AKI rose gradually with the increase in Mehran risk score (Figure 2 A, B). The preventive benefit of statin pretreatment was observed in patients with Mehran risk score of ≤5, 6 to 10, and 11 to 15. The number of subjects in the very high risk group with Mehran risk score of ≥16 was small, and statin pretreatment did not show the preventing effect for CI-AKI in this group. Overall, the homogeneity of the effect of statin pretreatment were indicated when comparing them across Mehran risk score strata ($\chi^2 = 6.37$, P for interaction = 0.095). The significant association between statin pretreatment and CI-AKI was observed for all patients while controlling for the Mehran risk score (χ^2 =

33.43, *P*<0.001). Moreover, the serum creatinine concentration was not available at 48- or 72- hour in 25% of the patients; therefore, we used the data obtained within 1 week after contrast exposure. We observed a similar relation in CI-AKI development between patients who had 48- or 72- hour and 1 week measurement of serum creatinine (OR: 0.39, 95% CI: 0.19-0.82 vs. OR: 0.33, 95% CI 0.21-0.52, respectively, *P* for interaction = 0.65).

Multivariate logistic regression analysis for primary endpoint showed that statin pretreatment was an independent predictor of the development of CI-AKI following PCI among all subjects after adjusting for propensity score (OR: 0.62, 95% CI: 0.40-0.97, *P*=0.036) (Table 4). Similar benefit was also confirmed among propensity score-matched subjects (OR: 0.31, 95% CI: 0.18-0.53, *P*<0.001) (Table 4).

The secondary composite endpoint of death or requiring dialysis within either 30, 180, and 360 days was significantly lower in patients with statin pretreatment than those in without statin pretreatment (within 30 days: 0.1% vs. 1.3%, *P*=0.002; within 180 days: 1.2% vs. 3.4%, *P*=0.002; within 360 days: 1.8% vs. 4.6%, *P*<0.001 for with versus without statin pretreatment, respectively), which was mainly attributed to the difference of mortality (Table 3). After propensity score matching, however, there were no significant differences in secondary endpoint between the 2 groups (Table 3). Because receiver-operating characteristics analysis derived the cut-off value of Mehran risk score was 7, with a sensitivity of 74% and a specificity of 62% for predicting composite secondary endpoint, the subjects were recategorized according to the cut-off value of Mehran risk score (≤7 or >7) and statin pretreatment. Kaplan-Meier curves showed that the patients with Mehran risk score of >7 and who did not receive statin pretreatment had worst clinical prognosis among all subjects (Figure 3A) and propensity

score-matched subjects (Figure 3B).

4. Discussion

In the present study, we evaluated the role of statin pretreatment for prevention of CI-AKI among consecutive patients undergoing PCI. The present study comprised an observational cohort of consecutive CAD patients who were treated with PCI, and the major findings of the study are as follows. First, the incidence of CI-AKI was 8.7% overall in consecutive and unselective patients who underwent PCI. The significant decrease in CI-AKI development following PCI was shown in patients with statin pretreatment after propensity score matching (OR: 0.31, 95% CI: 0.18-0.52, $P<0.001$). The patients with Mehran risk score of ≤15 had substantial benefit for preventing CI-AKI, and statin pretreatment was a negative independent predictor for CI-AKI after adjusting for propensity score. Second, clinical outcomes including death and requiring dialysis within 30, 180, and 360 days following PCI were not significantly different between patients with and without statin pretreatment among propensity score-matched subjects.

The incidence of CI-AKI has been an important potential concern because of its effect on morbidity and mortality [4]. Although the pathogenesis of CI-AKI is not well known, it has been hypothesized to be due to oxidative stress, reduction in renal blood flow, tubular obstruction, and direct toxicity to tubular epithelium [1,4,18]. Statins are mainly used as lipid-lowering agents and are also known to have pleiotropic effects, including increased nitric oxide production, antioxidant effects, and anti-inflammatory properties [19,20]. The rational for the use of statins for the prevention of CI-AKI relates to its pleiotropic effects, leading to reduction of renal oxidative stress and enhancement of

renal nitric oxide. Recently, Quintavalle et al. showed that pretreatment with atrovastatin prevents contrast-induced renal cell apoptosis by reducing reactive oxygen species production *in vitro* model [21].

There is general agreement that chronic kidney disease is the most crucial risk factor for CI-AKI, and CV is also a main procedure-related risk factor for CI-AKI [2,4,22]. The CV/GFR ratio has recently been reported to be a useful tool for predicting the development of CI-AKI, as well as the need for renal replacement therapy [6,23]. The other important risk factors for CI-AKI include age over 70 years, diabetes, congestive heart failure, dehydration, and concurrent administration of nephrotoxic agents, i.e., non-steroid anti-inflammatory drugs [2,4,22,24]. The mechanism and risk of CI-AKI are multifactorial, and therefore, identification of patients at high risk for the development of CI-AKI is of major importance. The Mehran risk score, based on comorbidities and procedural risk factors, is a scoring system that is useful for predicting the development of CI-AKI in patients undergoing non-emergent and emergent PCI [15,25]. In this study, we opted to perform risk stratification by using the Mehran risk score, which makes our study relevant and unique. Although the patients with a Mehran risk score of ≥16 had a very high incidence of CI-AKI and showed no significant effects of statin pretreatment, statin pretreatment provided substantial benefit of CI-AKI prevention in the patients with Mehran risk score of ≤15 in our study. Multivariate logistic analysis showed that statin pretreatment was a negative independent predictor of CI-AKI development even after adjustment or matching for propensity score.

The prophylactic benefit of statin for reduction of CI-AKI incidence has been investigated in several studies with conflicting results [8-12]. Patti et al. reported that the patients with a statin had a significantly lower incidence of CI-AKI than those

without a statin among 434 patients undergoing non-emergent PCI (incidence of CI-AKI was 3% with vs. 27% without statin, $P<0.0001$) [8]. Similarly, the benefit of statins in the prevention of CI-AKI was reported by Khanal et al. based on a large database of 29409 patients undergoing emergent and non-emergent PCI (incidence of CI-AKI was 4.4% with vs. 5.9% without statin, $P<0.0001$) [9]. However, Kandula et al. showed that statins were not associated with prevention of CI-AKI when adjusted for the propensity of receiving statins (OR: 1.6, 95% CI: 0.86-3.22, $P=0.12$) [10]. Although observational studies, such as those listed above, often have treatment bias for statin prescription, a few randomized controlled studies exist that address this topic. The PROMISS trial, which randomly allocated 274 patients with renal insufficiency to simvastatin 40 mg or placebo, showed no benefit for prevention of CI-AKI [11]. Recently, Patti et al. conducted the ARMYDA- CI-AKI randomized control trial, which showed that pretreatment with high-dose atorvastatin at 80 mg was effective in preventing CI-AKI in patients with acute coronary syndrome undergoing PCI (OR: 0.34, 95% CI: 0.12-0.97, $P=0.043$) [12].

The incidence of CI-AKI is associated with poor long-term clinical outcomes, but few studies of statin pretreatment have addressed long-term prognosis, such as requiring dialysis, morbidity, and mortality [18]. In our study, despite the significant decrease of CI-AKI with statin pretreatment, there were no significant differences in mortality and/or renal dysfunction requiring dialysis within 30, 180, and 360 days after propensity score matching. The considerable reason might be due to the current widespread use of statins for CAD patients after PCI. The effects of improving long-term clinical outcomes, such as mortality, as well as preventing CI-AKI, should be confirmed by well-designed, randomized controlled trial.

5. Study Limitations

Several limitations in the design of the ICAS registry should be mentioned. First, this study was based on a non-randomized observational retrospective design. The choice of statin was not allocated randomly but was decided by direction of the individual physician. Therefore, this might have introduced potential biases related to unmeasured or hidden covariates in selection of prescribed medications and leading to potential incomplete and/or inexact matching, even though multiple variables were adjusted by propensity score-matched and -adjusted analysis. Our study thus is inferior in comparative validity compared with a randomized, controlled trial. Moreover, because this study was an observational design, there were differences in the study subjects between with and without statin pretreatment on many of the measured covariates. We controlled for these between-group differences using propensity score-matching in order to attenuate the impact of treatment selection bias when estimating causal treatment effects. Propensity score-matching commonly entails creating pairs of treated and untreated subjects who have similar values of propensity score. However, a limitation to matching is the reduction in sample size that arises from regarding unmatched subjects. In our study, an appropriate match could not be identified for 32 % of patients with statin treatment after propensity score-matching. Despite this reduction in sample size, the significance of statin pretreatment for preventing CI-AKI was consistent in this analysis. Second, the collection of creatinine following PCI was constituted retrospectively, and it was difficult to obtain 48- or 72-hour measurement of serum creatinine for all patients, thereby leading to the use of an alternative solution by 1-week measurement in 25% of the whole patients. However, we observed a similar relation in

patients who had both 48- or72 –hour and 1-week measurement of serum creatinine, and thus our overall findings are likely extant. Third, there was a lack of precise information on statin dosing and noncompliance, and safety data was insufficient during the follow-up period. Forth, serum level of creatinine, especially in the elderly and female populations, who have low muscle mass, is an inexact measure of renal function. Fifth, the prevalence of CAD and the cholesterol level of the Japanese population are different from that of Western populations [26]. Japanese patients are more susceptible to statin treatment than are Westerners [27]. Other limitations included the lack of data regarding potential other nephrotoxic agents, such as non-steroidal anti-inflammatory drugs, in the present study. Despite these study limitations, we found that statin pretreatment was associated with a significant decrease in CI-AKI development in CAD patients who underwent PCI.

6. Conclusions

Our observational cohort analysis showed that statin pretreatment was associated with a significant decrease in the incidence of CI-AKI in CAD patients undergoing PCI. These results could not be incorporated to the subgroup of very high value of Mehran risk score, because of underpowered detecting significance of CI-AKI prevention. A large-scale, well-designed, multicenter randomized controlled trial would be necessary to address the effects of statin for preventing CI-AKI, as well as improving long-term clinical outcomes.

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simvastatin therapy in Japanese patients with hypercholesterolemia. Circ J 2002; 66:1087-1095.

Figure Legends

Figure 1. Study flow chart. PS = propensity score.

Figure 2. Incidence of contrast-induced nephropathy and statin pretreatment stratified by Mehran risk score among all (A) and propensity score-matched subjects (B). CI-AKI = contrast-induced acute kidney injury.

Figure 3. Kaplan-Meier curves showing freedom from secondary composite endpoint based on Mehran risk score and statin pretreatemt among all (A) and propensity score-matched subjects (B). MRS = Mehran risk score, PCI = percutaneous coronary intervention.

Figure 1

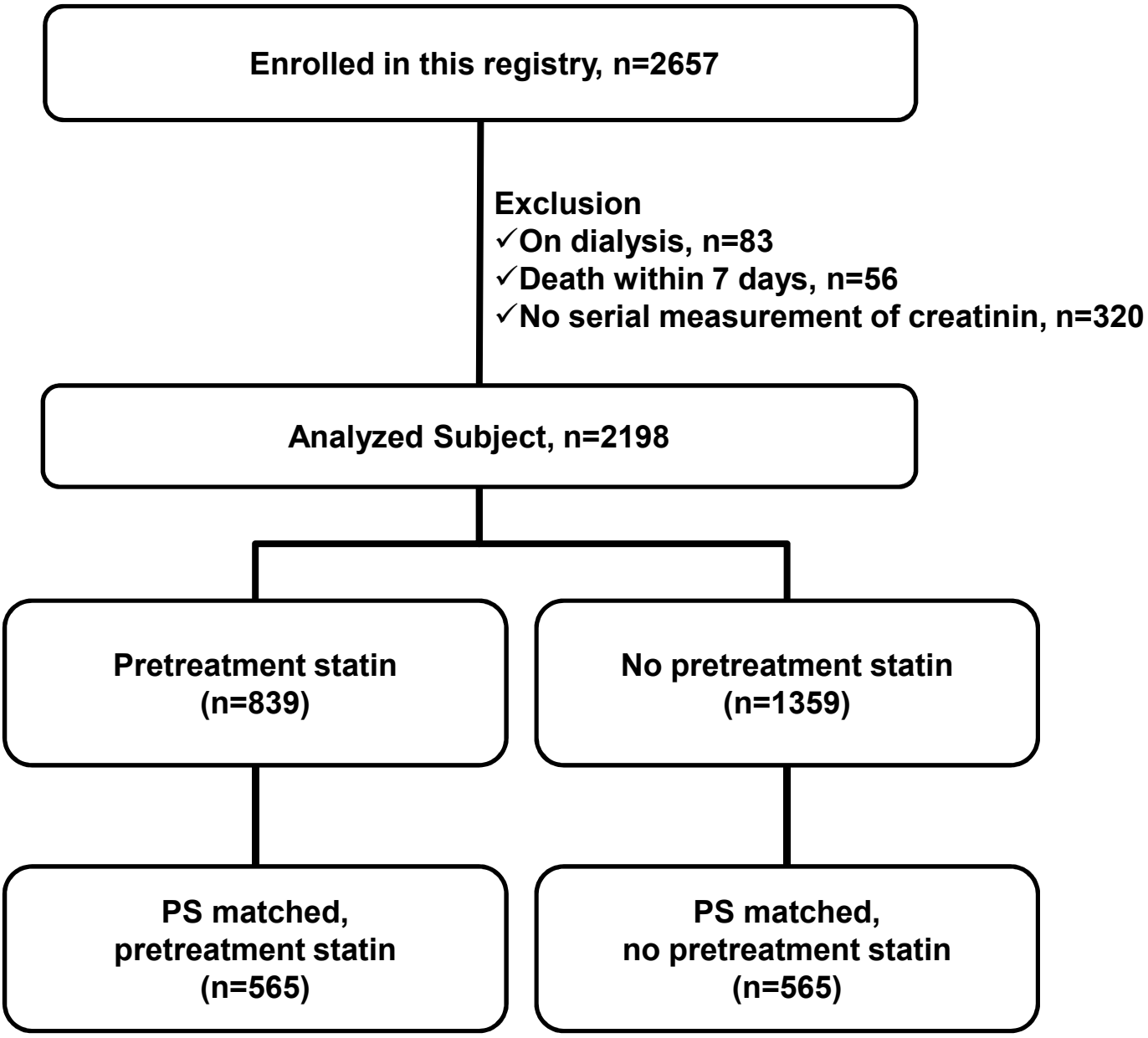

Enrolled in this registry, n=2657
Exclusion
✓On dialysis, n=83
✓Death within 7 days, n=56
✓No serial measurement of creatinin, n=320
Analyzed Subject, n=2198
Pretreatment statin (n=839)
No pretreatment statin (n=1359)
PS matched, pretreatment statin (n=565)
PS matched, no pretreatment statin (n=565)

Figure 2.A

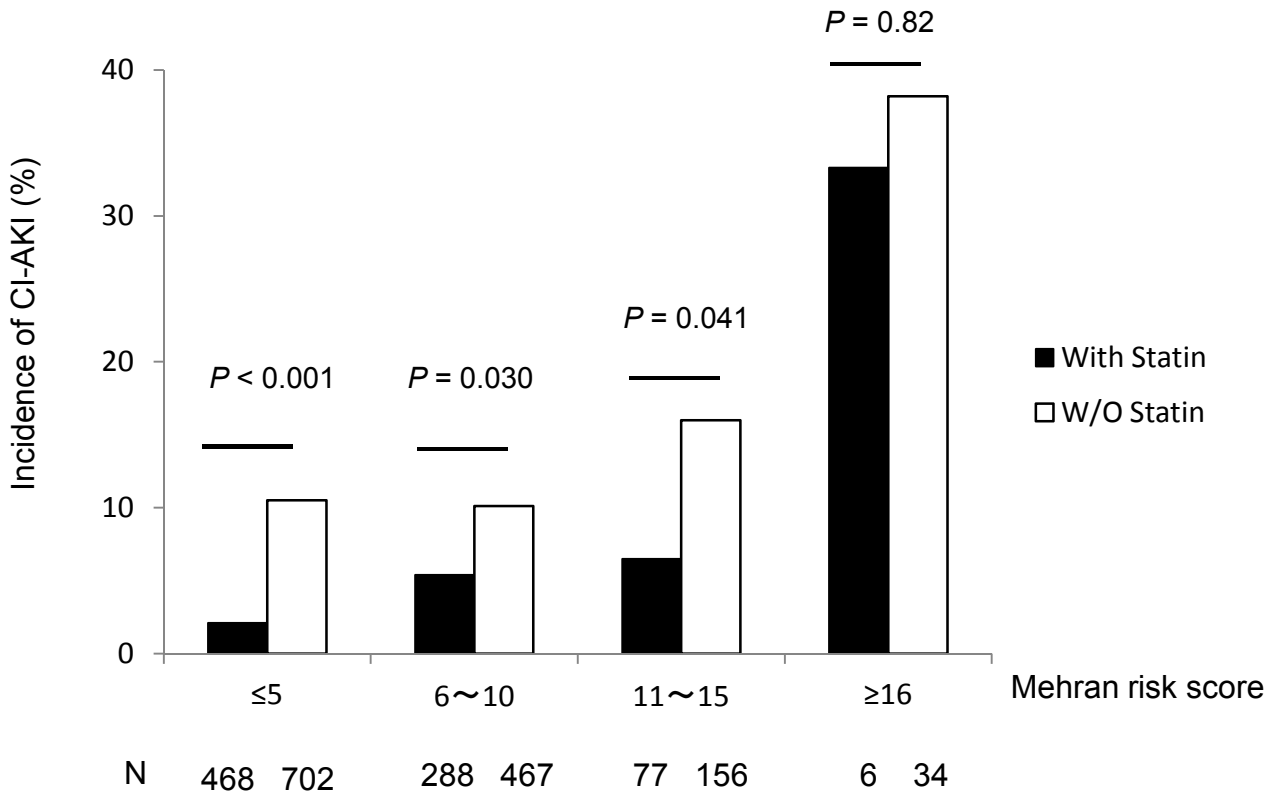


Figure 2.B

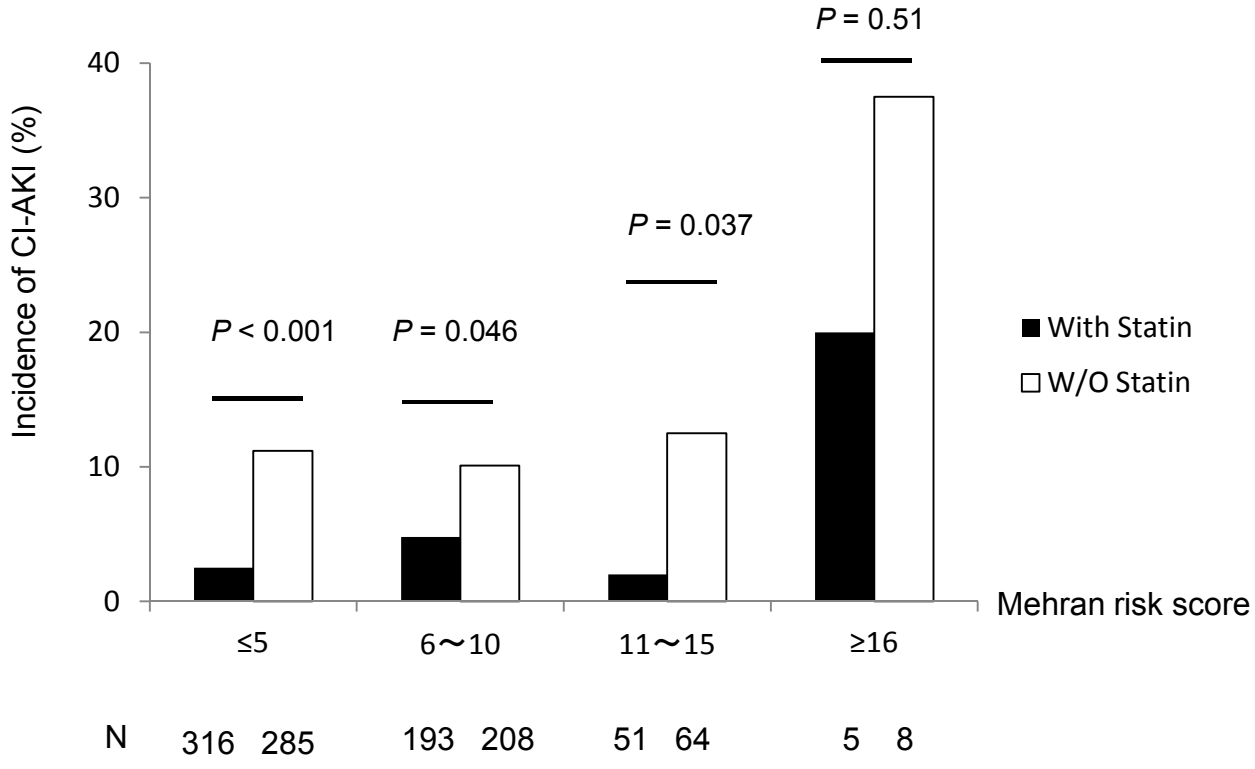
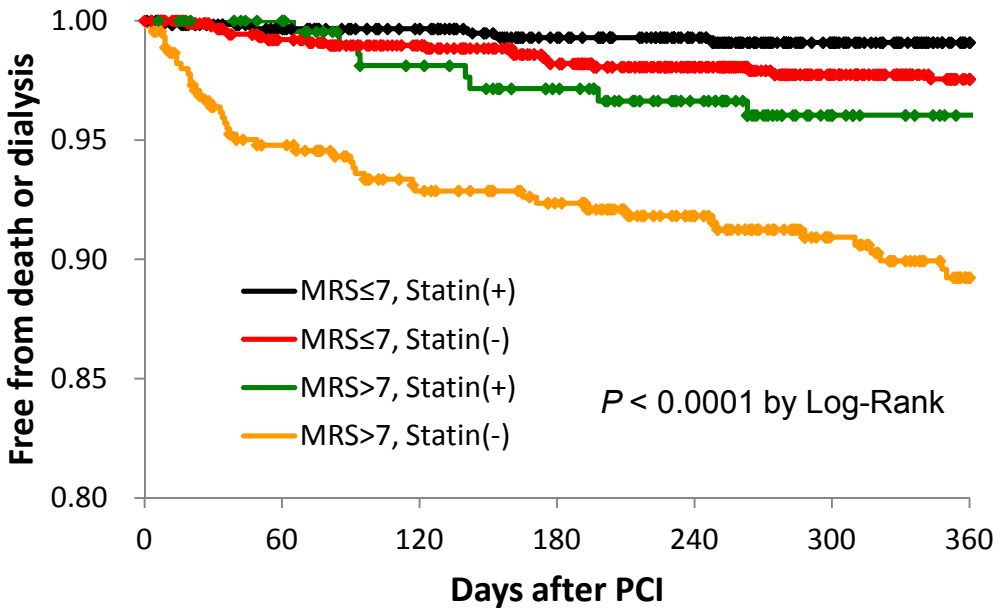
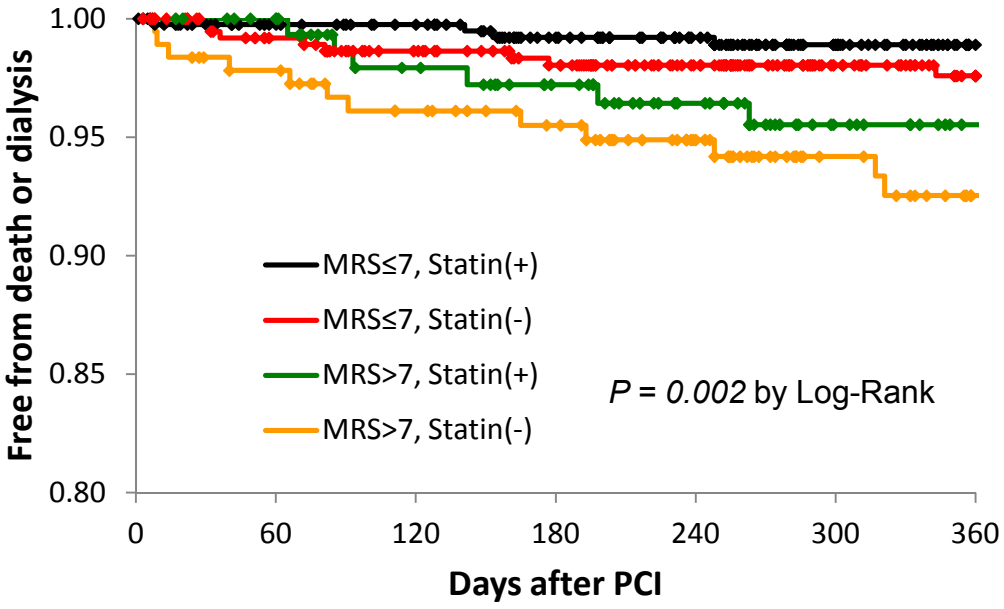


Figure 3A



MRS ≤7, Statin(+)	609	576	556	522	484	419	363
MRS ≤7, Statin(-)	909	857	807	753	673	565	495
MRS >7, Statin(+)	230	221	205	193	174	139	126
MRS >7, Statin(-)	450	409	378	360	321	280	244

Figure 3B



MRS ≤7, Statin(+)	408	385	375	350	326	281	245
MRS ≤7, Statin(-)	381	362	342	325	293	242	214
MRS >7, Statin(+)	157	152	138	129	115	94	84
MRS >7, Statin(-)	184	178	165	157	139	116	104

Table 1. Baseline patient characteristics

	All patients (n=2198)			PS-matched patients (n=1130)		
	With statin (*n*=839)	Without statin (*n*=1359)	*P* value	With statin (*n*=565)	Without statin (*n*=565)	*P* value
Age, years	69 ± 10	70 ± 11	0.004	70 ± 9	70 ± 11	0.66
Age ≥75 years	260 (31%)	531 (39%)	<0.001	194 (34%)	211 (37%)	0.32
Male sex	629 (75%)	1064 (78%)	0.07	440 (78%)	427 (76%)	0.40
Hypertension	650 (78%)	887 (65%)	<0.001	423 (75%)	406 (72%)	0.28
Diabetes mellitus	392 (47%)	471 (35%)	<0.001	233 (41%)	236 (42%)	0.90
Current smoker	179 (21%)	389 (29%)	<0.001	125 (22%)	111 (20%)	0.34
Chronic kidney disease	295 (35%)	475 (35%)	0.92	190 (34%)	210 (37%)	0.24
Family history of CVD	100 (12%)	113 (8.3%)	0.006	57 (10%)	57 (10%)	1.00
Previous PCI	264 (32%)	184 (14%)	<0.001	136 (24%)	137 (24%)	1.00
Previous CABG	89 (11%)	49 (4%)	<0.001	40 (7.1%)	41 (7.3%)	1.00
Prior myocardial infarction	197 (24%)	136 (10%)	<0.001	86 (15%)	94 (17%)	0.57
History of heart failure	64 (7.6%)	62 (4.6%)	0.003	35 (6.2%)	36 (6.4%)	1.00
History of stroke	81 (9.7%)	108 (7.9%)	0.17	54 (9.6%)	49 (8.7%)	0.68
History of peripheral artery disease	37 (4.4%)	36 (2.6%)	0.025	24 (4.2%)	21 (3.7%)	0.76
Body mass index, kg/m^2	24.9 ± 3.4	24.0 ± 3.5	<0.001	24.6 ± 3.5	24.4 ± 3.3	0.26
Acute coronary syndrome	174 (21%)	852 (63%)	<0.001	160 (28%)	181 (32%)	0.20
Acute myocardial infarction	93 (11%)	638 (47%)	<0.001	87 (15%)	104 (18%)	0.20
Culprit of LAD	376 (45%)	605 (45%)	0.89	262 (46%)	262 (46%)	1.00
Multivessel disease	232 (28%)	453 (33%)	0.005	159 (28%)	180 (32%)	0.19
Type B2/C	348 (42%)	608 (45%)	0.13	233 (41%)	236 (42%)	0.90
SYNTAX score	10 [6-16]	11 [7-19]	<0.001	10 [6-17.5]	10 [6-17]	0.88
Ejection fraction, %	64 [53–69]	60 [49–66]	<0.001	65 [54-69]	63 [54-68]	0.16
Ejection fraction ≤45%	96 (11%)	207 (15%)	0.01	62 (11%)	62 (11%)	1.00
Medications before contrast exposure						
Aspirin	572 (68%)	537 (40%)	<0.001	333 (59%)	331 (59%)	0.95
Clopidogrel	405 (48%)	320 (24%)	<0.001	221 (39%)	219 (39%)	0.95
Ticlopidine	108 (13%)	97 (7.1%)	<0.001	70 (12%)	62 (11%)	0.52
Beta-blocker	248 (30%)	231 (17%)	<0.001	144 (26%)	131 (23%)	0.41
ACEI and/or ARB	372 (44%)	389 (29%)	<0.001	206 (37%)	211(37%)	0.81
Calcium channel blocker	196 (23%)	175 (13%)	<0.001	119 (21%)	105 (19%)	0.33
Nitrate	157 (19%)	214 (16%)	0.07	104 (18%)	104 (18%)	1.00

Values are mean ± SD, median [first and third quartiles] or n (%).

ACEI indicates angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass grafting; CVD = cardiovascular disease; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; and PS = propensity score.

Table 2. Laboratory data and procedure-related variables

	All patients (n=2198)			PS-matched patients (n=1130)		
	With statin (*n*=839)	**Without statin (*n*=1359)**	***P* value**	**With statin (*n*=565)**	**Without statin (*n*=565)**	***P* value**
Laboratory data						
White blood cell count	6813 ± 2477	8248 ± 4153	<0.001	6967 ± 2731	7242 ± 4757	0.24
Hemoglobin, g/dl	13.6 ± 1.8	13.6 ± 1.9	0.33	13.7 ± 1.8	13.5 ± 1.9	0.07
Plasma glucose, mg/dl	142 ± 60	157 ± 79	<0.001	142 ± 62	148 ± 71	0.10
Hemoglobin A1c, %	6.3 ± 1.2	6.2 ± 1.4	0.05	6.2 ± 1.1	6.2 ± 1.3	0.89
Total cholesterol, mg/dl	178 ± 40	192 ± 39	<0.001	178 ± 42	189 ± 36	0.002
Triglyceride, mg/dl	152 ± 106	139 ± 125	0.01	147 ± 92	145 ± 104	0.74
HDL cholesterol, mg/dl	49.0 ± 17.7	48.1 ± 15.4	0.29	48.8 ± 19.7	48.1 ± 13.4	0.53
LDL cholesterol, mg/dl	104 ± 33	119 ± 33	<0.001	105 ± 33	115 ± 33	<0.001
Blood urine nitrogen, mg/dl	16.9 ± 6.5	17.2 ± 7.5	0.40	16.9 ± 5.9	17.1 ± 8.2	0.63
Creatinine, mg/dl	0.90 ± 0.38	0.90 ± 0.36	0.95	0.89 ± 0.27	0.91 ± 0.40	0.24
estimated GFR, ml/min/1.73m^2	60.5 ± 12.3	57.4 ± 13.6	0.08	66.6 ± 18.3	66.0 ± 19.1	0.61
Procedure-related variables						
Contrast volume, ml	177 ± 66	180 ± 64	0.34	176 ± 65	174 ± 66	0.62
CV/GFR ratio	2.9 ± 1.5	2.9 ± 1.6	0.57	2.8 ± 1.3	2.9 ± 1.4	0.62
Periprocedural hydration	124 (15%)	136 (10%)	0.001	78 (14%)	71 (13%)	0.60
Oral N-acetylcystein	16 (1.9%)	17 (1.3%)	0.22	8 (1.4%)	13 (2.3%)	0.27
Prophylactic dialysis	2 (0.2%)	4 (0.3%)	0.81	1 (0.2%)	2 (0.4%)	0.56
Mehran risk score	5.6 ± 3.6	6.1 ± 4.1	0.006	5.6 ± 3.7	6.0 ± 3.7	0.07

Values are mean ± SD or n (%).

CV/GFR indicates contrast volume/estimated glomerular filtration rate; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; and PS = propensity score.

Table 3. Primary and secondary endpoints

	All patients (n=2198)			PS-matched patients (n=1130)		
	With statin (*n*=839)	**Without statin (*n*=1341)**	***P* -value**	**With statin (*n*=565)**	**Without statin (*n*=565)**	***P* -value**
Primary endpoint						
CI-AKI	33 (3.9%)	159 (11.7%)	<0.001	20 (3.5%)	60 (10.6%)	<0.001
Secondary endpoints						
Death or requiring dialysis						
within 30 days	1 (0.1%)	18 (1.3%)	0.002	1 (0.2%)	4 (0.7%)	0.37
within 180 days	10 (1.2%)	46 (3.4%)	0.002	7 (1.2%)	14 (2.5%)	0.19
within 360 days	15 (1.8%)	63 (4.6%)	<0.001	12 (2.1%)	20 (3.5%)	0.21
Death						
within 30 days	1 (0.1%)	16 (1.2%)	0.005	1 (0.2%)	4 (0.7%)	0.37
within 180 days	9 (1.1%)	43 (3.2%)	0.001	7 (1.2%)	13 (2.3%)	0.26
within 360 days	14 (1.7%)	58 (4.5%)	<0.001	12 (2.1%)	18 (3.2%)	0.28
Requiring dialysis						
within 30 days	0 (0%)	2 (0.1%)	0.53	0 (0%)	0 (0%)	NA
within 180 days	1 (0.1%)	4 (0.3%)	0.65	0 (0%)	1 (0.2%)	1.00
within 360 days	1 (0.1%)	6 (4.4%)	0.26	0 (0%)	2 (0.4%)	0.50

Values are n (%).

CI-AKI indicates contrast-induced acute kidney injury, NA = not applicable; and PS = propensity score.

Table 4. Multivariate Logistic Analysis for Primary Endpoint

	All subjects		PS-matched subjects	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Statin pretreatment	0.62 (0.40-0.97)	0.036	0.31 (0.18-0.53)	<0.001
ACS	1.94 (1.15-3.27)	0.013	3.63 (2.26-5.85)	<0.001
EF ≤ 45%	1.97 (1.36-2.85)	<0.001	2.05 (1.11-3.77)	0.021
MRS, per increase	1.10 (1.06-1.14)	<0.001		

ACS indicates acute coronary syndrome; CI = confidence interval; EF = ejection fraction; MRS = Mehran risk score; OR = odds ratio; and PS = propensity score.

Covariates included age, male sex, statin pretreatment, acute coronary syndrome, ejection fraction ≤45%, multivessel disease, and Mehran risk score. When all subjects were analyzed, propensity score was also included into the model.