Association between dose reduction of renin-angiotensin-aldosterone system inhibitors before coronary artery angiography and acute kidney injury: a propensity score-matched study

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ABSTRACT
Objective: The aim of this study was to investigate the association between dose reduction of renin-angiotensin-aldosterone system inhibitors (RAASis) and Acute kidney injury (AKI). AKI, which is commonly observed in hospitalized patients, increases mortality. Although RAASis and coronary artery angiography (CAG) are reported to be risk factors for AKI, whether dose reduction of RAASis can prevent AKI after CAG remains unknown.

Methods: In this retrospective propensity score (PS)-matched cohort from the RWD database, which includes 20 million patients from 190 hospitals in Japan, we examined the impact of dose reduction of RAASis on the development of AKI after CAG. The subjects were patients with an estimated glomerular filtration rate (eGFR) of 15–60 mL/min/1.73 m², and the exposure of interest was the presence of a dose reduction in RAASis within 3 days before CAG was performed. Propensity score matching was performed with 19 baseline characteristics using a logistic regression model.

Results: We identified 3329 patients who were prescribed RAASis at least one month before admission and underwent CAG. Six hundred seventy-four patients had a dose reduction 3 days prior to undergoing CAG, and 2655 patients did not. AKI was observed in 34 (5.0%) patients in the reduction group and 137 (5.2%) patients in the control group. There was no significant difference in the primary outcome between the two groups in the PS-matched cohort (OR: 1.08, 95% CI: 0.70–1.66).

Conclusions: A reduction in the dose of RAASis did not prevent the development of AKI among patients undergoing CAG.

Introduction
Acute kidney injury (AKI), a condition that is observed in 10.5 to 22.0% of inpatients, increases mortality and prolongs the length of hospital stay1–3. Renin-angiotensin-aldosterone system inhibitors (RAASis) and coronary artery angiography (CAG) are reported to be risk factors for AKI4–6. Although some doctors empirically reduce the dose of RAASis before performing CAG, whether dose reduction of RAASis can prevent AKI remains unclear. Three randomized controlled trials (RCTs) were conducted to confirm the efficacy of the dose reduction of RAASis on renal function among patients undergoing CAG; however, there were no differences in the development of AKI between the reduction group and the control group in any of the studies7–10. These results may be due to the following two reasons. First, the sample sizes were small in all studies. Second, the RAASI dose was reduced within 24 h before CAG. The timing of reduction was too late in all studies considering the half-life of RAASis, which is reported to be up to 24 h11. For these reasons, a study with a longer reduction period and a larger sample size is needed to assess the efficacy of dose reduction of RAASis for preventing AKI. The objective of this study was to investigate the association between dose reduction of RAASis and AKI among patients undergoing CAG using a Japanese health care record database.

Methods
Study design and setting
The RWD database, which is administered by the Health, Clinic and Education Information Evaluation Institute (HCEI, Kyoto, Japan), was used for this retrospective cohort study12,13. The HCEI is a not-for-profit research and service foundation in Japan. Real World Data Co., Ltd. (Kyoto, Japan) supports the HCEI in data collection and standardization. The RWD database includes the data of 20 million patients from 200 hospitals in Japan. This information consists of demographic data, prescriptions, laboratory results, diagnoses with International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes (ICD-10 codes) and
inpatient and outpatient procedures. These data are handled by allocating a unique identifier to each individual. We did not link these data with any other databases.

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of Kyoto University and was registered in the University hospital Medical Information Network (registration number: R000057896). We performed this study in accordance with the ethical standards set down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was not needed because the data were anonymized.

**Data collection and definitions**

We included inpatients aged 18 or older who were prescribed RAASis for at least one month prior to admission and were undergoing CAG during hospitalization between April 2005 and March 2019. Only first admissions with CAG and those who had a creatinine measurement within 30 days prior to CAG were included in our study. To restrict the focus to patients at risk of AKI, only patients with an estimated glomerular filtration rate (eGFR) of 15–60 mL/min/1.73 m² were included. To minimize the influence of acute myocardial infarction, unstable angina and the dosage of contrast media, we focused on patients undergoing CAG without percutaneous coronary intervention. Patients undergoing dialysis within 3 days after admission were excluded. Patients with missing values for the primary diagnosis were also excluded because the primary diagnosis was treated as one of the explanatory variables in a previous study and may influence the incidence of AKI. The exposure of interest was the presence of a dose reduction in RAASis during the 3 days before CAG was performed. The definition of dose reduction in RAASis was the change in the ratio of the prescribed dose to the defined daily dose (dose/DDD), which is defined by the World Health Organization. We calculated the dose/DDD of RAASis for all hospitalization days. If the dose/DDD was reduced, the patient was considered to have received a dose reduction of the RAASi and was included in the reduction group. For example, even if there was a change from an angiotensin receptor blocker (ARB) to an angiotensin-converting enzyme inhibitor (ACEi), we did not consider that a reduction unless there was a change in the dose/DDD. We included both discontinuations and dose reductions in the exposure group to avoid misclassification of discontinuations of only one medication for patients prescribed two or more RAASis. The difference in the impact on the development of AKI between discontinuations and reductions (excluding discontinuations) was assessed in the subgroup analysis.

**Propensity score matching**

We calculated the propensity score (PS) for each patient to balance the baseline characteristics of each group. PSs were estimated using a logistic regression model. The explanatory variables for the model were age, sex, Charlson Comorbidity Index (CCI) score, intensive care unit admission, baseline serum creatinine defined as the last measured serum creatinine level before CAG, primary diagnosis on admission, infection, acute heart failure, hemoglobin, hyponatremia, transfusion, hydration with extracellular fluid, intra-aortic balloon pumping, N-acetyl cysteine, platinum-based chemotherapy, and the use of diuretics, amphotericin B, aminoglycosides, glycopeptides, and nonsteroidal anti-inflammatory drugs. The definitions of these explanatory variables are described in Supplementary Data, Table S1. To ensure balance between the two groups, calipers were applied to maintain statistical power. Standardized differences were used to assess comparability between the two matched cohorts.

**Sample size calculation**

We also estimated the required sample size to detect the difference in the development of AKI between the two groups because the present study was planned based on the hypothesis that previous studies did not include a sufficient number of patients. The incidence of AKI was set at 10% in the reduction group and 15% in the control group. The effect size was based on a systematic review of 3 RCTs. The required sample size was calculated to be 525 in the reduction group and 1050 in the control group, assuming an alpha error of 0.05, a power of 0.8, and an enrollment ratio of 1:2.

**Outcome measures**

The primary outcome was AKI defined as an absolute increase in serum creatinine of ≥0.3 mg/dl from baseline, which was defined as the last measured serum creatinine level before CAG, within 48 h or a relative increase in serum creatinine of ≥50% within 7 days. We adopted the definition of AKI as renal injury after contrast use. This is because the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines indicated that contrast-induced nephropathy should be evaluated under the same criteria as AKI. The secondary outcomes were the need for dialysis and inhospital mortality.

**Statistical analysis**

Continuous variables are reported as the means and standard deviations, and categorical variables are reported as numbers and percentages. First, we described the characteristics of the patients in each group. Binary logistic regression was used to assess significant univariate associations between the reduction group and the control group with the outcomes for the PS-matched cohort. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). We defined the main result as the OR in the PS-matched cohort.

Sensitivity analysis was performed by changing the period of time of dose reduction from 1 to 14 days to detect the appropriate timing of dose reduction of RAASis. We also...
performed subgroup analysis to investigate the interaction with age (≤65 and >65 years), type of RAASi (ARB, ACEi, aldosterone blocker and direct renin inhibitor (DRI)), history of diabetes, baseline eGFR (<30, 30–45 and ≥45 mL/min/1.73 m²) and dose reduction or discontinuation. Two post hoc sensitivity analyses were performed to confirm the influence of the duration of reduction and the selection bias of including patients without additional serum creatinine measurements within 7 days after CAG. P values with a two-sided test were reported, and p < .05 was considered to indicate statistical significance. We used R ver. 4.1.2 to perform all statistical analyses.

Results
We identified 11,172 patients who were prescribed RAASis at least one month before admission and who underwent CAG during hospitalization from April 2005 to March 2019. Finally, 7843 patients were excluded for reasons such as age, baseline eGFR, dialysis within three days after admission and no primary diagnosis, and 3329 patients were ultimately included in this retrospective cohort study (Figure 1). Six hundred seventy-four patients were included in the reduction group, and 2655 were included in the control group in the entire cohort. A total of 3329 patients were matched using PSs. After PS matching, 671 patients were matched in the control group, and 1336 were included in the control group in the entire cohort. The baseline characteristics of each group in the entire cohort and PS-matched cohort are described in Table 1. The standardized differences for all variables were balanced after PS matching. AKI was observed in 34 (5.0%) patients in the reduction group and in 137 (5.2%) patients in the control group in the entire cohort. The risk of developing AKI was not different between the reduction group and the control group in the entire cohort (OR: 0.98, 95% CI: 0.66–1.44). In terms of the need for dialysis and in-hospital mortality, there were no significant differences between the two groups among all subgroups.

Sensitivity analysis
We performed a sensitivity analysis by changing the periods of dose reduction of RAASis to 1, 3, 7 and 14 days. The OR was 1.22 (95% CI: 0.75–1.98) for the period of 1 day and 1.17 (95% CI: 0.83–1.66) for the period of 14 days. The results of the sensitivity analysis are shown in Table 3. There was no significant difference between the reduction group and the control group for any length of reduction in the PS-matched cohort. To examine the impact of the duration of RAASis reduction, a post hoc analysis was performed excluding patients with RAASi reduction in a short period of time before CAG was performed (Table S3). Another post hoc sensitivity analysis was performed to confirm the selection bias of including patients without additional serum creatinine measurements within 7 days after CAG (Table S4). The results of the post hoc analyses were consistent with the results of the main analysis.

Subgroup analysis
We performed subgroup analysis for age, type of RAASi, history of diabetes and baseline eGFR to investigate the interaction with the dose reduction of RAASis. The results of the subgroup analysis are presented in Table 4. In terms of the type of RAASi, the sample size of the DRI subgroup was not enough to calculate the odds ratio, and we could not assess the interaction with reduction. For the other 3 types of RAASis, age, history of diabetes, baseline eGFR and degree of reduction, no significant difference was observed between the two groups among all subgroups.

Discussion
In the analysis of the PS-matched cohort of 2007 patients undergoing CAG who were at risk of AKI, we did not find any association between the reduction in the dose of RAASis.
Our findings were consistent with those of previous studies. There were no associations between a reduction in RAASI dose and the development of AKI or contrast-induced nephropathy (CIN). We hypothesized that these negative results were due to the small sample size and the excessively short period of RAASI dose reduction. Although the current study was designed to resolve these issues, the results were consistent with those of previous studies.

One possible explanation for these results may be attributed to hydration. Generally, RAASI treatment reduces the blood flow of the glomerulus by lowering blood pressure and dilating efferent arterioles. Contrast media also reduces the blood flow of the glomerulus through vasoconstriction and dilating efferent arterioles. Contrast-induced nephropathy (CIN) is thought to develop due to the synergistic effect of the decrease in renal blood flow and the development of AKI or contrast-induced nephropathy (CIN). We hypothesized that these negative results were due to the small sample size and the excessively short period of RAASI dose reduction. Although the current study was designed to resolve these issues, the results were consistent with those of previous studies.

and the development of AKI. The results were not changed in the sensitivity analysis. Moreover, no interactions were observed between the dose reduction of RAASIs and age, the type of RAASI or baseline eGFR in the subgroup analysis. Although the dose reduction of RAASIs was not associated with in-hospital mortality, the risk of need for dialysis was significantly higher in the reduction group.

Our findings were consistent with those of previous randomized controlled trials and systematic reviews. In previous studies, there were no associations between a reduction in RAASI dose and the development of AKI or contrast-induced nephropathy (CIN). We hypothesized that these negative results were due to the small sample size and the excessively short period of RAASI dose reduction. Although the current study was designed to resolve these issues, the results were consistent with those of previous studies.

One possible explanation for these results may be attributed to hydration. Generally, RAASI treatment reduces the blood flow of the glomerulus by lowering blood pressure and dilating efferent arterioles. Contrast media also reduces the blood flow of the glomerulus through vasoconstriction. Acute kidney injury is thought to develop due to the synergistic effect of the decrease in renal blood flow caused by contrast and RAASI treatment. However, as shown in the present study, 49.1% of the control group received extracellular fluid infusion, which may have interfered with
the mechanism of AKI development. Hydration with extracellular fluid infusion may have closed the gap between the two groups and resulted in no difference. Some studies have reported that hydration can prevent the development of AKI after contrast use. Another possible explanation of our results is attributed to the effect of RAASis on decreasing distal tubular consumption for tubular reabsorption. Since hypoxic AKI in the situation is principally attributed to outer medullary hypoxia, RAAS blockade may maintain medullary oxygenation by attenuating the GFR. Moreover, the attenuation of RAAS blockade itself may mask the deterioration in kidney function by increasing the GFR.

Strengths and limitations

There are 3 strengths in this study. First, we applied PS matching to balance the baseline characteristics between the reduction group and the control group. In the absence of randomization, the establishment of a valid comparison has increasingly been found in previous studies. This method has been recommended for assessing the association between contrast and AKI. Moreover, this method allowed us to estimate the odds ratio directly. Second, the sample size was much larger than that in previous studies. Even in the systematic review, the cumulative sample size of the RCTs was just 522 for this clinical question, and no association was observed between dose reduction and the development of AKI. We calculated the required sample size in advance and performed the analysis with greater statistical power than that in previous studies. In addressing sample size issues, our study is meaningful because this issue cannot be resolved by RCTs. Considering that there was no significant difference between the two groups even with a sufficient sample size and that the OR was 1.08 in the PS-matched cohort, the potential effect size of the dose reduction of RAASis would be trivial compared to hydration and other interventions, which were reported to have ORs of 0.29–0.31. Finally, we performed a sensitivity analysis by changing the periods of reduction in the RAASi dose. The results were consistent from a period of 1 day to 14 days. Because various types of RAASis were prescribed to the subjects and the half-life varied from 2 to 24 h, this sensitivity analysis was absolutely needed to make our results robust.

Conclusions

A reduction in the dose of RAASis did not prevent the development of AKI among patients undergoing CAG in a Japanese health care record database.

Transparency

Declaration of funding

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**Author contributions**

H.H. conducted the analysis and wrote the first draft of the manuscript. M.T. redrafted the manuscript and commented on the analysis. K.K. advised on the study design and analysis.

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Not applicable.

**Data availability statement**

Data sharing is not permitted under HCEI policy. Readers who are interested in our dataset can contact HCEI for data availability (https://www.hcei.or.jp).

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