Renal impact of high-loading-dose statin pre-cardiac catheterization in patients with chronic kidney disease and long-term statin use

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Abstract. Previous studies have reported that short-term statin loading effectively protects statin-naive patients with mild renal insufficiency from contrast-induced acute kidney injury (CI-AKI). The aim of the present study was to determine whether patients with more advanced chronic kidney disease (CKD) and long-term statin therapy also benefit from high-loading statin pretreatment. A total of 256 consecutive patients with moderate-to-severe CKD receiving long-term statin therapy and undergoing percutaneous coronary intervention (PCI) or coronary artery angiography (CAG) were divided into the statin-loading group (n=34) and the no statin-loading group (n=222), depending on whether the respective patient received high-dose statin within 24 h prior to the intervention. The primary endpoint was the percent change in serum creatinine (SCr) levels. Additional endpoints included absolute change in SCr levels, estimated glomerular filtration rate (eGFR) at 48-72 h after contrast exposure, incidence rate of CI-AKI and composite in-hospital adverse events. The mean SCr decreased from baseline in either of the two groups, and the differences in the percent (P=0.930) and absolute change (P=0.990) in SCr levels were not significant between the two groups. Furthermore, no significant difference in the post-procedural eGFR was observed between the two groups. The incidence rates of CI-AKI (2.9 vs. 4.1%, P>0.999) and in-hospital adverse events (0.0 vs. 3.6%, P=0.602) were also similar between the two groups. Stratified analyses were then performed, which yielded results consistent with the above. Multiple linear regression indicated that the baseline eGFR value and current smoking status were independent factors affecting the post-procedural eGFR value, while high-dose statin loading was not. Therefore, statin reloading prior to intervention may not provide any further renal protection or decrease the occurrence of in-hospital adverse events in patients with moderate-to-severe CKD receiving long-term statin therapy, which warrants validation in prospective trials.

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Introduction

With the increasing demand in diagnostic and therapeutic cardiovascular interventions, the major concern regarding the use of contrast medium (CM) is the deterioration of renal function referred to as contrast-induced acute kidney injury (CI-AKI). Nash *et al* (1) reported CI-AKI as the third leading cause of hospital-acquired acute renal failure, accounting for 11% of all cases. The incidence of CI-AKI varies considerably, depending on the patient population studied (2,3). As the baseline renal function worsens, there is a sharp increase in the rate of CI-AKI, and up to 26.6% of patients with severe pre-existing chronic kidney disease (CKD) are at risk of developing CI-AKI (4). CI-AKI resolves spontaneously in most cases, although transient dialysis may occasionally be required. Approximately 18.6% of patients with moderate-to-severe CKD who develop CI-AKI progress to irreversible renal dysfunction, leading to prolonged hospital stay, elevated medical costs, poor long-term clinical outcome and increased risk of death, persistent dialysis or major adverse cardiovascular events (5,6). However, at present, no definitive treatment is available for this complication (7).

Statins are known to possess pleiotropic effects (anti-oxidant, anti-inflammatory and anti-thrombotic), independently of their intended effects on blood cholesterol levels (8,9). Statins also improve endothelial function (10), increase nitric oxide bioavailability (11), prevent CM-induced renal tubular epithelial cell apoptosis, restore survival signaling pathways (12) and reduce the uptake of iodinated CM from the urinary space (13), which may counteract the specific pathophysiological mechanisms underlying CI-AKI and exert renoprotective effects. Although several clinical trials have indicated that short-term high-loading-dose statin administration correlates with a significant reduction in the incidence of CI-AKI, and a recent Bayesian network meta-analysis comparing the relative efficacy of multiple pharmacological interventions concluded that high-dose statins plus hydration may be the most effective strategy for the prevention of

CI-AKI (12,14-20). These previous studies mainly focused on statin-naive patients, while frequently excluding patients with severe renal impairment.

In the real-world setting, patients diagnosed with coronary artery disease always receive long-term statin therapy and occasionally develop advanced CKD. Thus, the aim of the present study was to examine the effect of high-dose statin reload on renal function among patients with moderate-to-severe CKD and long-term statin use undergoing percutaneous coronary intervention (PCI) or coronary artery angiography (CAG).

Materials and methods

Study population. The present study was a single-center retrospective clinical trial performed at Peking University First Hospital (Beijing, China). Consecutive patients with stage-3 or -4 CKD on long-term statin treatment who were identified through a medical history review and underwent scheduled PCI or CAG between January 2012 and December 2015 were enrolled. The exclusion criteria were stage-1 or -2 CKD, end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, other causes of AKI prior to catheterization, unavailable serum creatinine (SCr) value 48-72 h after the procedure or missing data on CM dosage, acute ST-segment elevation myocardial infarction (STEMI), cardiogenic shock or hemodynamic instability, and administration of iodinated CM during the week preceding the procedure. Eligible patients were then assigned to the statin-loading group and the no statin-loading group, according to whether they were administered high-dose statins (atorvastatin ≥40 mg or rosuvastatin ≥10 mg) within 24 h prior to the procedure.

Study protocol. The angiographic reports saved in the Innova IGS 520 (GE Medical Systems SCS) and the corresponding medical records of the patients were retrieved and reviewed. The demographic data and medical history of the patients were recorded. The following clinical information was also documented: Final diagnosis, left ventricular ejection fraction (LVEF), category and dosage of chronically or pre-procedurally administered statins, baseline SCr and estimated glomerular filtration rate (eGFR), SCr peak level and eGFR value at 48-72 h after PCI or CAG, and occurrence of in-hospital adverse events, including dialysis, all-cause death, stent thrombosis, as well as cerebral infarction. The procedural characteristics, particularly preparatory hydration and type or volume of CM used, were recorded.

The eGFR values were calculated from baseline and peak post-procedural SCr concentrations using the CKD Epidemiology Collaboration equation for 'white and other', which illustrates the specific algorithm of eGFR (21). Renal function was classified according to the stages set by the National Kidney Foundation (USA) Kidney Disease Outcomes Quality Initiative as follows: Stage 1, CKD with eGFR ≥90 ml/min/1.73 m^2, considered normal; stage 2, CKD with eGFR 60-89 ml/min/1.73 m^2, considered mildly impaired; stage 3, CKD with eGFR 30-59 ml/min/1.73 m^2, considered moderately impaired; stage 4, CKD with eGFR 15-29 ml/min/1.73 m^2, considered severely impaired; and stage 5, CKD with eGFR <15 ml/min/1.73 m^2, considered ESRD (22).

Endpoints and definitions. Given the difference in baseline SCr levels between the two groups, the percent change of peri-procedural SCr levels was selected as the primary endpoint. Additional endpoints included the absolute value of SCr change, eGFR value at 48-72 h after PCI or CAG according to the CI-AKI definition, incidence rate of CI-AKI (defined as a SCr concentration increase by ≥0.5 mg/dl or ≥25% above baseline within 48-72 h after contrast exposure) (23) and composite in-hospital adverse events. The absolute difference in SCr levels was calculated as the baseline minus post-operative peak SCr concentration, while the percent change was the ratio of absolute change and baseline SCr concentration.

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) included unstable angina and non-STEMI. The contrast volume exceeding 140 ml was considered as a high-dose CM load (24).

Statistical analysis. Statistical analysis was performed using SPSS version 19.0 (IBM Corp.). The Shapiro-Wilk test was used to examine the normality of distribution. Normally distributed continuous variables were expressed as the mean ± standard deviation and analyzed using independent Student's t-tests. Non-normally distributed variables were presented as the median (interquartile range) and comparisons were performed using Mann-Whitney U-tests. All categorical data, expressed as absolute numbers (percentages) were compared between the two groups using Chi-squared or Fisher's exact tests. Stratified analyses were also performed in each pre-specified subgroup, and multiple linear regression was applied to adjust for age, sex, medical history and baseline differences in clinical and procedural factors. All statistical analyses were two-tailed. $P<0.05$ was considered to indicate statistical significance.

Results

Patient population and baseline characteristics. A total of 256 patients were considered eligible for final analysis and were assigned to the statin-loading group (n=34) or the no statin-loading group (n=222; Fig. 1).

The mean age of the participants was 71.38±10.27 years and 160 (62.5%) were male. There were no significant differences with respect to age, sex, height, body mass index, medical history or LVEF between the statin-loading and no statin-loading groups ($P>0.05$). The baseline SCr level and the percentage of severe renal insufficiency were similar between the two groups ($P>0.05$). The baseline eGFR value was numerically lower in the statin-loading group, but the difference was not statistically significant ($P=0.054$). Compared with that in the no statin-loading group, the number of patients diagnosed with NSTE-ACS was significantly higher in the statin-loading group (97.1 vs. 83.3%; $P=0.036$). No significant difference was observed regarding the categories of statins chronically administered ($P=0.255$ for atorvastatin and $P=0.262$ for rosuvastatin; Table I).

The number of vessels with stenosis ≥50% and stents deployed, culprit vessels, as well as usage of glycoprotein IIb/IIIa inhibitors, were well-balanced ($P>0.05$). Of the 256 patients, 63.3% received peri-procedural hydration (n=162), without any significant difference between the two groups (67.6 vs. 62.6%; $P=0.571$). However, the volume of CM and the proportion of patients receiving high-dose CM were

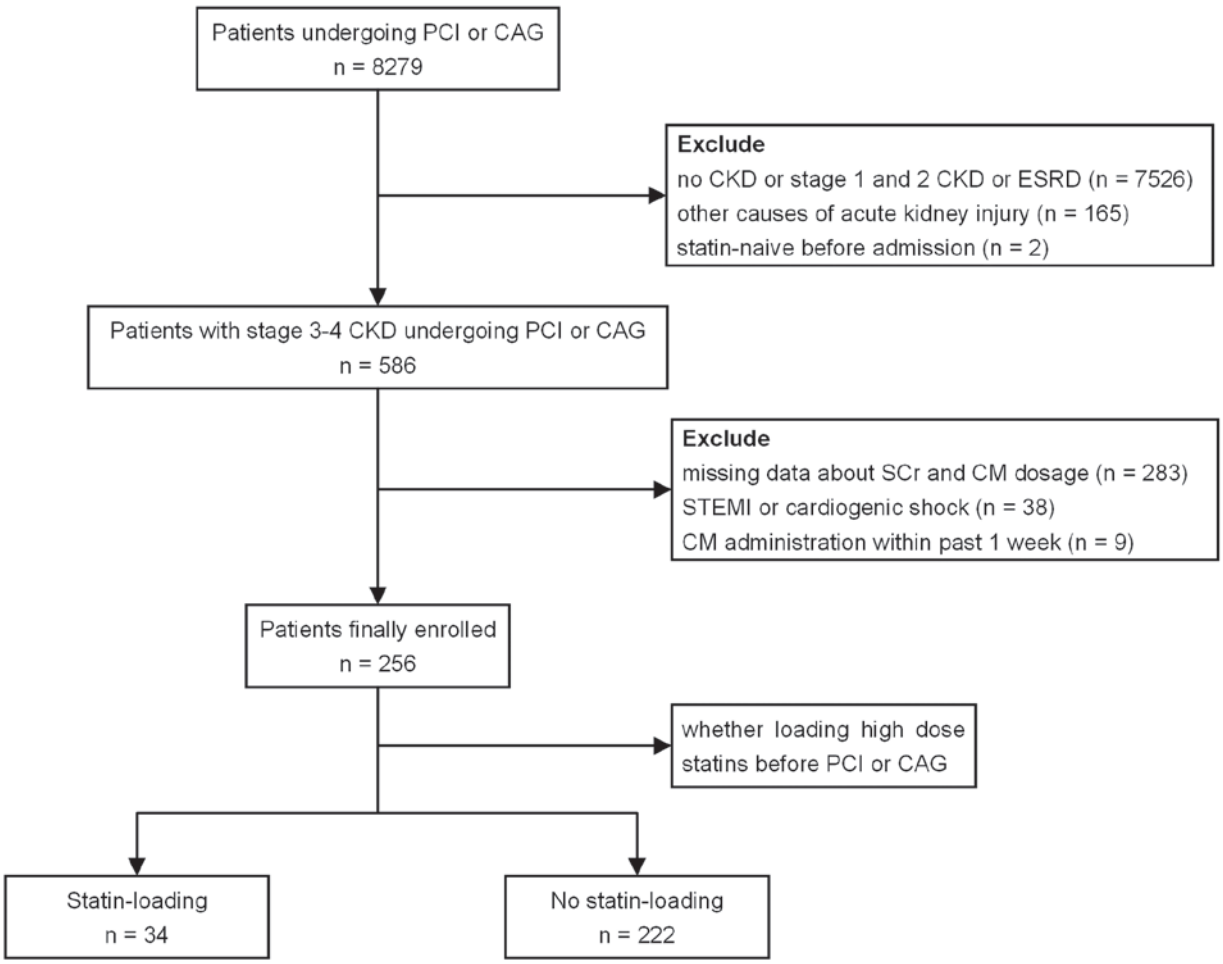

Figure 1. Study flowchart. CKD, chronic kidney disease; CAG, coronary artery angiography; PCI, percutaneous coronary intervention; ESRD, end-stage renal disease; SCr, serum creatinine; CM, contrast medium; STEMI, ST-segment elevation myocardial infarction.

significantly decreased in the statin-loading group (P=0.025 and P=0.017, respectively). In the statin-loading group, a markedly higher proportion of patients was exposed to iso-osmolar iodixanol than that in the no statin-loading group (52.9 vs. 23.9%; P<0.001; Table I).

Changes in renal function parameters. The normal range of SCr is 59-104 μmol/l for males and 45-84 μmol/l for females (25). A decrease in post-procedural peak SCr levels in either of the two groups was observed, while the percent change in the SCr concentration was not significantly different between the two groups (0.91±13.81 vs. 0.71±12.11%; P=0.930; Fig. 2). There was also no significant difference in the absolute SCr change (1.10±20.33 vs. 1.06±17.27 μmol/l; P=0.990; Fig. 2). The eGFR value at 48-72 h after PCI or CAG was above baseline and comparable between the two groups (P=0.119; Table II). The baseline and post-procedural SCr levels were slightly higher in the statin-loading group compared with those in the no statin-loading group (P=0.208 and P=0.252; Table II).

Incidence of CI-AKI. One patient (2.9%) in the statin-loading group and 9 patients (4.1%) in the no statin-loading group developed CI-AKI within 48-72 h of CM administration. The CI-AKI rate was similar between the two groups (P>0.999, Fisher's exact test; Fig. 3 and Table III).

In-hospital clinical outcome. No deaths were reported in either group. No dialysis, stent thrombosis or cerebral infarction occurred in the statin-loading group, whereas the corresponding incidence of dialysis, stent thrombosis and cerebral infarction in the no statin-loading group was 2.3, 0.9 and 0.5%, respectively. There was no significant difference in the in-hospital composite adverse events of all-cause death, dialysis, stent thrombosis and cerebral infarction after CM exposure (0.0 vs. 3.6%; P=0.602, Fisher's exact test; Table III).

Subgroup analyses. Stratified analyses according to the presence of severe renal functional impairment, concomitant diabetes mellitus, adequate hydration, administration of high-dose CM, selection of an iso-osmolar CM and advanced age (≥75 years) demonstrated consistent results when the statin-loading and no statin-loading groups were compared. Of note, in the high-dose CM and elderly patient subgroups, the eGFR value post-procedure was significantly lower in the statin-loading group compared with that in the no statin-loading group (P=0.034 and P=0.043, respectively; Table IV).

Multiple linear regression. The analysis revealed that a low baseline eGFR value (β=0.911, P<0.001) and current smoking status (smokers vs. non-smokers: β=-2.469, P=0.019) were significantly associated with a reduction in the eGFR

Table I. Baseline characteristics of patients.

Characteristic	Statin-loading group (n=34)	No-statin loading group (n=222)	P-value
Age (years)	70.41±11.89	71.52±10.02	0.558
Male	23 (67.6)	137 (61.7)	0.506
Height (cm)	165 (158.75-171.25)	165 (160.00-171.00)	0.677
BMI (kg/m^2)	27.01±5.13	26.00±3.51	0.297
Diabetes mellitus	15 (44.1)	100 (45.0)	0.919
Hypertension	28 (82.4)	195 (87.8)	0.408
Hyperlipidemia	25 (73.5)	144 (64.9)	0.321
Current smoking	10 (29.4)	60 (27.0)	0.771
Previous PCI	14 (41.2)	88 (39.6)	0.865
Previous CABG	1 (2.9)	9 (4.1)	>0.999
Previous MI	9 (26.5)	60 (27.0)	0.946
LVEF (%)	60.48±16.61	65.39±12.75	0.118
Cardiac presentation			
SCAD	1 (2.9)	37 (16.7)	0.036
NSTE-ACS	33 (97.1)	185 (83.3)	0.036
Baseline SCr (μmol/l)	139.41±33.80	129.82±42.27	0.208
Baseline eGFR (ml/min/1.73 m^2)	42.27±9.45	46.08±10.87	0.054
Severe CKD	4 (11.8)	21 (9.5)	0.755
Chronic statins administered			
Atorvastatin	29 (85.3)	170 (76.6)	0.255
Rosuvastatin	4 (11.8)	44 (19.8)	0.262
Number of ≥50% stenotic vessels	2.24±0.96	2.18±0.93	0.750
Culprit vessel			
LAD	29 (85.3)	184 (82.9)	0.726
LCX	20 (58.8)	135 (60.8)	0.825
RCA	23 (67.6)	145 (65.3)	0.790
LM	4 (11.8)	16 (7.2)	0.317
Graft vessel	0 (0.0)	4 (1.8)	>0.999
Number of stents	1.50±0.83	1.72±1.04	0.238
PCI	31 (91.2)	206 (92.8)	0.725
GPI administration	7 (20.6)	80 (36.0)	0.077
Hydration	23 (67.6)	139 (62.6)	0.571
CM type			
Iohexol	4 (11.8)	57 (25.7)	0.076
Iodixanol	18 (52.9)	53 (23.9)	<0.001
Iopamidol	7 (20.6)	65 (29.3)	0.294
Iopromide	5 (14.7)	47 (21.2)	0.383
CM dose (ml)	129.85±37.39	151.23±53.08	0.025
High-dose CM load	13 (38.2)	133 (59.9)	0.017

Values are expressed as the mean ± standard deviation, median (interquartile range) or n (%). BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; LVEF, left ventricular ejection fraction; SCAD, stable coronary artery disease; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; LM, left main; GPI, glycoprotein IIb/IIIa inhibitors; CM, contrast medium.

value at 48-72 h after PCI or CAG, after adjusting for age, sex, medical history, and baseline heterogeneities in clinical and procedural factors. By contrast, high-dose statin reload exerted no significant effect on the post-procedural eGFR value (P=0.618; Table V). The 'constant' β_0 in the equation represents the potentially significant influencing factors of the

Table II. Changes in renal function after administration of CM.

Renal function parameters	Statin-loading group (n=34)	No statin-loading group (n=222)	P-value
eGFR[a] (ml/min/1.73 m^2)			
Baseline	42.27±9.45	46.08±10.87	0.054
Post procedure (48-72 h)	43.69±11.35	47.26±12.54	0.119
SCr[b] (μmol/l)			
Baseline	139.41±33.80	129.82±42.27	0.208
Post procedure (48-72 h)	138.32±40.48	128.77±45.78	0.252

[a]eGFR values ≥90 ml/min/1.73 m^2 are considered normal (22). [b]The reference interval of serum creatinine is 59-104 μmol/l for males, whereas 45-84 μmol/l for females (25). eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

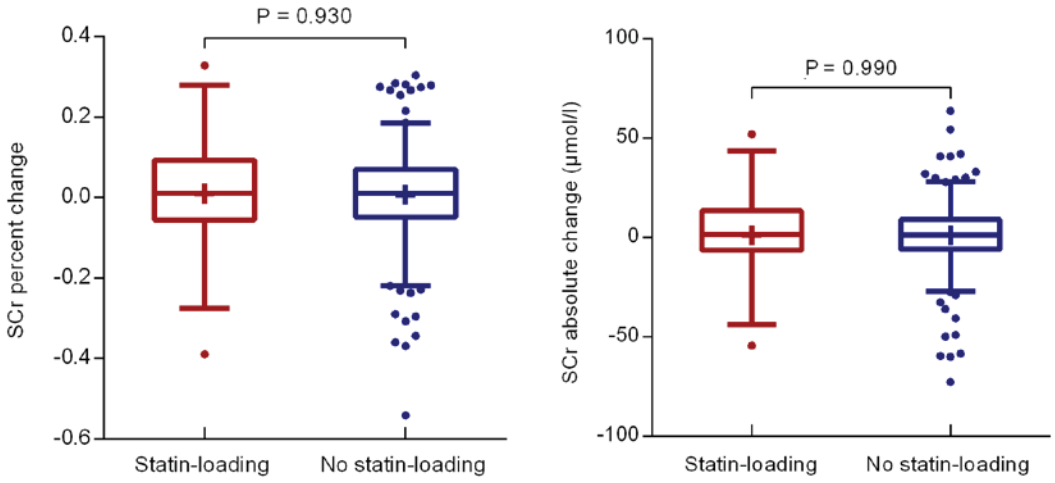

Figure 2. Percent and absolute change in peri-procedural SCr concentration. The SCr peak value at 48-72 h after percutaneous coronary intervention or coronary artery angiography in the two groups exhibited a decrease from baseline. However, there were no significant differences in percent (P=0.930) or absolute change (P=0.990) in SCr levels between the statin-loading and no statin-loading groups. SCr, serum creatinine.

post-procedural eGFR value not included as an independent variable (P<0.001; Table V).

Discussion

Several clinical trials have been designed to evaluate the efficacy of statins in the prevention of CI-AKI, with controversial results. Furthermore, only few studies have investigated the renoprotective role of statin reload in patients with moderate-to-severe CKD receiving long-term statin therapy who undergo cardiac catheterization (12,14-19,26-29). The major results of the present study indicate that, compared with no statin loading, high-dose statin pre-treatment does not further protect renal function, reduce the occurrence of CI-AKI or improve in-hospital clinical outcome for such patients.

An eGFR of <60 ml/min/1.73 m^2 is currently generally accepted as the threshold for risk of CI-AKI (30). Certain retrospective and observational trials indicated that prophylactic administration of statins prior to catheterization may be associated with lower risk of CI-AKI among CKD patients, and this early benefit translated into shorter hospital stay, along with improved long-term clinical outcome (31-34). Certain prospective, randomized and controlled trials also investigated whether peri-procedural high-dose statins efficiently protect the renal function of CKD patients.

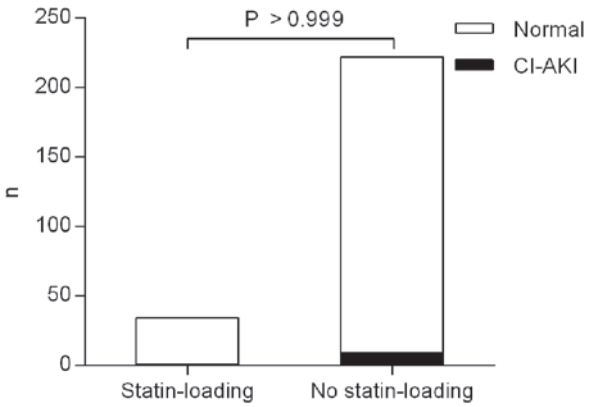

Figure 3. CI-AKI occurrence. The incidence rate of CI-AKI was comparable between the statin-loading and no statin-loading groups 2.9 vs. 4.1%, P>0.999; Fisher's exact test. CI-AKI, contrast-induced acute kidney injury.

Table III. CI-AKI occurrence and in-hospital adverse events.

In-hospital adverse event	Statin-loading group (n=34)	No statin-loading group (n=222)	P-value
CI-AKI	1 (2.9)	9 (4.1)	>0.999
Dialysis	0 (0.0)	5 (2.3)	-
Death	0 (0.0)	0 (0.0)	-
Stent thrombosis	0 (0.0)	2 (0.9)	-
Cerebral infarction	0 (0.0)	1 (0.5)	-
Composite endpoint	0 (0.0)	8 (3.6)	0.602

Values are expressed as n (%). CI-AKI, contrast-induced acute kidney injury.

Quintavalle *et al* (12) reported that 80 mg atorvastatin load within 24 h prior to CM exposure significantly reduced the incidence rate of CI-AKI in patients with moderate CKD undergoing PCI or CAG. Shehata and Hamza (14) investigated diabetic patients with mild-to-moderate renal impairment, and observed that the incidence of CI-AKI was lower among patients receiving atorvastatin 80 mg daily for 48 h prior to elective PCI. The TRACK-D trial, including 2,998 Chinese patients with type 2 diabetes mellitus coincident with mild-to-moderate CKD who underwent coronary or peripheral arterial angiography, demonstrated that short-term high-dose rosuvastatin lowered the rate of CI-AKI and worsening heart failure during a 30-day follow-up (15). Recently, a network meta-analysis, including 150 trials with 31,631 participants that synchronously assessed different treatments, reported that high-dose statins plus hydration may be regarded as the best strategy to prevent CI-AKI (20). Accordingly, in the present study, high-loading-dose statins were generally prescribed for higher-risk patients with lower baseline eGFR values.

In line with the results of the present study, peri-procedural high-dose simvastatin administration in patients with renal insufficiency undergoing CAG was not associated with any differences in the mean peak increase of SCr, incidence of CI-AKI, length of hospital stay or short-term clinical outcome in the PROMISS trial (35). Similarly, Toso *et al* (36) performed a prospective, single-center study on CKD patients, revealing that the mean increase in SCr, CI-AKI rate, in-hospital mortality and requirement for dialysis did not significantly differ between the high-dose atorvastatin and placebo groups. Consistent results were reported in all of the prospectively defined higher-risk subgroups (36). However, unlike those in the present study, one of the enrollment criteria in the PROMISS trial included normal or only mildly impaired renal function (baseline SCr ≥1.1 mg/dl). More importantly, recent statin users were excluded from all of the above-mentioned trials. By contrast, the present study included patients on chronic statin administration with coexisting moderate-to-severe CKD.

Acikel *et al* (19) compared the efficacy of short-term and long-term statin therapy for CI-AKI prevention. They demonstrated that the SCr and eGFR values at 48 h after elective CAG were significantly better in the high-dose atorvastatin and chronic statin therapy groups compared with those in control subjects, whereas no differences were observed in renal function parameters between the high-dose and chronic statin therapy groups. While certain results of the above study were similar to those of the present study, in terms of the comparable benefits of the two statin regimens, the discrepancy in the inclusion criteria of the two studies is noteworthy. Acikel *et al* (19) excluded patients with a moderate-to-severe decrease in eGFR, while the present study focused on a patient population with moderate-to-severe CKD.

In the NAPLES II trial, 80 mg atorvastatin load prior to CM exposure failed to lower the CI-AKI rate in the subgroup with severe CKD (12). Patti *et al* (33) also observed that patients treated with a variety of statins undergoing PCI exhibited a 90% risk reduction of CI-AKI, apart from those with a creatinine clearance <40 ml/min, possibly due to the multiple irreversible pathogenetic mechanisms underlying the development of advanced renal failure (33,37). One meta-analysis of 31 prospective randomized trials reported that the effect of statin therapy on renal outcome was markedly affected by kidney function, and the relative effect was significantly reduced in patients with more advanced kidney dysfunction (38). Since the majority of the patients analyzed in the present study had moderate-to-severe CKD, with severe CKD accounting for ~10% of the cases, it is reasonable to hypothesize that the beneficial effects of high-loading-dose statins on renal function are offset. This may also partly explain the significantly lower post-procedural eGFR values in the higher-risk statin-loading group observed in the high-dose CM and elderly patient subgroup analyses, despite the application of various precautionary strategies.

Lower creatinine clearance is associated with a higher frequency of death or myocardial infarction during the initial hospital stay and at 1 year among patients with CKD undergoing PCI. Furthermore, during the initial hospital stay, a stepwise increase in hemorrhagic complications with declining creatinine clearance is observed (39). The results of two previous large registry cohorts demonstrated that prescription of statins correlated with a significant improvement in subsequent outcomes, including death and composite endpoints of death, myocardial infarction and target vessel revascularization in the mild CKD stratum (40,41). According to the

Table IV. Subgroup analyses of differences in study endpoints.

Subgroup	Statin-loading	No statin-loading	P-value
eGFR (ml/min/1.73 m^2)			
<30			
Number of patients	4	21	
Change in SCr (%)	-7.08±8.31	3.84±12.44	0.108
Post-procedure eGFR	25.19±1.27	25.42±6.62	0.947
CI-AKI	0 (0)	2 (9.5)	>0.999
≥30			
Number of patients	30	201	
Change in SCr (%)	1.97±14.14	0.38±12.06	0.510
Post-procedure eGFR	46.15±9.64	49.54±10.68	0.103
CI-AKI	1 (3.3)	7 (3.5)	>0.999
Diabetes			
Yes			
Number of patients	15	100	
Change in SCr (%)	-3.44±10.38	0.15±12.38	0.289
Post-procedure eGFR	39.93±9.92	45.47±13.69	0.069
CI-AKI	0 (0)	5 (5)	>0.999
No			
Number of patients	19	122	
Change in SCr (%)	4.34±15.42	1.17±11.91	0.302
Post-procedure eGFR	46.66±11.77	48.73±11.37	0.463
CI-AKI	1 (5.3)	4 (3.3)	0.520
Hydration			
Yes			
Number of patients	23	139	
Change in SCr (%)	-1.61±14.71	0.16±12.53	0.543
Post-procedure eGFR	40.32±9.66	43.98±12.61	0.117
CI-AKI	1 (4.3)	7 (5.0)	>0.999
No			
Number of patients	11	83	
Change in SCr (%)	6.17±10.42	1.63±11.38	0.213
Post-procedure eGFR	50.74±11.80	52.75±10.38	0.554
CI-AKI	0 (0)	2 (2.4)	>0.999
CM dose (ml)			
≥140			
Number of patients	13	133	
Change in SCr (%)	-2.84±13.78	0.15±11.84	0.393
Post-procedure eGFR	39.96±9.85	47.58±12.46	0.034
CI-AKI	1 (7.7)	6 (4.5)	0.487
<140			
Number of patients	21	89	
Change in SCr (%)	3.23±13.64	1.54±12.51	0.585
Post-procedure eGFR	45.99±11.82	46.78±12.71	0.796
CI-AKI	0 (0)	3 (3.4)	>0.999
CM			
Iodixanol			
Number of patients	18	53	
Change in SCr (%)	-1.29±16.55	-0.18±14.23	0.784
Post-procedure eGFR	40.90±12.05	40.83±10.84	0.981
CI-AKI	1 (5.6)	2 (3.8)	>0.999

Table IV. Continued.

Subgroup	Statin-loading	No statin-loading	P-value
Other			
Number of patients	16	169	
Change in SCr (%)	3.39±9.85	0.99±11.39	0.417
Post-procedure eGFR	46.83±9.95	49.28±12.38	0.444
CI-AKI	0 (0)	7 (4.1)	>0.999
Age (years)			
≥75			
Number of patients	16	97	
Change in SCr (%)	2.16±15.83	-0.66±12.90	0.436
Post-procedure eGFR	40.29±11.35	46.61±11.48	0.043
CI-AKI	1 (6.3)	5 (5.2)	>0.999
<75			
Number of patients	18	125	
Change in SCr (%)	-0.20±12.09	1.77±11.40	0.498
Post-procedure eGFR	46.71±10.76	47.76±13.33	0.749
CI-AKI	0 (0)	4 (3.2)	>0.999

Values are expressed as the mean ± standard deviation or n (%). CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CM, contrast medium.

Table V. Multivariate analysis for post-procedural eGFR value.

Variable in model	Partial regression coefficient	t statistic	P-value
Constant (β_0)	11.335	3.574	<0.001
Statin loading	0.650	0.499	0.618
Age ≥75 years	-1.632	-1.794	0.074
Male sex	1.430	1.454	0.147
Diabetes mellitus	-0.969	-1.086	0.279
Hypertension	-0.629	-0.469	0.640
Hyperlipidemia	-0.965	-1.031	0.304
Current smoking	-2.469	-2.370	0.019
NSTE-ACS	-1.784	-1.454	0.147
Baseline eGFR[a]	0.911	20.136	<0.001
≥2 vessels diseased[b]	-0.478	-0.495	0.621
Iodixanol administration	-1.912	-1.852	0.065
High-dose CM load	-1.028	-1.137	0.257
Adequate hydration	-1.682	-1.698	0.091

[a]Continuous variable. [b]Including single left main lesion. eGFR, estimated glomerular filtration rate; CM, contrast medium; NSTE-ACS, non-ST-segment elevation acute coronary syndrome.

dyslipidemia management guidelines, patients diagnosed with ACS should receive moderate-to-high-intensity statin therapy for atherosclerotic cardiovascular disease as a secondary prevention (42,43). The patient-centered approach proposed by the National Lipid Association Expert Panel recommends that patients with ACS or stage-3B-4 CKD are classified as very high- or high-risk and, therefore, high-intensity statin therapy should be considered (44). The updated European Clinical Practice Guidelines also recommend that high-intensity statin therapy should be initiated as early as possible in recently diagnosed ACS or CKD patients (45). On the basis of this evidence, long-term statin administration must be advocated in CKD patients and those diagnosed with NSTE-ACS, as in the present study.

Distinct from previous studies, the peak SCr values within 48-72 h post-PCI or -CAG declined in the two groups of the present study, and the CI-AKI rate was merely 3.9%, which is notably lower compared with that reported in the literature; these results may be attributed to the sufficient preventive measures. The principles of CI-AKI prevention and management include using as low as reasonably achievable volumes of CM, selecting the least toxic iodinated CM, and hydration with isotonic crystalloid solution 12 h prior to and at least 24 h after the procedure (46-48). Thus, in the present study, in addition to statin administration, 63.3% of the patients received adequate hydration. Furthermore, the mean CM dosage (129.85±37.39 vs. 151.23±53.08 ml; P=0.025) was markedly lower and the proportion of iso-osmolar iodixanol use was higher in patients with lower baseline eGFR values.

There are several limitations to the present study. First, due to the retrospective design and lack of randomization, there was significant heterogeneity with respect to baseline clinical or procedural variables between the two groups, and a causal association cannot be verified from the present analyses. Second, the eligible patients in the statin-loading group were relatively few, and only a small proportion of patients developed in-hospital adverse events, making this trial underpowered and possibly inconclusive. Third, the enrolled patients were followed up for only 48-72 h, and the peak in

SCr levels may have been missed. However, the majority of the patients developing CI-AKI experience an increase in SCr >0.5 mg/dl within 24 h after CM exposure (49); hence, the SCr peak may have been missed in only a small number of cases. Although all the patients included in the present study were administered statins chronically, the definitive duration of statin treatment remains undetermined. Next, the endpoints of the present study were limited to in-hospital events; consequently, the impact of high-loading-dose statins on the medium- or long-term clinical outcome and permanent functional state of the kidney was not evaluated. In addition, the present study only used SCr or eGFR values to reflect renal function, whereas the levels of serum cystatin C, a more sensitive and reliable renal injury biomarker allowing an early diagnosis of CI-AKI (50), were not determined. Finally, the present study provided no information on the lipid profile of the patients, changes in the highly sensitive C-reactive protein levels or monitoring of statin-associated adverse effects.

In conclusion, routine short treatment with high-dose atorvastatin or rosuvastatin on the background of chronic therapy prior to cardiac catheterization confers no added benefit to the renal function of patients with moderate-to-severe CKD or a reduction of the risk of in-hospital adverse events. These results require confirmation in further prospective and multi-center clinical trials.

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Availability of data and material

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

CH collected, analyzed and interpreted the patient data, and was a major contributor in writing the manuscript. BoZ revised the manuscript and helped to interpret the data. BiZ analyzed the data for the work. XGW and QPS made contributions to the acquisition of data. MC designed the present study. All authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

The current study was a retrospective study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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