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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