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Early High-Dose Rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome

Results From the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome)

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Objectives This study sought to determine if in addition to standard preventive measures on-admission, high-dose rosuvastatin exerts a protective effect against contrast-induced acute kidney injury (CI-AKI).

Background Patients with acute coronary syndrome (ACS) are at high risk for CI-AKI, and the role of statin pre-treatment in preventing renal damage remains uncertain.

Methods Consecutive statin-naïve non-ST elevation ACS patients scheduled to undergo early invasive strategy were randomly assigned to receive rosuvastatin (40 mg on admission, followed by 20 mg/day; statin group n = 252) or no statin treatment (control group n = 252). CI-AKI was defined as an increase in creatinine concentration of ≥0.5 mg/dl or ≥25% above baseline within 72 h after contrast administration.

Results The incidence of CI-AKI was significantly lower in the statin group than in controls (6.7% vs. 15.1%; adjusted odds ratio: 0.38; 95% confidence interval [CI]: 0.20 to 0.71; p = 0.003). The benefits against CI-AKI were consistent, even applying different CI-AKI definition criteria and in all the pre-specified risk categories. The 30-day incidence of adverse cardiovascular and renal events (death, dialysis, myocardial infarction, stroke, or persistent renal damage) was significantly lower in the statin group (3.6% vs. 7.9%, respectively; p = 0.036). Moreover, statin treatment given on admission was associated with a lower rate of death or nonfatal myocardial infarction at 6 month follow-up (3.6% vs. 7.2%, respectively; p = 0.07).

Conclusions High-dose rosuvastatin given on admission to statin-naïve patients with ACS who are scheduled for an early invasive procedure can prevent CI-AKI and improve short-term clinical outcome. (Statin Contrast Induced Nephropathy Prevention [PRATO-ACS]; NCT01185938) (J Am Coll Cardiol 2014;63:71–9) © 2014 by the American College of Cardiology Foundation

Contrast-induced acute kidney injury (CI-AKI) represents a possible complication of diagnostic and/or therapeutic procedures that require administration of iodinated contrast medium and comports prolonged hospitalization, increased costs, and increased short- and long-term morbidity and mortality (1). The prognostic impact of CI-AKI depends on the degree of kidney injury and the persistence of renal function deterioration (2–3). The incidence of CI-AKI varies widely depending on the patient cohorts evaluated, definition criteria used, and preventive strategies adopted (4). Patients with acute coronary syndrome (ACS) have a 3-fold higher risk of developing CI-AKI, an often serious complication that produces persistent worsening of renal function in 30% of cases (2,5–9). Several different protocols have been studied in an effort to prevent CI-AKI (10). The

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

CI-AKI = contrast-induced acute kidney injury

eCrCl = estimated creatinine clearance

eGFR = estimated glomerular filtration rate

HMG-CoA = 3-hydroxyl-3-methylglutaryl coenzyme A

LVEF = left ventricular ejection fraction

NAC = *N*-acetylcysteine

NSTE = without ST-segment elevation

PCI = percutaneous coronary intervention

guidelines recommend prophylactic intravenous hydration, use of low- or iso-osmolar contrast medium and reduced dosages of contrast agents to decrease occurrence of CI-AKI (11,12).

Observational studies suggest that 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may reduce CI-AKI incidence, given heir antilipidemic and pleiotropic properties (antioxidant, anti-inflammatory, and antithrombotic effects) that may exercise nephroprotective action, thereby improving endothelial reactivity and reducing oxidative stress (1). However, the results of previous studies and meta-analyses of high-dose lipophilic statin administration before contrast administration (13–19) have proved disappointing.

The PRATO-ACS (Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome) study was a prospective, randomized trial designed to evaluate the impact of possible acute pleiotropic effects of a hydrophilic statin (rosuvastatin) on CI-AKI, myocardial damage, platelet aggregation, and immunomodulation in patients with ACS without ST-segment elevation (NSTE-ACS) selected to undergo early invasive strategy. This report examines the role of early administration (on admission) of high-dose rosuvastatin in preventing CI-AKI.

Methods

Patient population. The PRATO-ACS study was a single-center, prospective, randomized trial performed on NSTE-ACS patients scheduled for early invasive strategy. From August 2010 to July 2012, all consecutive NSTE-ACS patients (n = 973) admitted to our institution were considered for enrollment in the study. Exclusion criteria were: current statin treatment; high-risk features warranting emergency coronary angiography (within 2 h); acute renal failure or end-stage renal failure requiring dialysis, or serum creatinine ≥3 mg/dl; severe comorbidities which precluded early invasive strategy; contraindications to statin treatment; contrast medium administration within the previous 10 days; pregnancy; and refusal of consent. Only 543 eligible statin-naïve patients were randomized. Randomization was performed on admission by computerized open-label assignment, using an electronic spreadsheet with blocks of 50 patients each. Thus, 271 patients were assigned to receive high-dose rosuvastatin (statin group) and 272 patients no statin treatment (control group). After randomization, 39 patients were excluded from the final analysis because 17 had not undergone angiography and 22 did not complete creatinine determination. Thus, a total of 504 patients were analyzed: 252 treated with rosuvastatin and 252 controls. Figure 1 shows the enrollment criteria and the trial flow.

Study protocol. At the time of randomization, patients in the statin group received 40 mg of rosuvastatin followed by 20 mg/day (10 PM); the control group did not receive statin treatment. At discharge, statin group patients continued treatment with 20 mg/day rosuvastatin (10 mg/day for patients with estimated glomerular filtration rate [eGFR] <30 ml/min/m^2), whereas controls received 40 mg/day atorvastatin.

On admission, all patients were given unfractionated heparin, aspirin, and clopidogrel (loading dose of 600 mg followed by 150 mg/day). Percutaneous coronary intervention (PCI) was performed immediately after diagnostic angiography when appropriate. After coronary angiography, all patients continued to take aspirin (100 mg/day orally) indefinitely and clopidogrel (75 mg/day) for at least 12 months.

In accordance with our standard routine, all patients received intravenous hydration with isotonic saline (1 ml/kg/h, 0.9% sodium chloride for 12 h both before and after the procedure) and 1,200 mg of oral *N*-acetylcysteine (NAC) twice a day from the day before through the day after angiography. Hydration rate was reduced to 0.5 ml/kg/h in both arms for patients with left ventricular ejection fraction (LVEF) <40%. Any nephrotoxic medications (i.e., metformin, no steroidal anti-inflammatory drugs) were suspended on admission. Serum creatinine was measured at baseline (always before hydration) and at 24, 48, and 72 h after contrast medium administration; a further measurement was performed at 30 days in all CI-AKI cases. All tests, even after discharge, were done in our hospital laboratory with consistent methodology. Renal function was determined on the basis of estimated creatinine clearance (eCrCl), evaluated by applying the Cockcroft-Gault formula (20), and eGFR was calculated using the equation from the study by Levey et al. (21). The CI-AKI risk score was calculated as specified by Mehran et al. (5). The same nonionic, dimeric iso-osmolar contrast medium (iodixanol [Visipaque], GE Healthcare Ltd., Amersham, United Kingdom) was used in all cases. The Cigarroa formula was used a priori to estimate maximum contrast medium volume to be injected for each patient (22). High-contrast load was defined as the administration of a contrast volume of >140 ml (23). The subjects and the physicians performing the angiographic procedure were not aware of the assignment group. Adverse events were assessed by the attending physician on the basis of 30-day and 6-month clinical examinations. All clinical, angiographic, and biochemical data were recorded in a dedicated database. The protocol was approved by the hospital ethics committee, and all patients gave written informed consent.

Study endpoints and definitions. The primary endpoint was CI-AKI, defined as an increase in serum creatinine of ≥0.5 mg/dl or ≥25% over the baseline value within

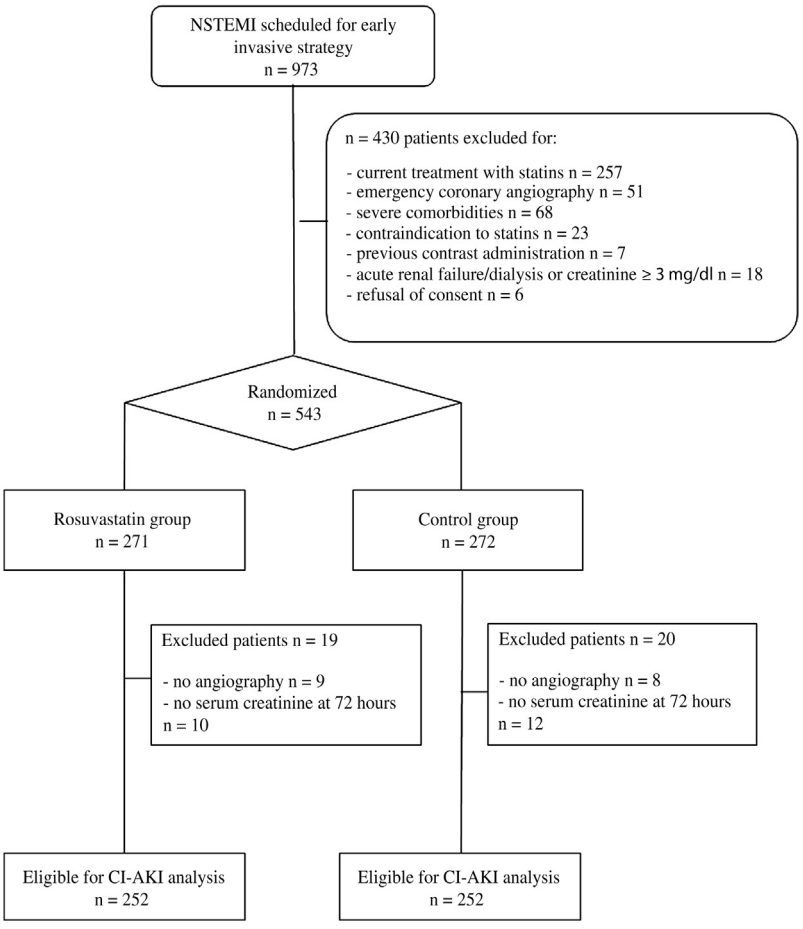

Figure 1 **Trial Flow**

Enrollment criteria and trial flow chart.

72 h after contrast agent administration (24). Additional endpoints were: 1) CI-AKI as defined by other criteria; 2) CI-AKI occurrence in pre-specified risk subgroups; 3) adverse cardiovascular and renal events at 30 days, including acute renal failure requiring dialysis, persistent renal damage, all-cause mortality, myocardial infarction, or stroke; and 4) all-cause mortality or nonfatal myocardial infarction rate at 6 months.

Other defining criteria for CI-AKI were an increase in serum creatinine of ≥0.5 mg/dl or ≥25% over baseline value within 48 h; an increase in creatinine of ≥0.3 mg/dl within 48 h; an increase in creatinine of ≥0.5 mg/dl within 72 h; an increase in creatinine of ≥0.3 mg/dl within 72 h; a decrease in eGRF of ≥25% within 72 h (6,10).

Pre-specified subgroups analyzed with regard to the primary endpoint were age < or ≥70 years of age, sex, diabetes mellitus, eCrCl < or ≥60 ml/min, LVEF ≤ or >45%, CI-AKI risk score ≤ or >5, contrast volume administered ≤ or >140 ml, PCI procedure, and clinical risk profile (high or not high). High-risk clinical profile for CI-AKI development was defined as the presence of at least 1 of the following characteristics: eCrCl <60 ml/min, age ≥70 years, diabetes mellitus, or LVEF ≤45% (8); all other patients were considered not high risk. Acute renal failure requiring dialysis was defined as a decrease in renal function requiring temporary hemodialysis, hemofiltration, or peritoneal dialysis within the first 5 days after contrast administration; persistent renal damage was defined as a decrease of ≥25% in eGFR values from baseline to 1 month post-angiography (6); myocardial infarction was defined in accordance with the universal definition (25). Procedure-related myocardial necrosis was not considered a reinfarction.

Sample size and statistical analysis. We evaluated adequate sample size considering the CI-AKI incidence in patients with NSTE-ACS who underwent early invasive strategy enrolled in a previous study, CLOTILDA (CLOpidogrel, upstream TIrofiban, in cath Lab Downstream Abciximab) (26), where 222 of 300 patients were statin naïve and did not receive statin treatment during hospitalization.

In that study group, the cumulative incidence of CI-AKI (defined as for the primary endpoint described earlier) was 18%, meaning that we needed at least 452 patients (226 per treatment group) to detect a 50% reduction in CI-AKI incidence in the statin group compared with the control group, with an 80% statistical power and 2-sided type 1 error of 5%. Our protocol required that each treatment group comprise at least 271 patients to allow for dropouts and/or incomplete data.

Categorical variables were summarized as percentages and continuous variables as mean ± SD or medians with interquartile range (IQR). The association between categorical variables and treatment groups was investigated by chi-square or Fisher exact tests. Parametric unpaired Student t test (with Satterthwaite's correction for degrees of freedom if necessary) or the analogous nonparametric test (Wilcoxon-Mann Whitney *U* test) was applied to evaluate differences for continuous variables between statin and control groups. Unconditional logistic analysis was performed to evaluate the efficacy of statin treatment on CI-AKI, adjusting for various potential prognostic and confounding factors (sex, age, diabetes, hypertension, low-density lipoprotein [LDL] cholesterol level, CrCl at baseline, LVEF, contrast volume, and CI-AKI risk score). The association between type of treatment and CI-AKI was expressed as the odds ratio (OR), and the 95% confidence interval (CI) also was reported. The same analysis was applied to all CI-AKI secondary definitions. The efficacy of rosuvastatin was also evaluated in pre-specified subgroups (age, sex, diabetes, eCrCl, LVEF, contrast risk score, contrast volume, PCI treatment, and clinical risk). The adjusted effect was controlled for the same prognostic and confounding factors, but the specific variable relative to each individual subgroup was excluded from the model for that subgroup. A p value less than 0.05 was considered significant (2-sided). All analyses were carried out using Stata 12 software (StataCorp LP, College Station, Texas).

Results

Patient population. Demographic, clinical, biochemical, angiographic, and procedural variables are presented in Table 1. There were no significant differences between the study and control groups regarding age, diabetes mellitus, reduced renal function, low ejection fraction, and clinical presentation. The majority (92%) of patients had NSTE myocardial infarction. High-risk clinical features for CI-AKI development were present in 71% of statin patients and 67% of controls. The time lapse between chest pain and randomization was 6 to 22 h and between randomization and contrast medium administration was 15 to 44 h without differences between the 2 groups. Coronary angiography was performed within 24 h in 54% of patients and within 48 h in 79% from time of admission. The two groups were well balanced regarding angiographic data, contrast agent dosage, therapeutic strategy after coronary angiography, and CI-AKI risk score. Percutaneous coronary angioplasty was performed in 66% of patients. The majority of patients (96%) had a CI-AKI risk score of ≤10. An additional angiographic procedure within 72 h after the first was necessary in 5% (n = 23) of cases.

CI-AKI occurrence. The primary endpoint of CI-AKI occurred in 55 patients (10.9%): 17 (6.7%) in the statin group and 38 (15.1%) in the control group, with a crude OR of 0.41 (95% CI: 0.22 to 0.74; p = 0.003) (Fig. 2). Even adjusting for age, sex, diabetes, hypertension, LDL cholesterol, estimated CrCl, LVEF, CI-AKI risk-score, and contrast volume, this OR remained highly significant (adjusted OR [ORadj]: 0.38; 95% CI: 0.20 to 0.71; p = 0.003). The absolute CI-AKI reduction in the statin group was 8.3%, meaning that the number needed to treat (NNT) was 12 patients to prevent 1 case of CI-AKI. There was no significant treatment interaction with the time lapse from statin administration (randomization) to contrast injection (p for interaction = 0.73).

Statin treatment on admission was associated with a consistent reduction in the incidence of CI-AKI when nonprimary endpoint CI-AKI criteria were used, such as the preferred CI-AKI endpoint of creatinine ≥0.3 mg/dl at 48 h (ORadj: 0.35; 95% CI: 0.15 to 0.83; p = 0.017) (Table 2). Table 3 shows significant reduction of CI-AKI development in all the pre-specified risk categories of patients. In particular, a significant reduction ranging between 54% and 65% was observed in patients with baseline eCrCl of <60 ml/min (p = 0.014), EF of <45% (p = 0.020), high-risk clinical features for CI-AKI development (p = 0.016), and in those subjected to PCI (p = 0.036). Moreover, the benefit of statin treatment was independent of sex, and a positive trend also was observed in older patients (p = 0.081) and in those with CI-AKI risk score >5 (p = 0.07), and when contrast volume >140 ml was used (p = 0.069).

After undergoing angiography, 57 patients went on to bypass surgery (of these, 3.7% in the statin group and 10% in the control group [p = 0.60] developed CI-AKI before surgery), and 114 were treated medically (of these, 7.4% in the statin group and 20% in the control group [p = 0.062] developed CI-AKI).

Adverse clinical events. Clinical follow-up at 30 days was completed for all 504 patients. Death and myocardial infarction at 30-day follow-up occurred in 3 of 55 patients with CI-AKI (5%) and 9 of 449 (2%) of patients (p = 0.1) without CI-AKI. Adverse cardiovascular and renal events in the 2 study groups are reported in Table 4. There were no cases of stroke. At 30 days, death or nonfatal myocardial infarction occurred in 4 patients in the statin group and 8 patients in the control group. Two patients in the control group had acute renal failure requiring in-hospital temporary hemofiltration. One patient with CI-AKI in the statin group died (in-hospital) before 30-day serum creatinine determination. Therefore, 17 of 54 of patients (31%) with CI-AKI showed persistent renal damage: 5 in the

Table 1 Baseline Demographic, Clinical, Biochemical, Angiographic, and Procedural Characteristics by Treatment Group

Characteristic	Statin (n = 252)	Control (n = 252)	p Value*
Age, yrs	66.2 ± 12.4	66.1 ± 13.5	0.91
Age ≥70 yrs	117 (46.4)	113 (44.8)	0.72
Male	166 (65.9)	165 (65.5)	0.93
BMI, kg/m^2	26.2 ± 3.7	26.6 ± 4.4	0.35†
Clinical presentation			
NSTE-MI	233 (92.4)	232 (92.1)	>0.90
Unstable angina	19 (7.5)	20 (7.9)	>0.90
Risk factors			
Hypertension	143 (56.7)	138 (54.8)	0.65
Diabetes mellitus	50 (19.8)	57 (22.6)	0.45
Active smoking	89 (35.3)	81 (32.1)	0.45
Total cholesterol >200 mg/dl	116 (46)	130 (51.6)	0.21
eCrCl, ml/min	69.9 ± 24.4	69.3 ± 24.9	0.81
eCrCl <30 ml/min	7 (2.8)	9 (3.6)	0.61
eCrCl <60 ml/min	105 (41.7)	105 (41.7)	>0.90
eGFR, ml/min/m^2	82.5 ± 2	82.6 ± 22	0.96
eGFR <60, ml/min/m^2	39 (15.5)	37 (14.7)	0.80
Previous MI	24 (9.5)	15 (5.9)	0.13
Previous PCI or CABG	30 (11.9)	18 (7.1)	0.07
Baseline LVEF, %	50 ± 9	50 ± 9	>0.90
EF <30%	15 (5.9)	14 (5.6)	0.85
EF <45%	84 (33.3)	85 (33.7)	0.93
High-risk clinical features	180 (71.4)	169 (67.1)	0.29
Laboratory variables at baseline			
Serum creatinine, mg/dl	0.95 ± 0.27	0.96 ± 0.28	0.89
Haemoglobin, mg/dl	14.1 ± 1.6	14.1 ± 1.6	0.77
cTn-I, ng/ml	2.3 ± 5.1	2.5 ± 7.0	0.41‡
CK-MB, ng/ml	19.2 ± 35.2	23.1 ± 48.8	0.34‡
LDL cholesterol, mg/dl	135.2 ± 38.6	135.8 ± 42.7	0.85
HDL cholesterol, mg/dl	40.2 ± 13.7	42.3 ± 13.3	0.08
Triglycerides, mg/dl	119.7 ± 62.8	118 ± 73	0.78†
Glycemia, mg/dl	131.7 ± 50.1	137.3 ± 53.4	0.23
Time intervals, h			
Symptom onset-to-randomization	10 (6–20)	11.5 (6–24)	0.11‡
Randomization-to-angiography	22.5 (14–43)	23 (15–45.5)	0.79‡
Randomization-to-angiography distribution time			
within 24 h	135 (53.6)	135 (53.6)	0.85
within 48 h	205 (81.3)	194 (76.9)	0.27
after 48 h	47 (18.6)	58 (23)	0.27
Hospital stay (days)	5 (4-7)	5 (4-7)	>0.90
Angiographic data and treatment:			
Multivessel disease	123 (48.8)	120 (47.6)	0.78
Contrast volume (ml)	149.7 ± 86.8	138.2 ± 77.8	0.14
Contrast volume >140 (ml)	117 (46.4)	101 (40.1)	0.15
Additional angiography			
within 72 h after first procedure	11 (4.4)	12 (4.8)	0.83
Management distribution			0.70
Medical treatment	54 (21.4)	60 (23.8)	
CABG	27 (10.7)	30 (11.9)	
PCI	171 (67.9)	162 (64.3)	
PCI data			
Multivessel PCI	58 (33.9)	46 (28.3)	0.21
Contrast volume, ml	183 ± 80	172 ± 72	0.18
Contrast volume >140 ml	111 (64.9)	97 (59.8)	0.20
Contrast nephropathy risk score	3 (1–6)	2 (1–5)	0.36‡
Score distribution:			0.62
<5	187 (74.2)	192 (76.6)	
6–10	57 (22.6)	49 (19.4)	
11–16	8 (3.2)	9 (3.6)	
>16	0 (0.0)	1 (0.4)	
Medications at coronary angiography			
Beta-blockers	113 (44.8)	103 (40.8)	0.41
ACE inhibitors	94 (37.3)	103 (40.8)	0.71
Angiotensin receptor blockers	25 (9.9)	28 (11.1)	0.77
Nitrates	73 (28.9)	66 (26.1)	0.54
Diuretics	68 (26.9)	71 (28.1)	0.84
Calcium channel blockers	28 (11.1)	26 (10.3)	0.88
GP IIb/IIIa inhibitors	31 (12.3)	37 (14.6)	0.51
Medications at discharge			
Beta-blockers	140 (55.7)	133 (52.7)	0.59
ACE inhibitors	130 (51.7)	131 (51.9)	>0.90
Angiotensin receptor blockers	25 (9.9)	25 (9.9)	>0.90
Nitrates	48 (19.1)	55 (21.8)	0.49
Diuretics	73 (29.1)	78 (30.9)	0.62
Calcium channel blockers	40 (15.9)	38 (15.1)	0.90

Values are ± SD, n (%), or median (interquartile range). *Parametric unpaired Student *t* test (with †Satterthwaite's correction for degrees of freedom) or the analogous nonparametric ‡Wilcoxon Mann-Whitney test was applied to quantitative variables. Chi-square or Fisher's exact test was used for categorical variables.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft; CK = creatine kinase; cTnI = cardiac troponin I; eCrCl = estimated creatinine clearance; eGFR = estimated glomerular filtration rate; GP = glycoprotein; HDL = high density lipoprotein; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial Infarction; NSTE-MI = without ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

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statin group and 12 in the control group. The 30-day combined occurrence of adverse cardiovascular and renal events was significantly lower in the statin than in the control group (3.6% vs. 7.9%, respectively; p = 0.036).

The 6-month clinical follow-up was completed in 499 of 504 patients (99%). Patients who developed CI-AKI presented a significantly higher rate of 6-month death or nonfatal myocardial infarction than patients without CI-AKI (12.7% vs. 4.5%, respectively; p = 0.02). A trend toward a lower rate of death or nonfatal myocardial infarction was observed in the statin group (3.6% vs. 7.2%, respectively; p = 0.07).

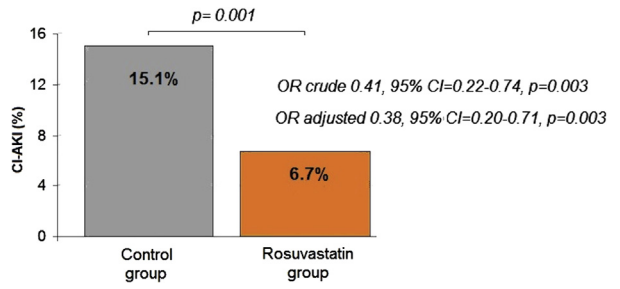

Figure 2 Incidence of Contrast-Induced Acute Renal Injury

Primary endpoint occurrence (increase in serum creatinine concentration of ≥0.5 mg/dl or ≥25% over baseline within 72 h) in the 2 study groups. CI = confidence interval; CI-AKI = contrast-induced acute renal injury; OR = odds ratio.

Discussion

This prospective, randomized study shows that in statin-naïve patients with NSTE-ACS undergoing early invasive strategy, the administration of high-dose rosuvastatin on admission resulted in a significantly lower incidence of CI-AKI and was associated with a better short-term clinical outcome.

Several studies indicate that the administration of statins has beneficial effects in limiting the occurrence of CI-AKI (15–18). Actually, in addition to their intended impact on blood cholesterol levels, statins are also known to have multiple nonlipid-lowering (pleiotropic) effects that could contribute to the reduction of cardiovascular morbidity and mortality (27) and limit impairment of renal function over time, especially in patients with chronic kidney disease (28). Given their antioxidant, antithrombotic, and anti-inflammatory properties, statins could reduce acute iatrogenic renal injury following iodinate contrast administration (1). Statins may also play a renoprotective effect by reducing renal tubulointerstitial inflammatory processes. Pre-clinical studies have shown that statins exert a dose-dependent inhibition of the receptor-mediated endocytosis process that is responsible for protein uptake in proximal tubular cells. Reduced protein trafficking in the proximal tubule may result in less inflammation, endothelial dysfunction, and tubulointerstitial fibrosis (29). One could assume that statin inhibition of this tubular reabsorption process might similarly reduce the uptake of iodinated contrast medium from the urinary space limiting those inflammatory, oxidative, and apoptotic processes resulting from the persistence of contrast medium in the peritubular tissue (30).

However, the results of previous studies and meta-analyses of short-term high-dose lipophilic statin administration before contrast injection (13–19) have proved disappointing. Although the pathogenesis of CI-AKI is not completely understood, multiple mechanisms may be involved, and inflammation plays an important role. This may result in more evident anti-inflammatory effects of high-dose statins in ACS patients who usually have high levels of inflammation and ongoing endothelial dysfunction. The pathophysiologic link between anti-inflammatory effects of statin treatment and renal protection against CI-AKI was well demonstrated in 2 recent small randomized studies conducted with selected ACS populations who underwent PCI (15,16). Xinwei et al. (15) showed that medium-term (7.1 ± 1.6 days) high-dose simvastatin (80 mg) was more effective than low-dose simvastatin (20 mg) in protecting kidney function after PCI, reducing the CI-AKI rate by 66% at 48 h (15.7% vs. 5.3%, respectively; $p < 0.05$) in ACS patients with ejection fraction >40%. Patti et al. (16) showed that high-dose atorvastatin (80 mg) administered 12 h before and continued for 48 h after PCI significantly prevented CI-AKI by 62% at 48 h (5% vs. 13.2%, respectively; $p < 0.05$) in patients with NSTE-ACS and baseline LVEF >30% (16).

Our PRATO-ACS study confirms and extends these interesting observations, although it presents several differences. In fact, this study included consecutive statin-naïve patients with NSTE-ACS scheduled for early invasive strategy independent of baseline cardiac and/or renal function and excluded only patients receiving dialysis or those with creatinine concentrations of ≥3 mg/dl. The majority of this study population presented a baseline high-risk profile for CI-AKI development: 92.3% presented with elevated cardiac biomarkers, and 71% were high-risk due to various adverse clinical features. Moreover, high-dose

Table 2 Cumulative Incidence of Primary and Additional Endpoints by Treatment Group*

Endpoint	Statin	Control	ORc (95% CI)	p Value	ORadj (95% CI)	p Value
Primary CI-AKI endpoint						
Creatinine ≥0.5 mg/dl or ≥25% within 72 h	17 (6.7)	38 (15.1)	0.41 (0.22–0.74)	0.003	0.38 (0.20–0.71)	0.003
Additional endpoints (different CI-AKI criteria)						
Creatinine ≥0.5 mg/dl or ≥25% within 48 h	16 (6.3)	30 (11.9)	0.50 (0.27–0.95)	0.033	0.48 (0.25–0.91)	0.025
Creatinine ≥0.3 mg/dl within 48 h	9 (3.6)	22 (8.7)	0.39 (0.17–0.86)	0.02	0.35 (0.15–0.83)	0.017
Creatinine ≥0.3 mg/dl within 72 h	11 (4.4)	27 (10.7)	0.38 (0.18–0.78)	0.009	0.36 (0.17–0.77)	0.009
Creatinine ≥0.5 mg/dl within 72 h	6 (2.4)	15 (5.9)	0.38 (0.15–1.01)	0.052	0.43 (0.15–1.23)	0.115
eGFR ≤25% within 72 h	14 (5.6)	29 (11.5)	0.45 (0.24–0.86)	0.015	0.44 (0.23–0.86)	0.016

*Unconditional logistic model was applied, and crude odds ratio (ORc) with 95% confidence interval (CI) was reported. Adjusted ORs were controlled (ORadj) for sex, age, diabetes, hypertension, LDL-cholesterol values, creatinine clearance at baseline, ejection fraction, contrast volume and CI-AKI risk score.

CI-AKI = contrast-induced acute kidney injury; eGFR = estimated glomerular filtration rate.

Table 3 Crude and Adjusted Odds Ratio for Primary Endpoint Occurrence in Pre-Specified Risk Subgroups

Subgroup	Events/Statin Group	Events/Control Group	OR_c (95% CI)	p Value	p for Interaction	OR_{adj} (95% CI)	p Value	p for Interaction
Age					0.07			0.06
≥70 yrs	13/117	22/113	0.52 (0.25–1.08)	0.081		0.55 (0.25–1.20)	0.136	
<70 yrs	4/135	16/139	0.23 (0.08–0.72)	0.011		0.19 (0.06–0.63)	0.006	
Sex					0.61			0.50
Male	11/166	22/165	0.46 (0.22–0.98)	0.046		0.44 (0.20–0.98)	0.044	
Female	6/86	16/87	0.33 (0.12–0.90)	0.030		0.28 (0.10–0.79)	0.017	
Diabetes mellitus					0.80			0.49
Yes	6/50	13/57	0.46 (0.16–1.32)	0.150		0.47 (0.15–1.51)	0.205	
No	11/202	25/195	0.39 (0.19–0.82)	0.013		0.32 (0.15–0.70)	0.004	
Baseline LVEF					0.76			0.88
≤45%	9/84	21/85	0.37 (0.16–0.85)	0.020		0.43 (0.17–1.05)	0.063	
>45%	8/168	17/167	0.44 (0.18–1.05)	0.065		0.37 (0.15–0.92)	0.033	
Baseline eCrCl					0.64			0.79
<60 ml/min	9/105	22/105	0.35 (0.15–0.81)	0.014		0.36 (0.15–0.87)	0.024	
≥60 ml/min	8/147	16/147	0.47 (0.20–1.14)	0.094		0.39 (0.15–1.00)	0.050	
PCI					0.62			0.76
Yes	12/171	23/162	0.46 (0.22–0.95)	0.036		0.41 (0.19–0.89)	0.024	
No	5/81	15/90	0.33 (0.11–0.95)	0.040		0.33 (0.10–1.03)	0.057	
High risk					0.22			0.35
Yes	16/180	30/169	0.45 (0.24–0.86)	0.016		0.44 (0.23–0.86)	0.017	
No	1/72	8/83	0.13 (0.02–1.08)	0.059		0.12 (0.01–1.04)	0.055	
Contrast volume					0.57			0.61
>140 ml	10/117	17/101	0.46 (0.20–1.06)	0.069		0.43 (0.17–1.06)	0.067	
≤140 ml	7/135	21/151	0.34 (0.14–0.82)	0.017		0.37 (0.15–0.94)	0.036	
CI-AKI risk score					0.73			0.52
≤5	8/187	22/193	0.35 (0.15–0.80)	0.013		0.31 (0.13–0.72)	0.007	
>5	9/65	16/59	0.43 (0.17–1.07)	0.070		0.56 (0.21–1.5)	0.247	

Unconditional logistic model was applied and crude and adjusted odds ratio (O_{Rc} and OR_{adj}, respectively) with 95% confidence interval (CI) are reported.
CI-AKI = contrast-induced acute kidney injury; eCrCl = estimated creatinine clearance; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

statin was administered on admission in the active treatment arm, whereas controls began statin treatment only at discharge.

We used a hydrophilic statin (rosuvastatin), which has acute pleiotropic effects (31). The choice of this specific statin was based on the beneficial clinical effects it exerts on both apparently healthy subjects without hyperlipidemia (LDL cholesterol levels: <130 mg/dl) but with elevated high-sensitivity C-reactive protein levels (>2.0 mg/l) (32) and patients with eGFR <60 ml/min/1.73 m^2 (33). Also, it is known that short-term treatment with rosuvastatin may improve eGFR independent of lipid fraction changes, suggesting pleiotropic mechanisms of action that carry with it beneficial renal effects (34). Furthermore, rosuvastatin exercises particularly potent HMG-CoA reductase inhibition with reduced tubular protein reabsorption (29). A final consideration is that this hydrophilic statin does not undergo cytochrome P-450 3A4 metabolism in the liver and thus does not interfere with the hepatic conversion of clopidogrel, the antiplatelet drug used in our study (35).

In the present study, early high-dose rosuvastatin administered in addition to standard CI-AKI preventive measures (hydration and iso-osmolar contrast medium administration) reduced the incidence of renal injury by 55%, with an absolute reduction of 8.3% and an NNT to prevent 1 event of 12.

The protective effect exerted by statin pre-treatment also remained statistically significant when different definition criteria of CI-AKI were applied. Moreover, the beneficial effects of rosuvastatin were consistent in all the pre-specified categories of risk including those with reduced renal function. Pre-existing renal dysfunction is known to be an important independent predictor of CI-AKI development especially in ACS patients (36). So far, the beneficial impact against CI-AKI exerted by short-term high-dose statin pre-treatment in patients with stable coronary artery disease and moderately reduced renal function (eCrCl ≤60 ml/min) is still debated (13,14,18). However, in the current study, we observed a significant reduction (59%) of CI-AKI rate in patients with ACS and renal dysfunction.

The majority (nearly 70%) of our enrolled study population presented baseline clinically high-risk characteristics for developing CI-AKI. This specific subgroup, when given high-dose rosuvastatin, demonstrated an absolute reduction in CI-AKI rate of 8.9% with an NNT to prevent 1 event of 11.

Beneficial effects of statin pre-treatment were observed in patients who underwent PCI. In particular, in this subgroup of patients absolute and relative reduction in CI-AKI rate after rosuvastatin pre-treatment were similar to those

Table 4 Adverse Clinical Events at 30 Days by Treatment Group

Event	Statin (n = 252)	Control (n = 252)	p Value*
Dialysis	—	2 (0.8)	0.50
Persistent CI-AKI	5 (2)	12 (4.8)	0.15
Myocardial infarction	2 (0.8)	5 (2)	0.45
Stroke	—	—	—
Overall deaths	2 (0.8)	3 (1.2)	>0.90
Overall adverse events (at least 1)	9 (3.6)	20 (7.9)	0.036

*Fisher's exact test was applied a part from for overall adverse events (chi-square test).
CI-AKI = contrast-induced acute kidney injury.

observed in previous studies using high-dose lipophilic statins (15,16). Moreover, rosuvastatin was efficacious also in patients with reduced baseline ejection fraction and higher CI-AKI risk score, both of which were independent predictors of persistent renal damage (3).

Early statin administration and clinical outcome. In this study, high-dose rosuvastatin treatment given on admission was associated with a significantly lower rate of 30-day adverse cardiovascular and renal events. This beneficial clinical impact was driven mostly by the reduction of persistent renal damage in the statin group.

The role of renal function as a prognostic factor for cardiovascular events has become recognized in recent years. Even small reductions in eGFR are associated with significant worsening of cardiovascular outcomes (37). Therefore, variations in renal function following contrast medium administration should be judged not only in the short term but also for medium- and long-term impact. Various percentages of patients who develop CI-AKI present with irreversible deterioration of renal function over time (2,3,6). Both transient and persistent renal damage have an important prognostic impact on cardiovascular and renal outcome following hospital discharge (2,3). Transient and persistent renal damage were independent predictors of long-term clinical outcome, increasing 1.6-fold and 2.5-fold, respectively, the risk of mortality, dialysis, or major cardiovascular events at 5-year follow-up (3). Our study includes persistent renal damage among the clinical endpoints and evidences that strategies that reduce the incidence of acute renal damage can lead to lower incidence of persistent renal function deterioration, with possible cardiovascular benefits.

The present study also confirms that patients who developed CI-AKI were at increased risk of death or nonfatal myocardial infarction 6 months after coronary angiography. However, patients treated with high doses of statins immediately on admission presented a better mid-term clinical outcome.

Clinical implications. Data from specific trials and meta-analyses support the routine use of statin therapy in patients with ACS. Guidelines suggest starting statin treatment before hospital discharge with the aim of achieving low-density lipoprotein cholesterol levels of 100 mg/dl (38). However, the critical issue of when to begin statin therapy (early vs. late during hospitalization or pre- vs. post-discharge) has not been examined in randomized studies, and it remains an unresolved issue (39). Our results, together with those that showed renal and myocardial protection following high-dose statins prior to PCI (15,16,40), support routine use of high-dose statin therapy on admission in statin-naïve patients with NSTE-ACS scheduled for early invasive strategy. It remains to be established whether re-loading with high-dose statin may augment renal protection also in ACS patients receiving chronic statin therapy.

Study limitations. This was an open-label study with a relatively small sample size. Too small a sample size means further limitations in statistical significance of subgroup data. In our study, too few patients had severely reduced baseline renal function (eCrCl $\leq$30 ml/min) or a high CI-AKI risk score to allow evaluation of the role of early statin administration in these high-risk subgroups, which require intensive CI-AKI prevention measures (9). However, our population is consecutive and representative of everyday clinical practice in the treatment of NSTE-ACS patients scheduled for early invasive strategy. Moreover, this is the first randomized study, which points out the critical issue of the timing (admission vs. discharge) of statin treatment in ACS patients.

In addition, routine pre-treatment with NAC was used in all patients. The association between NAC and rosuvastatin may not rule out the possibility of an interaction or a synergistic effect.

Conclusions

On admission, high-dose rosuvastatin therapy reduced CI-AKI occurrence and improved short-term clinical outcome in statin-naïve patients with NSTE-ACS scheduled for early invasive strategy.

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