Angiotensin II Receptor Blocker versus Angiotensin-Converting Enzyme Inhibitor for Postoperative Acute Kidney Injury after Cardiac Surgery

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Abstract

Background and aims: Acute Kidney Injury (AKI) after cardiac surgery is a serious complication and a risk factor of postoperative mortality. It has been suggested that Angiotensin II Receptor Blockers (ARBs) and Angiotensin-Converting Enzymes (ACE-Is) might be able to reduce the incidence of postoperative AKI after cardiac surgery. However, it remains unknown as to which of these drugs are better for protecting the renal function after cardiac surgery. We hypothesized that each of the ARBs and ACE-Is were able to differentially affect the postoperative AKI after cardiac surgery due to their differential drug efficacies. Thus, this current study investigated the association between the ARBs or ACE-Is and the postoperative AKI after cardiac surgery.

Methods: This retrospective single-center observational study was conducted in a community hospital. This study investigated 132 patients undergoing cardiac surgery with cardiopulmonary bypass between January 2013 and December 2015. The association between the incidence of AKI and the usage of ARBs or ACE-Is were analysed by using The Propensity Score Inverse Probability of Treatment Weighting (IPTW) method.

Results: Multiple logistic regression analysis after adjustment revealed that of the 132 patients examined, those receiving preoperative ARBs had significantly less incidence of postoperative AKI compared to the other patients (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.11-0.94; P=0.040). However, preoperative administration of ACE-Is were not associated with the incidence of postoperative AKI (OR, 0.73; 95% CI, 0.25-2.17; P=0.58).

Conclusions: Our analyses showed that ARBs rather than ACE-Is are potentially the preferable drug for perioperative renal protection. Prospective studies will need to be undertaken in order to elucidate the detailed effects of ARBs and ACE-Is on the kidney after undergoing cardiac surgery.

Keywords: Cardiac surgery; Logistic regression analysis; Cardiopulmonary bypass; Acute kidney injury; Angiotensin-converting enzymes

Introduction

Acute kidney injury (AKI) is a major postoperative complication after cardiac surgery. It has been reported that up to 30% of patients may develop AKI after cardiac surgery [1]. Even minimal increases in the serum creatinine levels (Cre) have been reported to worsen the survival rate [2]. Furthermore, postoperative AKI also increases short-term and long-term mortality, hospital course, and infectious complications [1,3]. Although the pathology of postoperative AKI after cardiac surgery has yet to be clearly defined, it is thought that many of the perioperative factors that cause ischemia-reperfusion injury and severe systemic inflammation could also be involved in postoperative AKI [4]. Previous studies have demonstrated that serum levels of angiotensin II (Ang II) increased during cardiac surgery and cardiopulmonary bypass (CPB) due to severe systemic inflammation [5]. Therefore, it is important to multilaterally modulate Ang II levels during cardiac surgery, as excessive Ang II can impair renal function [6]. Furthermore, therapeutic strategies using anti-Ang II agents may be able to prevent perioperative renal dysfunction.

Renin-Angiotensin System (RAS) blockers including angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE-Is) are used as anti-hypertensive drugs and cardiac or renal protective drugs. The benefit of using RAS blockers is that they decrease both Ang II and the activity of the angiotensin II type I (AT-I) receptor [7]. Although some studies have shown that RAS blockers decrease the incidence of postoperative AKI, the renal protective effects of RAS blockers in cardiac surgery remain controversial [8].

The functional mechanisms of ARBs differ from those observed for ACE-Is. ARBs selectively inhibit AT-I, while ACE-Is inhibit the conversion of Ang I to Ang II. Previous studies have compared the renal protective effects between ARBs and ACE-Is in chronic nephropathies and cardiovascular disease [9]. However, there have yet to be any studies focusing on the differential effects of ARBs and ACE-Is on postoperative AKI after cardiac surgery.

As RAS blockers are widely used for patients undergoing cardiac surgery, it is important to understand the difference in the perioperative effects on the kidney between the ARBs and ACE-Is. We hypothesized that each of the ARBs and ACE-Is were able to differentially affect the postoperative AKI after cardiac surgery due to their differential drug efficacies. Therefore, this retrospective study...
investigated the differences in the effects of ARBs and ACE-Is on the postoperative renal function after cardiac surgery.

**Methods**

**Patients**

This retrospective study was approved by the research ethics committee of Asahikawa City Hospital, Asahikawa, Japan (2016–No. 24, June 7th 2017) and was conducted in accordance with the Declaration of Helsinki. All patient data were anonymized prior to being analysed. The study retrospectively reviewed the medical records of adult patients who underwent cardiac surgery with CPB at Asahikawa City Hospital between January 2014 and December 2016. Emergency cases, patients with deep hypothermic arrest below 30°C during CPB, and patients with perioperative hemodialysis were excluded.

**Anesthetic and CPB management**

Premedication drugs were not administered in any of the patients in this study. General anesthesia was performed using midazolam, sevoflurane, fentanyl, remifentanil, and rocuronium. During CPB, we used propofol with a target-controlled infusion (TCI) pump. Depth of anesthesia was monitored using a bispectral index (BIS) monitor, with the value controlled between 40 and 60. Perfusionists maintained an appropriate circulation by monitoring arterial blood pressure with the use of near infrared spectroscopy (NIRS). Hypothermia during CPB was maintained around 34°C.

**Circulation management**

The circulation of all patients was managed by a Swan-Ganz catheter in order to optimize cardiac output (CO) and systemic vascular resistance (SVR) with the use of catecholamine, dilator, and cardiac pacing.

**ARB and ACE-I drugs**

We reviewed the electronic records of our hospital to determine the use of ARBs and ACE-Is. Administrations of all ARBs and ACE-Is were stopped on the morning of the operation. We divided the patients into three groups. Patients in Group ARB and in Group ACE-I were preoperatively prescribed ARB and ACE-I, respectively. Patients who did not preoperatively receive either ARB or ACE-I were classified as Group N.

**Variables**

All of the variable data for the patients were collected from the electronic or paper medical records of our hospital.

The demographic data included sex, age, body surface area (BSA), and the New York Heart Association (NYHA) classification. Preoperative variables included medical history, medications, and laboratory data. Based on the medical history, we chose patients who were current and ex-smokers, or who had cerebrovascular disease (CVD), arteriosclerosis obliterans (ASO), and atrial fibrillation (Af). Preoperative prescriptions included oral hypoglycemic drugs, insulin injections, beta-blockers, alpha blockers, calcium blockers, diuretics, statin, and antiplatelet drugs. For the preoperative laboratory data, we used the preoperative hematocrit, Cre, estimated glomerular filtration rate (eGFR), brain natriuretic peptide (BNP), and left ventricular ejection fraction (LVEF). The intraoperative variables evaluated included reoperation, the type of surgery (valve, coronary artery bypass graft (CABG), or valve and CABG), CPB time and aorta cross-clamping (AX) time, intraoperative use of intra-aortic balloon pumping (IABP), minimum rectal temperature, urine output during CPB, dosage of fentanyl, bleeding, total urine output, total balance and minimum oxygen delivery (DO₂) and maximum extraction ratio of oxygen (ERO₂) during CPB.

Arterial oxygen content (ml/100 ml) (CaO₂): 1.38*Hb (mg/dl)*arterial oxygen saturation (%) (SaO₂) + 0.003*O₂ tension (mmHg)

Oxygen delivery (ml/min/m²) (DO₂): CaO₂*10*CPBF flow (L/min/m²) (CPBF)

Oxygen consumption (ml/min/m²) (VO₂): DO₂–central venous oxygen saturation (%) (ScvO₂)*10*CPBF

ERO₂ (%): VO₂ / DO₂

**Acute kidney injury**

AKI was defined by using the Kidney Disease Improving Global Outcomes (KDIGO) classification. The criteria include the absolute change and percentage change in the Cre within 48 h after surgery. Patients who exhibited an increase in their Cre of 0.3 mg/dl or more or an increase of 150% more than baseline were diagnosed as AKI [10].

**Statistical analysis**

Continuous variables are expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR). We used the Shapiro-Wilk test to check whether the continuous variables followed normal distributions. An analysis of variance (ANOVA) was used to compare the values for each group. Frequencies are expressed as numbers and percentages, with comparisons of the frequencies performed by Fisher’s exact test.

![Figure 1: Study cohort. CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; CRF, chronic renal failure.](image-url)
### Table 1: Preoperative clinical characteristics of patients.

| Variable                     | Overall (n=132) | Group ARB (n=42) | Group ACE-I (n=25) | Group N (n=65) | p value |
|------------------------------|-----------------|-------------------|--------------------|----------------|---------|
| Demographic data            |                 |                   |                    |                |         |
| Male n (%)                   | 81/51 (61.2%)   | 28/14 (68.6%)     | 20/5 (20%)         | 33/32 (50.8%)  | 0.027   |
| Age, Year                    | 69 (63-74)      | 71 (65-75)        | 67 (62-75)         | 69 (58-74)     | 0.11    |
| BSA m²                       | 1.61 (± 0.17)   | 1.63 (± 0.159)    | 1.63 (± 0.159)     | 1.57 (± 0.162) | 0.3     |
| NYHA˚                        | 2.0 (1.0-2.0)   | 1.5 (1-4)         | 2 (2-2)            | 2 (1-2)        | 0.18    |
| Medication                   |                 |                   |                    |                |         |
| Oral Hypoglycemic drugs      | 23 (17.4%)      | 11 (26.2%)        | 2-8%               | 10 (15.4%)     | 0.16    |
| Insulin Injection            | 14 (10.6%)      | 4 (9.52%)         | 1-4%               | 9 (13.8%)      | 0.42    |
| Beta Blockers                | 42 (31.8%)      | 16 (38.1%)        | 10-40%             | 16 (24.6%)     | 0.22    |
| Alpha Blockers               | 2 (1.52%)       | 1 (2.38%)         | 0%                 | 1 (1.53%)      | 1       |
| Calcium Blockers             | 49 (37.1%)      | 17 (40.5%)        | 6 (24%)            | 26 (66.7%)     | 0.33    |
| Diuretics                    | 52 (39.4%)      | 17 (40.5%)        | 12 (48%)           | 23 (35.4%)     | 0.53    |
| Statin                       | 55 (41.7%)      | 17 (40.5%)        | 10-40%             | 28 (43.1%)     | 0.95    |
| Antiplatelet Drugs           | 53 (40.2%)      | 18 (42.9%)        | 8 (32%)            | 27 (41.5%)     | 0.67    |
| Medical History              |                 |                   |                    |                |         |
| Current Smoker               | 17 (12.9%)      | 4 (9.52%)         | 5 (20%)            | 8 (12.3%)      | 0.48    |
| Ex-smoker                    | 64 (48.5%)      | 21 (50.0%)        | 12-48%             | 31 (47.7%)     | 0.97    |
| CVD                          | 6 (4.55%)       | 4 (9.52%)         | 0%                 | 2 (3.08%)      | 0.27    |
| ASO                          | 15 (11.4%)      | 5 (11.9%)         | 2-8%               | 8 (12.3%)      | 0.88    |
| Af                           | 31 (23.5%)      | 8 (19.0%)         | 9 (36%)            | 14 (21.5%)     | 0.26    |
| Preoperative Laboratory Data |                 |                   |                    |                |         |
| Hematocrit %                 | 37.7 (± 4.26)   | 38.1 (± 4.03)     | 39.3 (± 3.55)      | 36.8 (± 4.47)  | 0.029   |
| Creatinine mg/dl             | 0.83 (0.68-0.97)| 0.87 (0.72-1.04)  | 0.88 (0.80-0.95)   | 0.76 (0.62-0.97)| 0.15    |
| eGFR ml/min/1.73m²           | 64.9 (± 19.0)   | 60.9 (± 18.4)     | 65.8 (± 11.8)      | 64.2 (± 21.3)  | 0.25    |
| BNP pg/ml                    | 40.6 (16.9-140) | 34.5 (21.9-99.2)  | 32.7 (15.2-128.6)  | 43.2 (15.7-154.0)| 0.8     |
| LVEF %                       | 65 (59-70)      | 66.0 (61.0-70.3)  | 61.0 (55.0-70.0)   | 65.5 (60.0-70.3)| 0.25    |

**Results**

**Study population**

The present study enrolled 226 patients. After excluding those who did not meet the study criteria, 132 patients remained and were analysed (Figure 1).

**Preoperative and intraoperative variables**

ARB was administered in 42 patients (32%), while 25 patients (18%) received ACE-I and 65 patients (49%) received neither ARB nor ACE-I.
Table 1 presents the preoperative characteristics of the patients. There were significant statistical differences found among the three groups for the sex ratio and the preoperative hematocrit of the patients.

Table 2 presents the intraoperative characteristics of the patients. No significant differences were observed among the three groups for any of the parameters.

| Variable                      | Overall (n=132) | Group ARB (n=42) | Group ACE-I (n=25) | Group N (n=65) | p value |
|-------------------------------|-----------------|------------------|--------------------|----------------|---------|
| Type of Surgery               |                 |                  |                    |                |         |
| Intraoperative IABP          | 3 (2.27%)       | 1 (2.38%)        | 2 (8%)             | 0 (0%)         | 0.07    |
| Reoperation                  | 6 (4.55%)       | 3 (7.14%)        | 0 (0%)             | 3 (4.55%)      | 0.4     |
| CABG                         | 41 (31.1%)      | 15 (35.7%)       | 8 (32%)            | 18 (27.7%)     | 0.66    |
| Valve                        | 89 (63.4%)      | 28 (66.7%)       | 18 (72%)           | 43 (66.2%)     | 0.91    |
| Both Surgeries               | 15 (11.4%)      | 7 (16.7%)        | 4 (16%)            | 4 (6.15%)      | 0.15    |
| Intraoperative Data          |                 |                  |                    |                |         |
| CPB time, min                | 172 (141-225)   | 168 (144-239)    | 176 (138-236)      | 171 (139-217)  | 0.6     |
| AX time, min                 | 99 (79-134)     | 97 (82-129)      | 104 (76-148)       | 100 (79-128)   | 0.97    |
| Minimum Rectal BT, C         | 34.0 (33.9-34.1)| 34.0 (33.9-34.1)| 34.0 (33.9-34.4)   | 34.0 (33.9-34.1)| 0.31    |
| Urine Output during CPB, ml/kg | 3.86 (2.60-6.30) | 3.39 (2.08-5.69) | 3.83 (3.08-6.30)   | 3.91 (2.79-6.30)| 0.43    |
| Dosage of Fentanyl, mg        | 40.0 (40.0-50.0)| 40.0 (40.0-50.0)| 45.0 (40.0-50.0)   | 40.0 (40.0-43.5)| 0.19    |
| Bleeding, ml                 | 1085 (608-1913) | 1100 (705-1678)  | 890 (640-1690)     | 1160 (590-2100)| 0.9     |
| Total Urine output, ml/kg    | 28.0 (19.0-38.4)| 27.5 (17.9-32.5)| 25.3 (15.9-38.0)   | 28.6 (20.6-44.6)| 0.19    |
| Total Balance, ml            | -515 (-1123-465)| -250 (-758-958)  | -390 (-1160-460)   | -660 (-1320-340)| 0.11    |
| Minimum DO, ml/min/m²         | 281 (243-329)   | 287 (258-335)    | 288 (247-328)      | 278 (237-322)  | 0.95    |
| Maximum ERO₂, %              | 23 (21-26)      | 23 (21-26)       | 24 (22-27)         | 24 (21-26)     | 0.61    |

Table 2: Intraoperative clinical characteristics of patients.

Incidence of postoperative AKI

Postoperative AKI occurred in 32 out of the 132 total patients (24%). AKI occurred in 5 patients (12%) of Group ARB, in 6 patients (24%) of Group ACE-I, and in 21 patients (32%) of group N (P=0.055) (Figure 2).

Univariate and multivariate logistic regression analyses

There were 132 patients examined by these analyses. Univariate logistic regression analysis demonstrated that the BSA, preoperative use of ARB and diuretics, preoperative hematocrit, preoperative atrial fibrillation, valve surgery, CPB time and AX time were significantly related to the postoperative AKI (P<0.05, Table 3). Table 4 shows the results of multivariate logistic stepwise regression analysis. AX time was excluded from multivariate logistic regression because of multicollinearity between CPB time and AX time. The stepwise regression model indicated that there were four variables (preoperative hematocrit, CPB time, and preoperative use of ARB and diuretics) that had a strong relationship with the postoperative AKI. ARB use was found to be associated with postoperative AKI (adjusted OR 0.22, 95% CI 0.059-0.66, P=0.012, Table 4).
| Variable                          | OR   | 95% CI       | P value |
|----------------------------------|------|--------------|---------|
| **Demographic data**             |      |              |         |
| Male                             | 0.76 | 0.33-1.71    | 0.50    |
| Age                              | 1.03 | 0.99-1.08    | 0.15    |
| BSA                              | 0.073| 0.0056-0.83  | 0.039   |
| NYHA                             | 1.66 | 0.96-2.91    | 0.068   |
| **Medication**                   |      |              |         |
| ACE-I                            | 0.98 | 0.33-2.61    | 0.82    |
| ARB                              | 0.32 | 0.10-0.83    | 0.029   |
| Oral hypoglycemic drugs          | 1.13 | 0.38-3.03    | 0.82    |
| Insulin injection                | 1.29 | 0.33-4.18    | 0.69    |
| Beta Blocker                     | 1.40 | 0.60-3.20    | 0.43    |
| Alpha Blocker                    | NA   | NA           | NA      |
| Calcium blockers                 | 1.02 | 0.44-2.31    | 0.96    |
| Diuretics                        | 4.25 | 1.86-10.2    | 0.00078 |
| Statin                           | 0.67 | 0.28-1.51    | 0.34    |
| Antiplatelet drugs               | 0.72 | 0.31-1.64    | 0.45    |
| **Medical history**              |      |              |         |
| Current smoker                   | 0.96 | 0.25-2.96    | 0.99    |
| Ex-smoker                        | 0.55 | 0.24-1.24    | 0.16    |
| CVD                              | 1.60 | 0.21-8.63    | 0.60    |
| ASO                              | 0.45 | 0.067-1.74   | 0.31    |
| AF                               | 3.80 | 1.59-9.17    | 0.0027  |
| **Preoperative laboratory data** |      |              |         |
| Hematocrit                       | 0.86 | 0.77-0.94    | 0.0025  |
| Creatinine                       | 0.96 | 0.25-3.16    | 0.95    |
| eGFR                             | 1.00 | 0.98-1.02    | 0.93    |
| BNP                              | 1.00 | 1.00-1.00    | 0.65    |
| LVEF                             | 0.99 | 0.95-1.03    | 0.45    |
| **Type of Surgery**              |      |              |         |
| Intraoperative IABP              | NA   | NA           | NA      |
| Reoperation                      | 1.60 | 0.21-8.63    | 0.99    |
| CABG                             | 0.43 | 0.15-1.08    | 0.99    |
| Valve                            | 3.31 | 1.26-10.4    | 0.024   |
| Both surgeries                   | 0.45 | 0.067-1.74   | 0.99    |
| **Intraoperative data**          |      |              |         |
| CPB time                         | 1.01 | >1.00-1.02   | 0.010   |
| AX time                          | 1.01 | >1.00-1.02   | 0.0075  |
| Minimum rectal BT                | 0.95 | 0.64-1.56    | 0.80    |
| Urine output during CPB          | 1.03 | 0.97-1.11    | 0.59    |
| Dosage of fentanyl               | 0.99 | 0.94-1.03    | 0.52    |
| Bleeding                         | 1.00 | 1.00-1.00    | 0.066   |
| Total urine output               | 1.00 | 0.99-1.02    | 0.59    |
| Total balance                    | 1.00 | 1.00-1.00    | 0.81    |
| Minimum DO<sub>2</sub>           | 1.00 | <1.00-1.01   | 0.41    |
| Maximum ERO<sub>2</sub>          | 1.21*103 | 0.12-1.54*107 | 0.13 |

**Table 3**: Univariate logistic regression analysis between AKI and perioperative factors.

**Propensity score IPTW method**

There were 132 patients examined by this analysis. After using the IPTW method to adjust the perioperative variables, we found that the use of ARB was significantly associated with less incidence of postoperative AKI (adjusted OR 0.33, 95% CI 0.11-0.94, P = 0.040). However, the use of ACE-I was not associated with the postoperative AKI (adjusted OR 0.73, 95% CI 0.25-2.17, P=0.58) (Table 5).

| Variable                  | OR   | 95% CI       | P value |
|---------------------------|------|--------------|---------|
| Preoperative Hematocrit   | 0.87 | 0.77-0.97    | 0.013   |
| Diuretics                 | 3.27 | 1.30-8.54    | 0.013   |
| CPB time                  | 1.01 | >1.00-1.02   | 0.033   |
| ARB                       | 0.22 | 0.059-0.66   | 0.012   |

**Table 4**: Multivariable regression analysis.

**Table 5**: multivariable regression analysis with propensity score Inverse Probability of Treatment Weighting (IPTW) method.

**Discussion**

We hypothesized that each of the ARBs and ACE-Is were able to differentially affect the postoperative AKI after cardiac surgery due to their differential drug efficacies. Current study findings demonstrated the possibility that preoperative ARBs can decrease the incidence of postoperative AKI. In addition, preoperative hematocrit, CPB time, and the use of diuretics were associated with postoperative AKI.

AKI is an important postoperative complication and can increase long- and short-term mortality, hospital course and infectious complications [1,3]. It has been reported that after cardiac surgery, up to 30% of postoperative patients have postoperative AKI [1]. Important causes of AKI after cardiac surgery include renal cellular ischemia, as well as tubular epithelial and vascular injury [4]. There are many factors that have been considered to be risks of ischemic kidney injury after cardiac surgery including, hemodynamic variation during...
the operation and CPB, perioperative anemia, existing comorbidities and anti-auto regulation drugs (e.g., ARBs, ACE-Is and non-steroidal anti-inflammatory drugs) [1]. Systemic inflammation has also been reported to be a cause of AKI after cardiac surgery [4]. It has been reported that the invasive procedures and contact of the blood components with the artificial surface of the CPB are responsible for a lot of the pro-inflammatory responses that occur during the cardiac surgery [4].

In order to reduce the incidence of AKI after cardiac surgery, anesthesiologists need to take into account the complex perioperative factors that are present. Excessive increases in Ang II, which can be induced by the cardiac surgery and CPB, are considered to be one of the causes of postoperative renal dysfunction [5,6]. Thus, it is important to multilaterally control perioperative Ang II to ensure the renal function will be preserved.

Ang II in the kidney activates multiple intracellular signalling pathways and induces vasoconstriction, inflammation, renal cell growth, mutagenesis, apoptosis, migration and differentiation through AT-I activation. Thus, Ang II plays an important role in the pathogenesis of renal injury. Ang II also activates angiotensin II receptor type II (AT-II), which has renal protective effects such as vasodilation and anti-proliferation of the renal cells (Figure 3) [11].

**Figure 3:** Drug efficacies of ARB or ACE-I. ARB: Angiotensin Receptor Blocker; ACE-I: Angiotensin-Converting Enzyme Inhibitor; Ang I: Angiotensin I; Ang II: Angiotensin II; AT-I: Angiotensin II Receptor Type I; AT-II: Angiotensin II Receptor Type II.

Many patients who undergo cardiac surgery have been previously administered RAS blockers in order to treat hypertension and progression of renal and cardiac disease. As one of the benefits of treatments with RAS blockers is a decrease in the activity of AT-I, clinicians consider these blockers to be renal protective drugs. Preoperative use of RAS blockers on the day of the operation is considered to be contraindicated as these drugs can cause intraoperative hypotension and renal hypo-perfusion during the surgical procedure [12]. However, there is evidence that suggests the withdrawal of RAS blockers prior to cardiac surgery may reduce the incidence of AKI [13]. Therefore, at our institute, RAS blockers are stopped on the day of the operation in all of our patients.

At the present time, the association between the preoperative long-term use of RAS blockers and the postoperative AKI remains unclear. One meta-analysis has shown that long-term RAS blocker therapy was associated with significant reductions in the risk of AKI [14]. On the contrary, another meta-analysis indicated that long-term use of RAS blockers was associated with increased odds for postoperative AKI [8]. It is possible that differences in the withdrawal period, and the type of RAS blockers used might have affected these outcomes.

The effects and renal protective pathway associated with ARBs and ACE-Is are known to differ. For example, previous studies have compared the use of ARBs and ACE-Is in chronic nephropathies and cardiovascular disease. Study results showed that ARBs and ACE-Is do provide the same benefits with regard to the progression of chronic renal disease [9]. However, the efficacies seen during chronic treatments might not be the same during surgeries and CPB due to the occurrence of renal cellular ischemia and strong systemic inflammation. Interestingly, there has yet to be a study comparing the postoperative renal protective effects between ARBs and ACE-Is.

Our current results showed the patients with ARBs had a lesser incidence of postoperative AKI versus ACE-Is. It is possible that differences in the drug efficacies between ARBs and ACE-Is might have been responsible for the difference in the incidence of AKI. ACE-Is decrease the activity of not only AT-I but also AT-II through suppression of the Ang II production [9]. On the other hand, ARBs selectively inhibit AT-I and suppress Ang II production in the kidney at the same time in order to maintain adequate AT-II activity (Table 3) [11]. Thus, the differential action on AT-II by ARBs and ACE-Is may be the reason for the different outcomes observed in our current study.

Our results also showed that the use of ACE-Is was not associated with postoperative AKI. Furthermore, it has been reported that ACE-Is are associated with another renal protective pathway that causes increases in bradykinin and nitric oxide, with a net result of vasodilation [15]. However, other previous studies have reported conflicting results, with ACE-Is either not associated with postoperative AKI or shown to increase the incidence of postoperative AKI [16,17]. Only a few cohort studies and one randomized controlled trial have confirmed the perioperative renal protective effects of ACE-Is [18,19]. During CPB, serum bradykinin levels can progressively increase [19]. Thus, due to the excessive bradykinin, ACE-Is may induce inadequate low perfusion, which can subsequently lead to ischemic-reperfusion renal injury.

In addition, our results also showed that preoperative hematocrit, CPB time, and the use of diuretics were associated with postoperative AKI. Moreover, there are many studies that have reported that preoperative anemia and CPB time are associated with postoperative AKI after cardiac surgery [1,4]. According to one retrospective study, the use of diuretics was considered to be a risk factor of postoperative AKI after non-cardiac surgery because the patients with preoperative use of diuretics had more preoperative complications (including heart failure or chronic renal disease) and thus they could not tolerate the perioperative volume variation [20,21]. In contrast, however, other studies have shown that the use of diuretics was not related to postoperative AKI after cardiac surgery [22]. Therefore, when all of the
results are taken together, the use of preoperative diuretics for patients undergoing cardiac surgery remains controversial.

There were some limitations for this current study. First, the type and dosage of the ARBs or ACE-Is used in each patient differed. Since half-lives and efficacies can vary from drug to drug, the effects on the kidney preoperatively might also vary even if all of the ARBs and ACE-Is were withdrawn on the morning of the operation. Second, it was not possible to evaluate the association between the circulation parameters, including amounts of catecholamine, dilator, CO, and SVR, and the postoperative AKI, as these parameters can constantly change during an operation. Moreover, as we considered these parameters to be very unstable and clinically meaningless factors with regard to AKI, we did not evaluate these in this study. However, during CPB, the circulation was evaluated by using DO2 and ERO2. Third, this study only evaluated a small number of patients. As a result, the analytical power of this study may not have been sufficient. Therefore, a further prospective study will need to be undertaken in the future in order to definitively investigate the effects of ARBs or ACE-Is on the kidney.

Conclusion

Patients with a preoperative use of ARBs had a lesser incidence of postoperative AKI after cardiac surgery compared to ACE-Is. These results suggest that ARBs may be a preferable drug for perioperative renal protection versus ACE-Is. Further prospective studies will need to be performed in order to elucidate the detailed effects of ARBs or ACE-Is on the postoperative kidney after cardiac surgery.

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