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Renin-Angiotensin-Aldosterone System Blockade in Critically Ill Patients Is Associated with Increased Risk for Acute Kidney Injury

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Acute kidney injury (AKI) is a major clinical problem and a predictor of outcomes in critically ill patients who frequently required treatments in the intensive care unit (ICU). Renin-angiotensin-aldosterone system (RAAS) blockers are commonly used for treating hypertension but demands caution because of accompanying illnesses including AKI. The aim of this study was to evaluate whether the use of RAAS blockers affected the incidence of AKI in ICU patients. From a total of 26,287 patients who were admitted to the ICU from January 2003 to December 2013 were included in the final analyses. The primary outcome was the incidence of AKI based on the prescription of RAAS blockers. The secondary outcomes were all-cause mortality. RAAS blocker users were more likely to develop AKI ($P < 0.001$) and remained an independent risk factor for AKI (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.37-1.79; $P < 0.001$) after adjusting confounding factors. There was no significant difference in the cumulative 90-day survival rate between the RAAS blocker users and non-users ($P = 0.381$). However, the adjusted mortality risk associated with AKI was 1.38 (95% CI, 1.22 to 1.56; $P < 0.001$) and increased as the severity of AKI stage increased from 1 to 3: 1.17 (1.02 to 1.36), 1.77 (1.45 to 2.16), and 1.93 (1.55 to 2.41; $P < 0.01$ for the trend). RAAS blockers may have a harmful influence to increase the incidence of AKI and temporary withholding of these medications may deserve careful consideration in ICU patients.

Keywords: acute kidney injury; intensive care unit; mortality; outcomes; renin-angiotensin-aldosterone system blocker
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Introduction

Acute kidney injury (AKI) commonly develops in up to 67% of critically ill patients in intensive care units (ICUs) (Vivino et al. 1998; de Mendonca et al. 2000; Chertow et al. 2006) and is associated with more complicated hospital stay and an increased risk of death (ranging from 28% to 90% of patients with AKI) (Uchino et al. 2005; Hoste et al. 2006). These results may be due to various definitions of AKI, as more than 35 definitions of AKI have been reported (Kellum 2002). Renin-angiotensin-aldosterone system (RAAS) blockade is achieved with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), which reduces cardiovascular mortality in diverse clinical situations (Arora et al. 2008). RAAS blockers have been shown to be effective at treating hypertension and decreasing cardiovascular mortality and morbidity. These agents are commonly used to treat hypertension, coronary artery disease, congestive heart failure, and diabetic nephropathy (Casas et al. 2005; Winkelmayer et al. 2006; Lakhdar et al. 2008; Matchar et al. 2008). The long-term use of RAAS blockers can provide end-organ protection and reduce adverse events in patients with cardiovascular disease (CVD) and chronic kidney disease (CKD) (Stojiljkovic and Behnia 2007).

Although the use of RAAS blockers increases the survival rate of patients with CVD and prevents the progression of renal problems, these medications have been associ-

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ated with the development of AKI in settings where maintenance of glomerular filtration requires efferent arteriolar constriction, which is blocked by RAAS blockades (Schoolwerth et al. 2001; Toto 2001). However, the impact of RAAS blockade on outcomes in critically ill patients who are susceptible to AKI remains uncertain. Thus, we examined the association between the use of RAAS blockers and the development of AKI in critically ill patients in the ICU, as well as with the major outcomes of patients with AKI.

Materials and Methods

Study design and setting

This retrospective study analyzed the effect of RAAS blockers on the emergence of AKI in critically ill patients.

Study population

We analyzed patients admitted to the ICU at Gachon University Gil Medical Center from January 2003 until December 2013. A total of 58,643 patients were screened. Selected patients were excluded, including those < 18 years old (n = 10,782) and patients who were initially admitted to facilities other than the ICU (n = 21,557). Patients without baseline creatinine levels were also excluded (n = 17). Therefore, 26,287 patients were included in the final analyses. This study was approved by the Institutional Review Board (IRB) at Gachon University Gil Medical Center (GAIRB2014-300). We performed analyses in a retrospective observational design without additional interventions; hence, the IRB waived the requirement to obtain signed informed consent.

Variables

Clinical data were collected using a standardized form from electronic medical records at the time of ICU admission. Baseline data included demographics (age and sex), biochemical data (blood gas analysis, white blood cell count [WBC], levels of hemoglobin [Hb], hematocrit [Hct], platelets, blood urea nitrogen [BUN], creatinine, albumin, erythrocyte sedimentation rate [ESR], and highly sensitive C-reactive protein [hs-CRP]), clinical data (mechanical ventilation, sepsis at admission, use of inotropes, and transfusion), comorbidities before ICU admission identified through ICD-10 diagnosis (history of CKD, diabetes mellitus [DM], preexisting hypertension [HTN], CVD, chronic liver disease [CLD], asthma, chronic obstructive pulmonary disease [COPD]), and use of potentially nephrotoxic medications (ACEIs, ARBs, non-steroidal anti-inflammatory drugs [NSAID], intravascular contrast media within 24 hours of developing AKI, and recent [< 6 months] history of chemotherapy with platinum-based regimen). Estimated glomerular filtration rate (eGFR) was calculated according to the four-variable Modification of Diet in Renal Disease (MDRD) Study equation.

Cardiovascular risk factors were evaluated at enrollment. HTN was defined as a documented blood pressure ≥ 140/90 mmHg or a prescription for an antihypertensive agent. A positive history of CVD was defined as a documented history of myocardial infarction, angina pectoris, ischemic heart disease, cerebrovascular accident, atrial fibrillation or flutter, or peripheral atherosclerotic vascular disease. DM was defined as treatment with an oral anti-diabetic agent or insulin. The definition of CKD was mainly based on evidence of kidney damage (proteinuria estimated by dipstick as trace or greater) with underlying disease or eGFR (< 60 ml/min/1.73 m^2) (National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Group 2002).

Outcomes

The primary outcome was the development of AKI as defined by KDIGO Clinical Practice Guideline for AKI (Kidney Disease: Improving Global Outcomes (KDIGO) Work Group 2012), which is a relative increase ≥ 50% from the baseline value or an absolute increase in serum creatinine value ≥ 0.3 mg/dl within 48 hours. AKI is staged for severity according to the following criteria; stage 1, increase in serum creatinine ≥ 0.3 mg/dl, or ≥ 1.5- to 2 fold from baseline; stage 2, > 2- to 3- fold from baseline; stage 3, > 3- fold from baseline, or ≥ 4.0 mg/dl, or needed to initiate renal replacement therapy. The risk factors for development of AKI were assessed from the point of ICU admission. The secondary outcome was all-cause mortality at 90 days.

Statistical analysis

We obtained data for age, sex, history, AKI risk factors, and laboratory findings. Data are shown as means ± standard deviations or percentages. The *t*-test, the χ^2 test, or Fisher's exact test was used to assess the mean differences or proportions of variables, as appropriate. Variables were selected was based on all measured clinical and suspected prognostic factors for outcome. Multivariate logistic regression analyses were conducted to reveal independent risk factors for developing of AKI and to obtain the odds ratio (OR) and 95% confidence interval (CI). Multiple Cox regression models were used to determine the hazard ratio (HR) and risk factors for death at 90 days.

We performed analyses with the stepped regression models. First, we conducted logistic regressions using demographic variables (Model 1). Second, we included co-morbidities (CKD, DM, HTN, CVD, CLD, COPD, and asthma) (Model 2). Third, we added other AKI risk factors, such as sepsis, transfusion, and use of inotropes, a ventilator, aminoglycosides, vancomycin, colistin, amphotericin, NSAIDs, contrast medium, and chemotherapy (Model 3). Finally, we added laboratory findings to the model (Model 4). SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analyses. P value < 0.05 was considered to indicate significance.

- Model 1: Use of a RAAS blocker and patient demographics such as age and sex.
- Model 2: Use of a RAAS blocker, demographics, and co-morbidities, such as CKD, DM, HTN, CVD, CLD, COPD, and asthma.
- Model 3: Use of a RAAS blocker, demographics, co-morbidities, and other AKI risk factors, such as sepsis, transfusion, and the use of inotropes, use of a ventilator, and administration of aminoglycosides, vancomycin, colistin, amphotericin, NSAIDs, contrast media, and chemotherapy.
- Model 4: Use of a RAAS blocker, demographics, co-morbidities, other AKI risk factors, and laboratory findings, such as Hb, hs-CRP, albumin, SO_2, WBC count, platelet count, and HCO_3.

Results

Baseline characteristics

The patients included this study were admitted to the ICU at our hospital from January 1, 2003 to December 31, 2013. A total of 26,287 eligible patients were enrolled for analyses of the 58,643 screened subjects (Fig. 1).

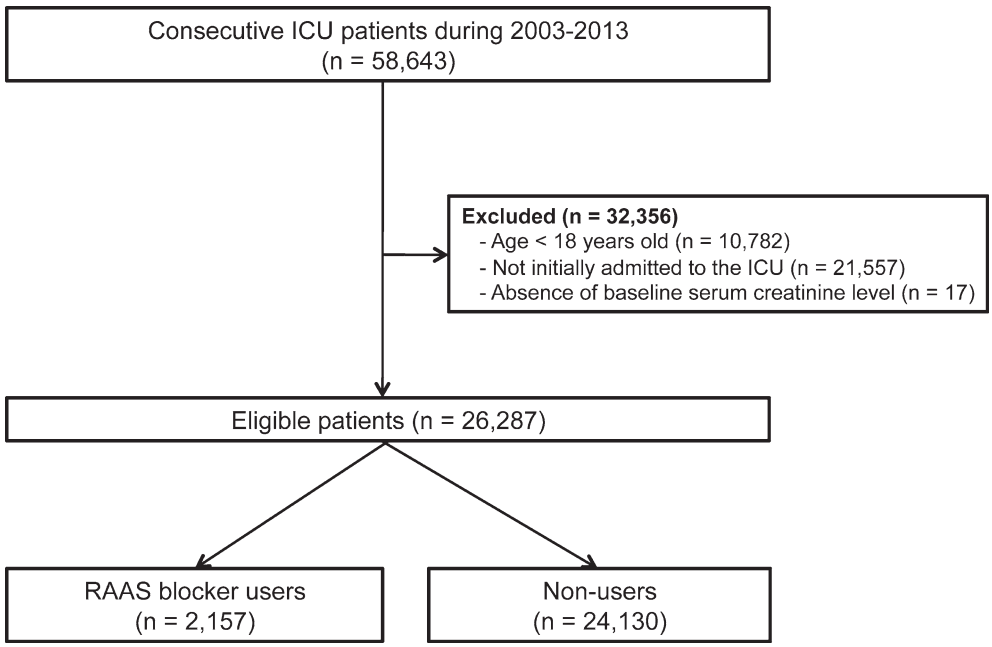

Fig. 1. Cohort formation.

The baseline characteristics of the study subjects are described in Table 1. RAAS blockers were prescribed for 8.2% (2,157 of 26,287) of patients. The number of multiple (≥ 2) RAAS blocker users is 186. Female and older patients were more commonly RAAS blocker users. These patients also commonly had CKD, sepsis, DM, HTN, and previous CVD and were more likely to have received inotropes and mechanical ventilator care.

Development of AKI and risk factors

The RAAS blocker users showed a significantly higher rate of developing AKI during their ICU stay than that of non-users (49.7% vs. 17.3%, P < 0.001; Table 1). In univariate analyses, the use of RAAS blockers was significantly associated with the development of AKI. The following factors were also related to the development of AKI: older age; female sex; CKD; DM; HTN; CVD; CLD; COPD; asthma; sepsis; use of inotropes; history of transfusion; use of a ventilator; use of nephrotoxic agents, such as aminoglycosides, vancomycin, amphotericin, NSAIDs, and contrast media; history of platinum-based chemotherapy within 6 months of ICU admission; and laboratory findings, such as blood gas analysis, WBC, Hb, Hct, platelets, BUN, creatinine, albumin, ESR, and hs-CRP (data not shown). Even after adjusting for these covariates, the use of a RAAS blocker was significantly associated with the development of AKI (OR, 1.56; 95% CI, 1.37-1.79; P < 0.001; Table 2). There are no differences for development of AKI between single and multiple RAAS blocker users (data not shown).

Incidence and risk factors for 90-day mortality

We also examined the cumulative 90-day all-cause mortality rates of the RAAS blocker users and non-users. A univariate analysis demonstrated that the use of a RAAS blocker was associated with increased patient mortality at 90 days (data not shown). However, statistical significance disappeared in the multivariate analysis (HR, 0.91; 95% CI, 0.75-1.12; P = 0.381; Table 3, Fig. 2A). Nevertheless, the adjusted mortality risk for developing AKI was 1.38 (95% CI, 1.22-1.56, P < 0.001), and the risk increased as AKI stage increased (i.e., for stages 1, 2, and 3: HR, 1.17; 95% CI 1.02-1.36; P = 0.030; HR, 1.77; 95% CI, 1.45-2.16; P < 0.001; and HR, 1.93; 95% CI, 1.55-2.41; P < 0.001; respectively) compared with that in the no AKI group (Table 3, Fig. 2B). AKI severity also tended to increase the risk of death (P < 0.01 for the trend, Table 3). There are no differences for 90-day all-cause mortality between single and multiple RAAS blocker users (data not shown).

Discussion

This study evaluated the association between use of a RAAS blocker and the development of AKI and mortality rates in critically ill patients in an ICU. We found that ICU patients receiving a RAAS blocker developed AKI significantly more frequently. In addition, the cumulative 90-day mortality was higher in patients who developed AKI, and the risk increased continuously as AKI severity increased, even after adjusting for covariates. These findings are particularly important because of the continued use of a RAAS blocker for renal and cardiac protection in this population.

The pathophysiology of developing AKI during the use of a RAAS blocker is not completely understood and is likely multifactorial. Angiotensin II preferentially constricts the efferent arterioles in glomeruli. Therefore, RAAS blockers are efferent arteriole dilatators. RAAS blockers may cause AKI when maintenance of glomerular

Table 1. Baseline characteristics of the study subjects.

	Non-users N = 24,130 (91.8%)	RAAS blocker users N = 2,157 (8.2%)	P
Age (years)	57.4 ± 16.1	66.5 ± 12.9	< 0.001
Female gender	8,660 (35.9%)	986 (45.7%)	< 0.001
Past history			
CKD	151 (0.6%)	185 (8.6%)	< 0.001
DM	1,865 (7.7%)	912 (42.3%)	< 0.001
HTN	2,349 (9.7%)	1,559 (72.3%)	< 0.001
CVD	2,831 (11.7%)	1,725 (80.0%)	< 0.001
CLD	1,541 (6.4%)	113 (5.2%)	0.035
COPD	650 (2.7%)	185 (8.6%)	< 0.001
Asthma	613 (2.5%)	221 (10.2%)	< 0.001
AKI risk factors			
Sepsis	3,703 (15.3%)	718 (33.3%)	< 0.001
Inotropes	8,717 (36.1%)	786 (36.4%)	< 0.001
Transfusion	10,431 (43.2%)	893 (41.4%)	0.100
Ventilator	5,737 (23.8%)	582 (27.0%)	< 0.001
Use of aminoglycoside	2,064 (8.6%)	59 (2.7%)	< 0.001
Use of vancomycin	1,651 (6.8%)	147 (6.8%)	0.962
Use of colistin	235 (1.0%)	17 (0.8%)	0.396
Use of amphotericin	40 (0.2%)	4 (0.2%)	0.781
Use of NSAID	12,912 (53.5%)	755 (35.0%)	< 0.001
Use of contrast media	3,092 (12.8%)	162 (7.5%)	< 0.001
Platinum based chemotherapy within 6 months	139 (0.6%)	13 (0.6%)	0.876
Laboratory findings			
PH	7.4 ± 0.2	7.4 ± 0.1	< 0.001
PCO_2 (mmHg)	34.6 ± 12.1	35.2 ± 13.4	0.070
PO_2 (mmHg)	95.1 ± 51.8	86.5 ± 45.5	< 0.001
HCO_3 (mEq/L)	22.1 ± 4.6	21.3 ± 5.0	< 0.001
SO_2 (%)	91.8 ± 15.1	89.0 ± 17.7	< 0.001
WBC ($\times 10^3/mm^3$)	11.8 ± 5.9	11.1 ± 5.3	< 0.001
Hb (g/dL)	12.6 ± 2.9	11.4 ± 2.8	< 0.001
Hct (%)	36.6 ± 8.0	33.6 ± 8.1	< 0.001
Platelet ($\times 10^3/mm^3$)	221.5 ± 93.5	225.6 ± 91.1	0.047
BUN (mg/dL)	22.6 ± 67.7	37.5 ± 32.4	< 0.001
Creatinine (mg/dL)	1.3 ± 1.6	2.6 ± 3.1	< 0.001
Albumin (g/dL)	3.7 ± 0.7	3.7 ± 0.6	< 0.001
eGFR (mL/min/1.73m²)	76.7 ± 37.8	50.9 ± 36.8	< 0.001
ESR (mm/hr)	22.2 ± 24.2	27.5 ± 25.6	< 0.001
hs-CRP (mg/dL)	4.4 ± 7.1	4.3 ± 7.0	0.482

filtration requires constriction of efferent arterioles (Schoolwerth et al. 2001; Toto 2001). The use of a RAAS blocker and concomitant emergence of AKI could change hemodynamic stability or extracellular fluid volume. Maintaining GFR becomes dependent upon the prevailing effect of angiotensin II on the efferent glomerular arteriole during renal hypoperfusion and/or significant volume depletion.

RAAS blockers have been used for treating hypertension and preventing CVD. Hence, it is an important area of research to investigate the effects of using a RAAS blocker on the risk of AKI under certain circumstances. Our previous retrospective study showed that the use of a RAAS blocker during coronary angiography has harmful influence to increase the incidence of contrast-induced AKI (Rim et al. 2012). Furthermore, the use of a RAAS blocker in a perioperative cardiovascular surgery setting may increase the incidence of AKI (Cittanova et al. 2001; Arora et al. 2008). Several studies have reported that a common cause of ICU admission is the use of a RAAS blocker in patients

Table 2. Multivariate logistic regression analysis of the development of AKI in critically ill patients administered a RAAS blocker.

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI), P	OR (95% CI), P	OR (95% CI), P	OR (95% CI), P
RAAS	4.23 (3.86-4.64), < 0.001	1.74 (1.55-1.95), < 0.001	1.69 (1.51-1.91), < 0.001	1.56 (1.37-1.79), < 0.001

Model 1: adjusted for demographics (age, female sex, use of RAAS, and AKI).
Model 2: adjusted for demographics, and co-morbidities (model 1 + CKD, DM, HTN, CVD, CLD, COPD, and asthma).
Model 3: adjusted for demographics, co-morbidities, and AKI risk factors (model 2 + sepsis, inotropes, transfusion, ventilator, aminoglycosides, vancomycin, colistin, amphotericin, NSAID, contrast media, and chemotherapy).
Model 4: adjusted for demographics, co-morbidities, AKI risk factors, and laboratory findings (model 3 + Hb, hs-CRP, albumin, SO_2, WBC, platelets, and HCO_3).

Table 3. Multivariate Cox regression analysis for mortality in critically ill patients administered a RAAS blocker and the AKI stages.

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI), P	OR (95% CI), P	OR (95% CI), P	OR (95% CI), P
RAAS	1.01 (0.87-1.18), 0.901	1.05 (0.88-1.25), 0.601	1.00 (0.83-1.19), 0.966	0.91 (0.75-1.12), 0.381
AKI	2.30 (2.07-2.55), < 0.001	2.25 (2.02-2.50), < 0.001	1.46 (1.31-1.62), < 0.001	1.38 (1.22-1.56), < 0.001
Stage 1	1.80 (1.59-2.03), < 0.001	1.75 (1.54-1.99), < 0.001	1.20 (1.05-1.36), < 0.001	1.17 (1.02-1.36), 0.030
Stage 2	3.18 (2.68-3.77), < 0.001	3.11 (2.61-3.71), < 0.001	1.87 (1.57-2.23), < 0.001	1.77 (1.45-2.16), < 0.001
Stage 3	4.30 (3.57-5.18), < 0.001	4.22 (3.50-5.10), < 0.001	2.28 (1.89-2.76), < 0.001	1.93 (1.55-2.41), < 0.001

Model 1: adjusted for demographics (age, female sex, use of RAAS, and AKI).
Model 2: adjusted for demographics, and co-morbidities (Model 1 + CKD, DM, HTN, CVD, CLD, COPD, and asthma).
Model 3: adjusted for demographics, co-morbidities, and AKI risk factors (model 2 + sepsis, inotropes, transfusion, ventilator, aminoglycosides, vancomycin, colistin, amphotericin, NSAIDs, contrast media, and chemotherapy).
Model 4: adjusted for demographics, co-morbidities, AKI risk factors, and laboratory findings (model 3 + Hb, hs-CRP, albumin, SO_2, WBC, platelets, HCO_3).

with severe sepsis and infectious disease (Blanco et al. 2008; Plataki et al. 2011). One recent study showed that the use of these medications is independently related to the development of AKI in patients in septic shock (Plataki et al. 2011).

Several studies have described about the association between AKI and hospital and long-term mortality rates after discharge (Hou et al. 1983; Bagshaw et al. 2006; Morgera et al. 2008). AKI after major interventions for treating CVD, such as percutaneous coronary angiography or coronary artery bypass grafting, is closely associated with long-term patient mortality (Gupta et al. 2005; Loef et al. 2005; Bagshaw et al. 2006; Hobson et al. 2009). A large retrospective study demonstrated that the risk and outcomes associated with AKI in critically ill patients with and without cardiovascular or respiratory organ failure at admission in an ICU (Sileanu et al. 2015). Those authors also confirmed the risk and mortality of AKI associated with and without organ failure. They suggested that low-risk patients have better survival rates than high-risk patients, and that low-risk patients have significantly increased mortality when they develop AKI. However, some authors (Wang et al. 2014) reported an association between ACEI use and clinically important outcomes after analyzing data from a large, multicenter randomized trial including critically ill patients with AKI requiring dialysis. From their results, there was no significant association with all-cause mortality at 90 days based on ACEI use. Similarly, in our results, there was no significant difference in the cumulative 90-day survival rates between RAAS blocker users and non-users. However, patients with AKI had a higher mortality risk than patients without AKI. Moreover, in another study, AKI can lead to an increased risk of post-discharge mortality in patients who survive after discharge (Lafrance and Miller 2010). They also indicated that adjusted mortality was higher in severe stages of AKI (AKI stages 1-3 of 1.36-1.59). Similar results were observed in our study (adjusted morality risk from AKI stages 1-3 of 1.17-1.93).

Our results suggest that RAAS blockers may accelerate the development of AKI, but some limitations of the study should be mentioned. First, this was a retrospective observational study. No random group allocation was performed; however, unmeasured variables may have led to bias. Therefore, it is necessary to determine whether withholding a RAAS blocker at the time of ICU admission decreases the incidence of AKI and improves long-term survival rate. Although we consider the patients' severity scores when we analyzed the data, we could not recruit the degree of severity such as acute physiology, age and chronic health evaluation (APACHE) II score or sequential organ failure assessment (SOFA) score from our data sources. In order to address these issues, we performed multiple regres-

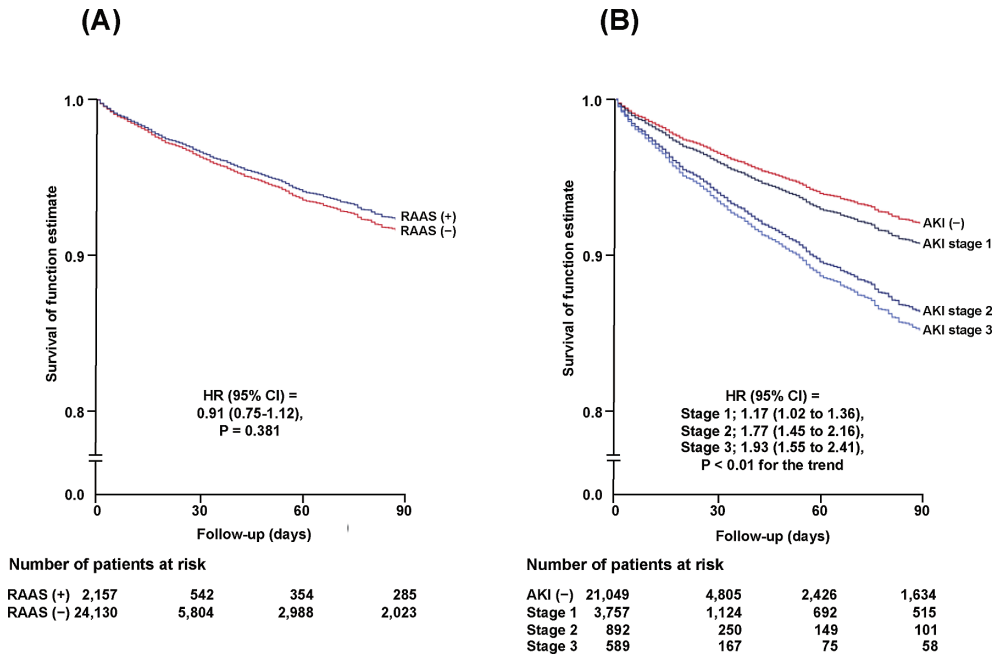

Fig. 2. Multivariate Cox regression analysis for 90-day survival rate.
(A) The 90-day survival rate according to the use of RAAS blockers.
The cumulative 90-day survival rate between RAAS blocker users and non-users was not significant (HR of RAAS blocker users, 0.91; 95% CI, 0.75-1.12; P = 0.381).
(B) The 90-day survival rate according to AKI stages.
The hazards ratio (HR) of the mortality risk related to AKI was 1.38 (95% CI, 1.22-1.56; P < 0.001) and increased as AKI stage increased from 1 to 3 (HR, 1.17; 95% CI, 1.02-1.36; HR, 1.77; 95% CI, 1.45-2.16; and HR, 1.93; 95% CI, 1.55-2.41; P < 0.01 for the trend) after adjusting for confounders.

sion analyses with various models to minimize differences in the baseline characteristics. Second, we could not evaluate whether withholding RAAS blocker therapy at the time of ICU admission caused a withdrawal effect. Some institutes use "sick day rules", such as withholding antihypertensive medications and diuretics when their patients are acutely ill to help decrease the incidence of community-acquired AKI (Anathhanam and Lewington 2013). Future studies with our subjects may be necessary. Finally, this investigation was conducted at the ICU of a single tertiary referral center and included one ethnic group. Further multi-center investigations of the effect of RAAS blockade on AKI in critically ill patients need to be conducted in patients of other ethnic and racial groups. Despite these limitations, our investigation is the only large observational analysis that provides evidence that RAAS blockade exacerbates AKI in patients undergoing treatment in the ICU.

In summary, although the incidence of AKI in association with the use of a RAAS blocker in patients admitted to the ICU is uncertain, our results indicate that use of a RAAS blocker is associated with AKI. Large, multi-center, randomized trials are needed to confirm whether temporarily withholding these medications affects ICU patient outcomes.

Conflict of Interest

The authors declare no conflict of interest.

References

Anathhanam, S. & Lewington, A.J. (2013) Acute kidney injury. *J. R. Coll. Physicians Edinb.*, **43**, 323-328.

Arora, P., Rajagopalam, S., Ranjan, R., Kolli, H., Singh, M., Venuto, R. & Lohr, J. (2008) Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin. J. Am. Soc. Nephrol.*, **3**, 1266-1273.

Bagshaw, S.M., Mortis, G., Doig, C.J., Godinez-Luna, T., Fick, G.H. & Laupland, K.B. (2006) One-year mortality in critically ill patients by severity of kidney dysfunction: a population-based assessment. *Am. J. Kidney Dis.*, **48**, 402-409.

Blanco, J., Muriel-Bombin, A., Sagredo, V., Taboada, F., Gandia, F., Tamayo, L., Collado, J., Garcia-Labattut, A., Carriedo, D., Valledor, M., De Frutos, M., Lopez, M.J., Caballero, A., Guerra, J., Alvarez, B., et al. (2008) Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. *Crit. Care*, **12**, R158.

Casas, J.P., Chua, W., Loukogeorgakis, S., Vallance, P., Smeeth, L., Hingorani, A.D. & MacAllister, R.J. (2005) Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*, **366**, 2026-2033.

Chertow, G.M., Soroko, S.H., Paganini, E.P., Cho, K.C., Himmelfarb, J., Ikizler, T.A. & Mehta, R.L. (2006) Mortality after acute renal failure: models for prognostic stratification and risk

adjustment. *Kidney Int.*, **70**, 1120-1126.
Cittanova, M.L., Zubicki, A., Savu, C., Montalvan, C., Nefaa, N., Zaier, K., Riou, B. & Coriat, P. (2001) The chronic inhibition of angiotensin-converting enzyme impairs postoperative renal function. *Anesth. Analg.*, **93**, 1111-1115.
de Mendonca, A., Vincent, J.L., Suter, P.M., Moreno, R., Dearden, N.M., Antonelli, M., Takala, J., Sprung, C. & Cantraine, F. (2000) Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med.*, **26**, 915-921.
Gupta, R., Gurm, H.S., Bhatt, D.L., Chew, D.P. & Ellis, S.G. (2005) Renal failure after percutaneous coronary intervention is associated with high mortality. *Catheter. Cardiovasc. Interv.*, **64**, 442-448.
Hobson, C.E., Yavas, S., Segal, M.S., Schold, J.D., Tribble, C.G., Layon, A.J. & Bihorac, A. (2009) Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*, **119**, 2444-2453.
Hoste, E.A., Clermont, G., Kersten, A., Venkataraman, R., Angus, D.C., De Bacquer, D. & Kellum, J.A. (2006) RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit. Care*, **10**, R73.
Hou, S.H., Bushinsky, D.A., Wish, J.B., Cohen, J.J. & Harrington, J.T. (1983) Hospital-acquired renal insufficiency: a prospective study. *Am. J. Med.*, **74**, 243-248.
Kellum, J.A. (2002) The Acute Dialysis Quality Initiative: methodology. *Adv. Ren. Replace. Ther.*, **9**, 245-247.
Kidney Disease: Improving Global Outcomes (KDIGO) Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.*, **2**, 1-138.
Lafrance, J.P. & Miller, D.R. (2010) Acute kidney injury associates with increased long-term mortality. *J. Am. Soc. Nephrol.*, **21**, 345-352.
Lakhdar, R., Al-Mallah, M.H. & Lanfear, D.E. (2008) Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. *J. Card. Fail.*, **14**, 181-188.
Loef, B.G., Epema, A.H., Smilde, T.D., Henning, R.H., Ebels, T., Navis, G. & Stegeman, C.A. (2005) Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J. Am. Soc. Nephrol.*, **16**, 195-200.
Matchar, D.B., McCrory, D.C., Orlando, L.A., Patel, M.R., Patel, U.D., Patwardhan, M.B., Powers, B., Samsa, G.P. & Gray, R.N. (2008) Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann. Intern. Med.*, **148**, 16-29.
Morgera, S., Schneider, M. & Neumayer, H.H. (2008) Long-term outcomes after acute kidney injury. *Crit. Care Med.*, **36**, S193-197.
National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Group (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am. J. Kidney Dis.*, **39**, S1-266.
Plataki, M., Kashani, K., Cabello-Garza, J., Maldonado, F., Kashyap, R., Kor, D.J., Gajic, O. & Cartin-Ceba, R. (2011) Predictors of acute kidney injury in septic shock patients: an observational cohort study. *Clin. J. Am. Soc. Nephrol.*, **6**, 1744-1751.
Rim, M.Y., Ro, H., Kang, W.C., Kim, A.J., Park, H., Chang, J.H., Lee, H.H., Chung, W. & Jung, J.Y. (2012) The effect of renin-angiotensin-aldosterone system blockade on contrast-induced acute kidney injury: a propensity-matched study. *Am. J. Kidney Dis.*, **60**, 576-582.
Schoolwerth, A.C., Sica, D.A., Ballermann, B.J. & Wilcox, C.S. (2001) Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation*, **104**, 1985-1991.
Sileanu, F.E., Murugan, R., Lucko, N., Clermont, G., Kane-Gill, S.L., Handler, S.M. & Kellum, J.A. (2015) AKI in low-risk versus high-risk patients in intensive care. *Clin. J. Am. Soc. Nephrol.*, **10**, 187-196.
Stojiljkovic, L. & Behnia, R. (2007) Role of renin angiotensin system inhibitors in cardiovascular and renal protection: a lesson from clinical trials. *Curr. Pharm. Des.*, **13**, 1335-1345.
Toto, R. (2001) Angiotensin II subtype 1 receptor blockers and renal function. *Arch. Intern. Med.*, **161**, 1492-1499.
Uchino, S., Kellum, J.A., Bellomo, R., Doig, G.S., Morimatsu, H., Morgera, S., Schetz, M., Tan, I., Bouman, C., Macedo, E., Gibney, N., Tolwani, A. & Ronco, C. (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*, **294**, 813-818.
Vivino, G., Antonelli, M., Moro, M.L., Cottini, F., Conti, G., Bufi, M., Cannata, F. & Gasparetto, A. (1998) Risk factors for acute renal failure in trauma patients. *Intensive Care Med.*, **24**, 808-814.
Wang, A.Y., Bellomo, R., Ninomiya, T., Lo, S., Cass, A., Jardine, M. & Gallagher, M. (2014) Angiotensin-converting enzyme inhibitor usage and acute kidney injury: a secondary analysis of RENAL study outcomes. *Nephrology*, **19**, 617-622.
Winkelmayer, W.C., Fischer, M.A., Schneeweiss, S., Levin, R. & Avorn, J. (2006) Angiotensin inhibition after myocardial infarction: does drug class matter? *J. Gen. Intern. Med.*, **21**, 1242-1247.