International Journal of Cardiology 171 (2014) 243–249

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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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ARTICLE INFO

Article history:
Received 20 July 2013
Received in revised form 1 October 2013
Accepted 12 December 2013
Available online 22 December 2013

Keywords:
Statin
Contrast-induced acute kidney injury
Mehran risk score
Propensity score

ABSTRACT

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 a 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

☆ Grant support: none.
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http://dx.doi.org/10.1016/j.ijcard.2013.12.017

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 Fig. 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 h after PCI. When it was not available at 48 or 72 h 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 <60 ml/min/1.73 m^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, the 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 h 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 non-parametric Mann–Whitney test were used to determine the 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 group.

Because the use of a statin was decided by individual physicians, a propensity score was calculated to adjust for the 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 the propensity score: demographic data such as age and 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 (Fig. 1). The maximum difference in the propensity score allowed for a match was 0.015 [17]. Second, propensity scores were used for the adjustment for multivariate analysis [17]. Multivariate logistic analysis was performed to determine the

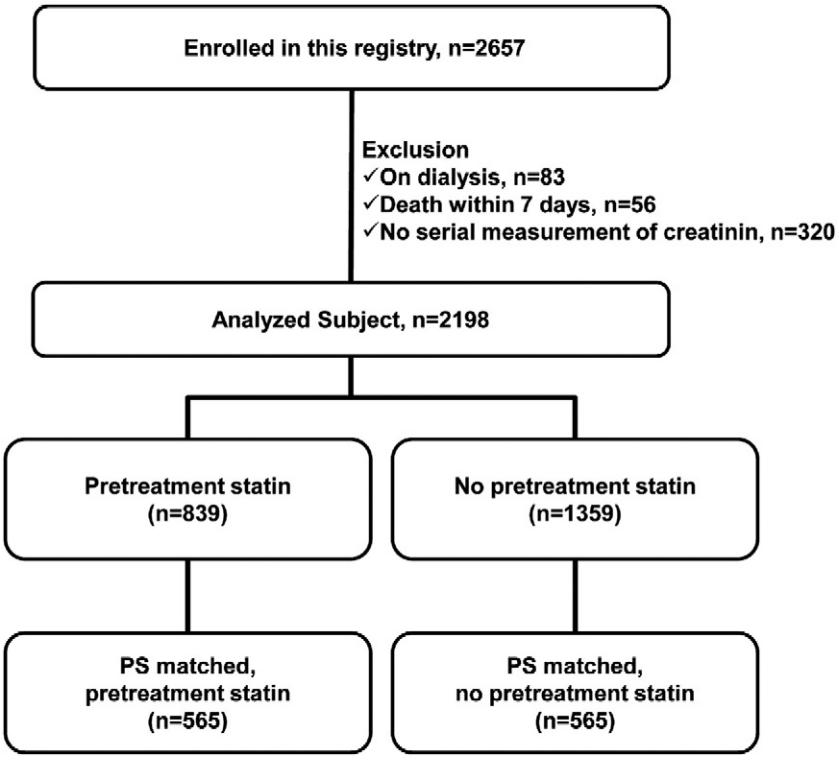

Fig. 1. Study flow chart. PS = propensity score.