UC Davis

UC Davis Previously Published Works

Title

The effects of preoperative renin-angiotensin system inhibitors on outcomes in patients undergoing cardiac surgery.

Permalink

<https://escholarship.org/uc/item/34d3g9xd>

Journal

Journal of cardiothoracic and vascular anesthesia, 27(4)

ISSN

1053-0770

Authors

Shi, Pengcai
Li, Zhongmin
Young, Nilas
et al.

Publication Date

2013-08-01

DOI

10.1053/j.jvca.2013.01.012

Peer reviewed

The Effects of Preoperative Renin-Angiotensin System Inhibitors on Outcomes in Patients Undergoing Cardiac Surgery

Pengcai Shi, MD,*^{||} Zhongmin Li, PhD,[†] Nilas Young, MD,[‡] Fuhai Ji, MD,*[§] Yuelan Wang, MD, PhD,*
Peter Moore, MD, PhD,^{||} and Hong Liu, MD^{||}

Objective: The effects of preoperative (pre-op) renin-angiotensin system (RAS) inhibitors on outcomes in patients undergoing cardiac surgery remain uncertain. The aim of this study was to evaluate whether the use of pre-op RAS inhibitors affected major outcomes of cardiac surgery.

Design: A retrospective cohort study.

Setting: A university teaching hospital.

Participants: Patients undergoing cardiac surgery between January 1, 2001 and December 31, 2011.

Interventions: One thousand two hundred thirty-nine patients who received pre-op RAS inhibitors were compared with those who did not (control group, n = 1,083).

Measurements and Main Results: Acute kidney injury (AKI) was defined using Acute Kidney Injury Network classification. Patients in the RAS inhibitors group presented with higher comorbidities. Pre-op RAS inhibitors

therapy was associated with the reduction in the incidence of AKI (27.2% v 34.0%, $p < 0.001$), septicemia (1.9% v 3.5%, $p = 0.019$), and operative mortality (2.99% v 4.62%, $p = 0.039$). After adjusted propensity scores and multivariate logistic regression, the pre-op RAS inhibitors were found to have protective effects against AKI (odds ratio [OR]: 0.764, 95% confidence interval [CI]: 0.670-0.873, $p < 0.001$), septicemia (OR: 0.515, 95% CI: 0.348-0.761, $p > 0.001$), and operative mortality (OR: 0.539, 95% CI: 0.348-0.758, $p < 0.001$).

Conclusion: The results suggested that pre-op RAS inhibitor therapy was associated with significant reductions in the risk of AKI, operative mortality, and septicemia.

© 2013 Elsevier Inc. All rights reserved.

KEY WORDS: renin-angiotensin system inhibitors, acute kidney injury, cardiac surgery

CARDIAC SURGERY REMAINS the therapy of choice for advanced coronary artery disease or severe valve diseases.¹ Patients undergoing cardiac surgery are still at significantly higher risk for postoperative major adverse events. There has been great progress in surgical techniques and perioperative care over the past decades. Cardiac surgery has become individualized with regard to on-pump or off-pump procedures, minimally invasive procedures, robotic surgeries, and various myocardial protection strategies.^{2,3} However, these significant developments are counteracted by the presence of increasing comorbidities in the aging patient population. Mortality rates have not decreased over the past decade; thus, it is imperative to explore better strategies to reduce the risk for major adverse events after cardiac surgery.

The renin-angiotensin system (RAS) plays important roles in atherosclerosis, hypertension, left ventricular hypertrophy, myocardial infarction (MI), and congestive heart failure (CHF). RAS inhibitors, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs), have been shown to be effective in treating hypertension and decreasing cardiovascular mortality and morbidity. Commonly, they are used to treat hypertension, coronary artery disease, CHF, and diabetic nephropathy.⁴⁻⁷ It has been reported that long-term use of RAS inhibitors can provide end-organ protection and reduce cardiovascular and renal events in the patients with cardiovascular and kidney diseases.⁸ However, the role of preoperative (pre-op) RAS inhibitors in patients undergoing cardiac surgery remains undefined, and the existing data from literature still are contradictory. Studies have found that pre-op ACEi reduced postoperative troponin release and protected renal functions in patients undergoing cardiac surgery.⁹⁻¹¹ But other studies have shown that pre-op ACEi/ARBs use either is associated with a higher risk (27.6%) for postoperative acute kidney injury (AKI) or has no effects on renal function at all after cardiovascular surgery.^{12,13} Thus, the aim of this study was to test the hypothesis that patients on RAS drugs would have worse outcomes due to the potential of renal injury.

METHODS

A retrospective cohort study was performed involving patients (n = 3,089) undergoing cardiac surgery including coronary artery bypass graft (CABG) and/or valve surgeries and CABG with other cardiac surgeries at a single US medical center from January 1, 2001 to December 31, 2011. The study was reviewed and approved by the local Institutional Review Board, and informed consent was waived.

Inclusion criteria were (1) patients ≥ 18 years old, (2) CABG and/or valve surgery, (3) CABG and/or valve surgeries plus other procedures, and (4) procedures performed on cardiac pulmonary bypass (CPB). The exclusion criteria were (1) deep hypothermic circulatory arrest and (2) surgery involving ascending aortic surgery. Of all patients,

From the *Department of Anesthesiology, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, China; [†]Department of Internal Medicine, University of California Davis School of Medicine, Sacramento, CA; [‡]Division of Cardiothoracic Surgery, University of California Davis School of Medicine, Sacramento, CA; [§]Department of Anesthesiology, the First Affiliated Hospital of Soochow University, Suzhou, China; and ^{||}Department of Anesthesiology and Pain Medicine, University of California Davis School of Medicine, Sacramento, CA.

Supported by: Departments of Anesthesiology and Pain Medicine, Heart Center and Internal Medicine of University of California Davis Health System; Department of Anesthesiology, Shandong Provincial Qianfoshan Hospital and Department of Anesthesiology, the First Affiliated Hospital of Soochow University. This study was supported by grant from Jiangsu Province's by Key Provincial Talents Program, China (to FJ), by Jiangsu Province's Six Major Peak Talents Program, China (to FJ) and by Suzhou science and No.SYS201111 (to FJ) from Technology Bureau's program, China.

Address reprint requests to Hong Liu, MD, Department of Anesthesiology and Pain Medicine, University of California Davis School of Medicine, Sacramento, CA. E-mail: hualiu@ucdavis.edu, and Yuelan Wang, MD, PhD, Department of Anesthesiology, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan 250014, China.

© 2013 Elsevier Inc. All rights reserved.

1053-0770/2601-0001\$36.00/0

<http://dx.doi.org/10.1053/j.jvca.2013.01.012>

2,322 met the inclusion criteria. All patients treated with ACEi/ARBs for at least 2 weeks constituted the RAS inhibitor group. They were compared with the remaining patients who had not received ongoing RAS inhibitor therapy (non-RAS inhibitor group) preoperatively.

Data were abstracted from a single institution's Society of Thoracic Surgeons (STS) database and hospital medical records, including demographics, pre-op risk factors, pre-op medications, intraoperative data, postoperative cardiocerebral events, renal function, and operative mortality. Independent investigators prospectively collected the data on each patient during the course of hospitalization.

The primary outcome was operative mortality, which is defined as any death occurring during the acute episode of care in which the surgery was performed, even after 30 days, and deaths occurring after discharge from the hospital, but within 30 days of the procedure unless the cause of death clearly is unrelated to the surgery. Secondary outcomes were AKI, perioperative MI, heart block, cardiac arrest, permanent stroke, and transient stroke. Other outcomes also included the following: readmission ≤ 30 days, deep sternum infection, septicemia, the postoperative length of hospital stay (LOS; d), the length of intensive care unit (ICU) stay (h), and the time on a ventilator (h).

Based on the STS database criteria, perioperative MI was defined by using the following criteria:

- For an MI that occurred < 24 hours postoperatively, CK-MB must be ≥ 5 times the upper limit of normal, with or without new Q-waves present in 2 or more contiguous electrocardiogram (ECG) leads—no symptoms required.
- An MI occurring > 24 hours postoperatively by at least one of the following criteria: (1) evolutionary ST-segment elevations, (2) development of new Q-waves in 2 or more contiguous ECG leads, (3) new or presumably new left bundle-branch block pattern on the ECG, or (4) the CK-MB (or CK if MB not available) must be ≥ 3 times the upper limit of normal value.
- Heart block: defined as a new heart block requiring the implantation of a permanent pacemaker of any type before discharge.
- Permanent stroke: defined as a postoperative stroke (any confirmed neurologic deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 hours.
- Transient stroke or transient ischemic attack: defined as loss of neurologic function that was abrupt in onset but with the complete return of function within 24 hours.
- Readmission ≤ 30 days: defined as the patient who was readmitted to an acute care facility as an in-patient within 30 days from the date of initial surgery for any reason.
- Deep sternum infection: defined as, within 30 days postoperatively, a deep sternum infection involving muscle, bone, and/or mediastinum requiring operative intervention and having all of the following conditions: (1) wound opened with an excision of tissue (incision and drainage) or re-exploration of mediastinum, (2) positive culture unless patient on antibiotics at the time of culture or no culture obtained, and (3) treatment with antibiotics beyond perioperative prophylaxis.
- Septicemia: defined as the patient who had septicemia (required positive blood culture) postoperatively.
- The LOS: defined as the total number of days the patient was in the hospital postsurgery.
- The length of ICU stay: defined as the total number of hours the patient was in the ICU postsurgery.
- Length on ventilator: defined as the total number of hours the patient was on a ventilator postoperatively in the ICU.
- Last creatinine level: defined as the creatinine level closest to the date and time prior surgery but prior to anesthetic management.

- Postoperative creatinine level: defined as the postoperative creatinine level; if more than 1 level was obtained, the highest level within 48 hours was coded.

The remaining definitions are available at <http://www.sts.org>.

AKI was defined using Acute Kidney Injury Network (AKIN) classification creatinine criteria¹⁴: Stage I, increase in serum creatinine by ≥ 0.3 mg/dL or increase to $\geq 150\%$ to 200% from baseline (postoperative creatinine level divided by last creatinine level); stage II, increase in serum creatinine to $> 200\%$ to 300% from baseline; and stage III, increase in serum creatinine to $> 300\%$ from baseline or serum creatinine level ≥ 4 mg/dL or treatment with new renal replacement therapy.

Bivariable analysis was performed between RAS inhibitors and each pre-op risk factor and surgery outcomes. The chi-square test was used for categorical variables, and the Student t-test was used for continuous variables. To mitigate selection bias in RAS inhibitor use, the authors computed the propensity score; that is, the conditional probability of each patient receiving RAS inhibitors with a multivariate logistic regression model that includes patient demographic and clinical risk factors. For real-time prediction of impact in using RAS inhibitor on surgery outcomes, 3 separate propensity-weighted multivariable logistic regression models were developed for operative mortality, postoperative AKI, and postoperative septicemia. Parsimonious models with a backward selection method from all candidate risk factors ($\alpha = 0.05$) were presented. The candidate risk factors were selected based on the literature reviews, clinical plausibilities, and variables collected in the database. These variables included RAS inhibitors, age, sex, race, procedure status, surgery type, body mass index, diabetes, hypertension, dyslipidemia, hypercholesterolemia, renal failure (RF), smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, previous MI, CHF, ejection fraction (EF), intra-aortic balloon pump (IABP), CPB time, and aortic cross-clamp time. All differences in statistical analysis were considered significant if $p < 0.05$. All data analyses were conducted with SAS version 9.3 (Cary, NC).

RESULTS

Demographic and clinical data of those patients are presented in Table 1. There were no significant differences in age, sex, body mass index, procedure status, smoking, peripheral vascular disease, last creatinine level, RF, CHF, pre-op inotropes, and pre-op β -blocker uses between the 2 groups. There were more Caucasian/white patients and more chronic lung diseases in the non-RAS inhibitors group. Patients who received pre-op RAS inhibitor therapy were more likely to have diabetes, hypertension, dyslipidemia, cerebrovascular disease, previous MI, lower EF, IABP, pre-op aspirin, lipid-lowering medications, and nitrates. Intraoperative characteristics, including CPB time and aortic cross-clamp time, were similar in both the groups (Table 1).

Overall, the operative mortality was 3.7% (87/2,322). This study showed that the operative mortality was 2.99% (37/1,239) for patients who received pre-op RAS inhibitors and 4.62% (50/1,083) for patients who did not take pre-op RAS inhibitors ($p = 0.039$, odds ratio [OR]: 0.636, 95% confidence interval [CI]: 0.42-0.981) (Fig. 1). After excluding patients with pre-op RF, the total numbers of patients assessed for renal function outcome were 1,128 in the RAS inhibitor group and 985 in the non-RAS inhibitor group. There were significant differences between the RAS inhibitor group (27.2%) and the non-RAS inhibitor group (34.0%) in the incidence of AKI ($p < 0.001$, OR: 0.726, 95% CI: 0.602-0.874) (Fig. 1). There

Table 1. Patient Demographic Data and Clinical Characteristics

Variables	RAS Inhibitors		p Value
	No (n = 1,083)	Yes (n = 1,239)	
Age (y)	62.5 (12.9)	62.2 (11.5)	0.572
Female	325 (30.0)	391 (31.6)	0.420
BMI (kg/m ²)	29.1 (6.8)	29.5 (6.2)	0.066
Race: white	737 (68.1)	746 (62.6)	0.006
Elective surgery	531 (49.0)	544 (43.9)	0.572
Diabetes	317 (29.3)	523 (42.2)	0.420
Smoking	581 (53.7)	728 (58.8)	0.013
Chronic lung disease	170 (15.7)	178 (14.4)	0.046
CVD	159 (14.7)	220 (17.8)	0.046
PVD	144 (13.3)	166 (13.4)	0.943
Previous MI	332 (30.7)	523 (42.2)	<0.001
CHF	387 (35.7)	491 (39.6)	0.054
EF (%)	53.0 (12.4)	50.0 (13.6)	<0.001
IABP	101 (9.3)	172 (13.9)	<0.001
Hypertension	698 (64.5)	1,032 (83.3)	<0.001
Last creatinine level (mg/dL)	1.28 (1.13)	1.32 (1.24)	0.407
Dyslipidemia	749 (69.2)	978 (78.9)	<0.001
Renal failure	98 (9.1)	111 (9.0)	0.940
Pre-op β -blocker	559 (51.6)	676 (54.6)	0.156
Pre-op inotropes	27 (2.0)	18 (1.50)	0.110
Pre-op aspirin	681 (62.9)	974 (78.6)	<0.001
Pre-op lipid-lowering medications	563 (52.0)	780 (63.0)	<0.001
Pre-op nitrates	77 (7.1)	134 (10.8)	0.002
CPB time (min)	188.6 (76.5)	191.8 (73.2)	0.294
Aortic cross-clamp time (min)	138.4 (59.3)	142.5 (58.3)	0.817
Propensity score	0.472 (0.172)	0.588 (0.149)	<0.001

NOTE. Values are numbers of patients (%) for categoric variables and mean $\pm$ SD for continuous variables; $p < 0.05$ is considered as statistically significant.

Abbreviations: RAS, renin-angiotensin system; BMI, body mass index; CVD, cerebrovascular disease; PVD, peripheral vascular disease; MI, myocardial infarction; CHF, congestive heart failure; EF, ejection fraction; IABP, intra-aortic balloon pump; Pre-op, preoperative; CPB, cardiopulmonary bypass.

was a significant difference between the 2 groups in AKI stage I patients (23.1% *v* 28.2%, $p = 0.007$). Although the results were in favor of the RAS inhibitor group, there were no statistical significances between the 2 groups in stage II and III groups. There was a significant difference between the RAS inhibitor group and non-RAS inhibitor group in the incidence of septicemia (1.9% *v* 3.5%, $p = 0.019$, OR: 0.543, 95% CI: 0.324-0.912) (Fig. 1). There were no significant differences in perioperative MI, heart block, cardiac arrest, permanent stroke, transient stroke, deep sternum infection, and readmission ≤ 30 days between 2 groups (Fig. 1). There were also no significant differences in the length of ICU stay, the length on a ventilator, and the LOS between the 2 groups. Conditional logistic regression models were performed to identify risk factors for operative mortality, AKI, and septicemia.

Pre-op RAS inhibitor treatment was an independent protective factor for mortality (OR: 0.539, 95% CI: 0.384-0.758, $p < 0.001$). Other risk factors were advanced age, female gender, non-white race, RF, chronic lung disease, IABP, lower EF, and CPB time (Table 2).

Pre-op RAS inhibitor treatment was an independent protective factor against AKI (OR: 0.764, 95% CI: 0.67-0.873, $p < 0.001$). Advanced age, diabetes, hypertension and chronic lung disease, valve surgery, and urgent surgery were risk factors of AKI (Table 3).

Pre-op RAS inhibitor treatment was an independent protective factor against septicemia (OR: 0.515, 95% CI: 0.348-0.761, $p < 0.001$). Female, non-white race, RF, previous MI, CPB time, urgent surgery, and valve surgery were risk factors for septicemia (Table 4).

The discriminatory ability of the multivariate logistic model was acceptable for operative mortality (C statistic: 0.819), AKI (C statistic: 0.651), and septicemia (C statistic: 0.827). The model was well calibrated among deciles of observed and expected risks for operative mortality (Hosmer-Lemeshow χ^2 : 13.2803, $p = 0.1026$), AKI (Hosmer-Lemeshow χ^2 : 7.8721, $p = 0.4461$), and septicemia (Hosmer-Lemeshow χ^2 : 10.3563, $p = 0.2409$).

DISCUSSION

The authors thought that patients on RAS inhibitors would do worse due to the potential cause of renal injury, but they actually did better. However, this study demonstrated that the pre-op RAS inhibitors reduced the incidence of postoperative AKI, septicemia, and operative mortality in patients undergoing cardiac surgery despite a sicker patient population. To the best of the authors' knowledge, this is the first study utilizing the AKIN classification to evaluate the renal outcome in patients who received RAS inhibitors under cardiac surgery and this study demonstrated that pre-op RAS inhibitors possess renal protective effect.

Fig 1. Effects of RAS inhibitors on outcomes in patients undergoing cardiac surgery. Values are presented as number of patients and (%); AKI is assessed in RAS inhibitor group (n = 1,128) versus non-RAS inhibitor group (n = 985) after excluding patients with preoperative renal failure. RAS, renin-angiotensin system; peri-MI, perioperative myocardial infarction; OR, odds ratio; CI, confidence interval; p < 0.05 is considered as statistically significant.

AKI or acute renal failure after cardiac surgery is now referred to collectively as cardiac surgery-associated AKI and associated with significantly poor outcomes including increased short- and long-term mortalities.¹⁵ Operative mortality is 1% to 5% in patients who developed AKI and up to 24% in patients who required acute dialysis.¹⁶ Its pathogenesis includes exogenous and endogenous toxins, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation, and oxidative stress.¹⁷

Table 2. Multivariable Logistic Regression Model for Operative Mortality after Cardiac Surgery

Risk Factor	OR	95% CI	p Value
Preoperative RAS inhibitors	0.539	0.384-0.758	<0.001
Age (y)			
< 65	Reference		
65-74	1.158	0.762-1.759	0.4927
75-84	1.913	1.261-2.902	0.0023
> 85	2.579	0.963-6.908	0.0595
Procedure status			
Elective	Reference		
Urgent	2.005	1.357-2.961	<0.001
Female v male	1.551	1.097-2.191	0.0129
Non-white v white	1.318	0.933-1.862	0.1178
Renal failure	2.229	1.465-3.392	<0.001
Chronic lung disease	1.722	1.369-2.167	<0.001
IABP	1.996	1.315-3.028	0.0012
EF (%)	0.979	0.967-0.991	<0.001
CPB time (min)	1.01	1.008-1.012	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; RAS, renin-angiotensin system; EF, ejection fraction; CPB, cardiopulmonary bypass.

Angiotensin II increases the proliferation and migration of vascular smooth muscle cells and contributes to endothelial dysfunction, promoting the activity of nicotinamide adenine dinucleotide phosphate and xanthine oxidase, which are the main sources of oxygen free radicals.¹⁸ Moreover, angiotensin II also can increase the expression of proinflammatory factors.¹⁹

Studies have found that the patients receiving even short-term (2 d) RAS inhibitors prior to CABG surgery had improved cardiac and renal functions following cardiac surgery.²⁰⁻²³ In a study of 536 patients, the pre-op ACEi was associated with a decreased incidence of postoperative AKI (OR: 0.48, 95% CI: 0.23-0.77, p = 0.04) after on-pump CABG surgery.¹¹ Furthermore, pre-op RAS inhibitors also have shown renal protection in high-risk surgical populations. Age was one of the independent risk factors for postoperative AKI.²⁴ In a study of aged patients undergoing cardiac surgery, the incidence of postoperative the RF in the RAS inhibitor group was 1.6% v 7.6% in the non-RAS inhibitor group and an OR was 0.19 (95% CI: 0.04-0.84, p = 0.029).¹⁰ However, Ouzounian et al failed to find the benefits of RAS inhibitors in a similar clinical setting.¹³ But there was a question in their patient population for assessing the RAS inhibitors on renal outcomes, the inclusion criteria should be patient without pre-op RF requiring dialysis, or pre-existing RF (defined by documented history of RF or creatinine level > 2). If they had excluded the patients with pre-op RF, the incidence of new-onset RF would be 6.36% in patients with RAS inhibitors v 7.98% in patients without RAS inhibitors (p < 0.05) and RAS inhibitors would reduce the incidence of new-onset RF.

On the contrary, Miceli et al found that the ACEi was associated with an increased risk of postoperative renal dysfunction (PRD). There was a significant difference between

Table 3. Multivariable Logistic Regression Model for Postoperative Acute Kidney Injury Following Cardiac Surgery

Risk Factor	OR	95% CI	p Value
Preoperative RAS inhibitors	0.764	0.67-0.873	<0.001
Age (y)			
<65	Reference		
65-74	1.015	0.864-1.193	0.8533
75-84	1.322	1.096-1.596	0.0036
Procedure status			
Elective	Reference		
Urgent	1.138	0.99-1.308	0.069
Surgery type			
CABG only	Reference		
CABG + Valve(s)	1.536	1.252-1.884	<0.001
CABG + Others	1.272	0.928-1.743	0.1348
Valve/Valve + Others	1.381	1.149-1.659	<0.001
Diabetes	1.304	1.13-1.506	<0.001
Hypertension	1.461	1.235-1.728	<0.001
Chronic lung disease	1.166	1.035-1.313	0.0114

Abbreviations: OR, odds ratio; CI, confidence interval; RAS, renin-angiotensin system; CABG, coronary artery bypass graft; BMI, body mass index.

the ACEi group and control group in the risk of PRD (7.1% v. 5.4%, OR: 1.36, 95% CI: 1.1-1.67, $p = 0.006$). They defined PRD as a serum creatinine level $> 200 \mu\text{mol/L}$ plus an increase of at least 1.5 times the preoperative baseline concentrations.²⁵ But there was a problem in their study that the pre-op renal function was unknown, so the results are questionable. Although these studies were assessing postoperative acute renal failure or AKI, they used different criteria or definitions, which likely led to different conclusions. It is very important to use a universal definition of AKI. This lack has resulted in substantial differences in the reported incidence and outcomes.

In the past decade, the renal injury definition/criteria has been evolved from the proposed AKI criteria in 2001 to the risk, injury, failure, loss of kidney function, and end-stage renal disease (RIFLE) classification in 2004 and the AKIN classification in 2007. AKIN classification proposed new diagnostic criteria, which is defined as an abrupt (within 48 h) reduction in kidney function signified by an absolute increase in serum creatinine of $\geq 0.3 \text{ mg/dL}$ (or 1.5 fold from the baseline), or a reduction in urine output to $< 0.5 \text{ mL/kg/h}$ for > 6 hours.²⁶ An earlier diagnosis would assist with treatment and avoid dehydration, excessive diuretic use, and other nephrotoxic intervention.

In this study, the authors chose to use AKIN classification instead of STS specifications. AKIN classification has a higher sensitivity and specificity, and it can describe the severity levels that predict the prognosis. There is accumulating evidence that small increments in serum creatinine are associated with adverse outcomes that are manifested in increased short-term morbidity/mortality and worsening of longer-term outcomes, including 1-year mortality.²⁷

This study demonstrated that the incidence of septicemia was decreased significantly in patients who received pre-op RAS inhibitors. Pre-op RAS inhibitors can reduce the incidence of septicemia by 46%. In a logistic regression model for

postoperative septicemia, the pre-op RAS inhibitors use was an independent protective factor for septicemia. Sepsis and septicemia are 2 closely related medical conditions, both involving widespread inflammation and infection. There were limited reports about the effect of RAS inhibitors on septicemia in patients undergoing cardiac surgery. However, a study in laboratory animals exposed to endotoxin demonstrated that the RAS inhibition played an important role in decreasing oxidative stress and endothelial dysfunction.²⁸ RAS inhibitors could improve endothelium-dependent relaxation by decreasing endothelial-derived adhesion molecule production. These also have also been demonstrated to improve gut perfusion and reduce end-organ failure in critically ill patients.²⁹ Studies also have found that RAS inhibitors can prevent lipopolysaccharide-induced septic shock and block lipopolysaccharide-induced inflammatory response in animal models. The authors suggested that enalapril would be a good therapeutic agent for sepsis.³⁰

The reduction of septicemia in the RAS inhibitor group was likely to be associated with the reduction of AKI. Accumulating data indicated that AKI could trigger immune, metabolic, and hormonal response pathways. Septicemia and AKI are bidirectional. Sepsis is the most common precipitating factor for AKI in hospitalized patients, and, similarly, patients with AKI are predisposed to sepsis. AKI not only complicates the course of sepsis, but also appears to predispose patients to further development of sepsis.³¹

This study showed that the pre-op RAS inhibitor therapy reduced the mortality by 35%. In a multivariate logistic regression model for operative mortality, age, sex, urgent surgery, RF, chronic lung diseases, IABP, and CPB time are all risk factors of operative mortality, and pre-op RAS inhibitor therapy has a protective effect on operative mortality. The mechanism of the reduction of operative mortality in patients who received RAS inhibitors was likely associated with the renal protective effect of RAS inhibitors. AKI and septicemia are statistically significant risk factors for operative mortality. The reductions of AKI and septicemia in the RAS inhibitor group may also have played a key role in decreasing operative mortality.

Table 4. Multivariable Logistic Regression Model for Postoperative Septicemia Following Cardiac Surgery

Risk Factor	OR	95% CI	p Value
Preoperative RAS inhibitors	0.515	0.348-0.761	<0.001
Female v male	1.569	1.069-2.303	0.0213
Non-white v white	1.743	1.189-2.556	0.0044
Procedure status			
Elective	Reference		
Urgent	1.551	1.025-2.348	0.0377
Surgery type			
CABG only	Reference		
CABG + valve (s)	4.57	2.564-8.17	<0.001
Valve/valve + others	3.008	1.599-5.659	<0.001
Diabetes	1.835	1.231-2.737	0.0029
Renal failure	1.859	1.016-3.403	0.0443
Previous MI	1.983	1.317-2.986	<0.001
CPB time (min)	1.006	1.004-1.009	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; RAS, renin-angiotensin system; CABG, coronary artery bypass graft; MI, myocardial infarction; CPB, cardiopulmonary bypass.

There is a debate about whether to stop or continue the RAS inhibitors prior to cardiac surgery. Some believe that RAS inhibitors are associated with intraoperative hypotension and low cardiac output after bypass and others may disagree.³² In a prospective observational study, Drenger et al suggested that continuous treatment with ACEi was associated with substantive reductions of risk of nonfatal events.³³ In a review, Auron et al suggested that full discussion of the potential implications of perioperative RAS inhibitors therapy with the surgical team is important, and strategies to ensure careful monitoring and maintenance of adequate intravenous volume before induction of anesthesia are essential.³⁴

This study had several limitations. One challenge in conducting observational studies is to draw inferences that are acceptably free from influences by overt and/or potential hidden biases, including potential multiple and uncontrollable confounding factors, such as physician bias on selection of

patients and medications. Although multivariate regression was used in this study to reduce overt biases, the potential flaws of a nonrandomized study may remain. A second limitation was that this study only focused on ACEi and there are other interventions, such as statins, that have significant benefits on outcomes after cardiac surgery. Same as steroids, it could potentially improve cardiac surgery outcomes.^{35,36} Thirdly, this was a single-center study with the data from a 10-year period. Nevertheless, further multicenter studies are needed.

This study demonstrated that pre-op RAS inhibitor use was an independent protective factor against AKI and septicemia. It can reduce the incidence of AKI, septicemia, and operative mortality and improve outcomes in patients undergoing cardiac surgery.

ACKNOWLEDGMENT

The authors wish to thank Ms. Sharon McKee for her effort in editing the language.

REFERENCES

1. Rosenfeldt FL, Wilson MD, Buxton BF, et al: Coronary artery bypass surgery provides long-term results superior to percutaneous coronary intervention. *Heart Lung Circ* 21:1-11, 2012
2. Cooper EA, Edelman JJ, Wilson MK, et al: Off-pump coronary artery bypass grafting in elderly and high-risk patients—A review. *Heart Lung Circ* 20:694-703, 2011
3. Schmitto JD, Mokashi SA, Cohn LH: Past, present, and future of minimally invasive mitral valve surgery. *J Heart Valve Dis* 205: 493-498, 2011
4. Matchar DB, McCrory DC, Orlando LA, et al: Systematic review: Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med* 148:16-29, 2008
5. Winkelmayr WC, Fischer MA, Schneeweiss S, et al: Angiotensin inhibition after myocardial infarction: Does drug class matter? *J Gen Intern Med* 21:1242-1247, 2006
6. Lakhdar R, Al-Mallah MH, Lanfear DE: 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* 4:181-188, 2008
7. Casas JP, Chua W, Loukogeorgakis S, et al: Effect of inhibitors of the rennin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. *Lancet* 366:2026-2033, 2005
8. Stojiljkovic L, Behnia R: Role of rennin-angiotensin system inhibitors in cardiovascular and renal protection: A lesson from clinical trials. *Curr Pharm Des* 13:1335-1345, 2007
9. Benedetto U, Melina G, Capuano F, et al: Preoperative angiotensin-converting enzyme inhibitors protect myocardium from ischemia during coronary artery bypass graft surgery. *J Cardiovasc Med (Hagerstown)* 9: 1098-1103, 2008
10. Barodka V, Silvestry S, Zhao N, et al: Preoperative renin-angiotensin system inhibitors protect renal function in aging patients undergoing cardiac surgery. *J Surg Res* 167:e63-e69, 2011
11. Benedetto U, Sciarretta S, Roscitano A, et al: Preoperative angiotensin-converting enzyme inhibitors and acute kidney injury after coronary artery bypass grafting. *Ann Thorac Surg* 86:1160-1166, 2008
12. Arora P, Rajagopalam S, Ranjan R, et al: 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, 2008
13. Ouzounian M, Buth KJ, Valeeva L, et al: Impact of preoperative angiotensin-converting enzyme inhibitor use on clinical outcomes after cardiac surgery. *Ann Thorac Surg* 93:559-564, 2012
14. Ostermann M, Chang RW: Challenges of defining acute kidney injury. *QJM* 104:237-243, 2011
15. Ronco C, Kellum JA, Bellomo R: Cardiac surgery-associated acute kidney injury. *Int J Artif Organs* 31:156-157, 2008
16. Chertow GM, Christiansen CL, Cleary PD, et al: Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med* 155:1505-1511, 1995
17. Bellomo R, Auriemma S, Fabbri A, et al: The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). *Int J Artif Organs* 31:166-178, 2008
18. Griendling KK, Minieri CA, Ollerenshaw JD, et al: Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res* 74:1141-1148, 1994
19. Ruiz-Ortega M, Ruperez M, Lorenzo O, et al: Angiotensin II regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. *Kidney Int Suppl* 62:S12-S22, 2002
20. Colson P, Ribstein J, Mimran A, et al: Effect of angiotensin converting enzyme inhibition on blood pressure and renal function during open heart surgery. *Anesthesiology* 72:23-27, 1990
21. Türker H, Dönmez A, Zeyneloğlu P, et al: Effects of enalaprilat infusion on hemodynamics and renal function in patients undergoing cardiac surgery. *Anadolu Kardiyol Derg* 4:296-300, 2004
22. Wagner F, Yeter F, Bisson S, et al: Beneficial hemodynamic and renal effects of intravenous enalaprilat following coronary artery bypass surgery complicated by left ventricular dysfunction. *Crit Care Med* 31: 1421-1428, 2003
23. Ryckwaert F, Colson P, Ribstein J, et al: Haemodynamic and renal effects of intravenous enalaprilat during coronary artery bypass graft surgery in patients with ischaemic heart dysfunction. *Br J Anaesth* 86:169-175, 2001
24. Sirvinskas E, Andrejaitiene J, Raliene L, et al: Cardiopulmonary bypass management and acute renal failure: Risk factors and prognosis. *Perfusion* 23:323-327, 2008
25. Miceli A, Capoun R, Fino C, et al: Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol* 54:1778-1784, 2009
26. Mehta RL, Kellum JA, Shah SV, et al: Acute Kidney Injury Network (AKIN): Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11:R31-R39, 2007

27. Lassnigg A, Schmidlin D, Mouhieddine M, et al: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. *J Am Soc Nephrol* 15:1597-1605, 2004
28. Lund DD, Brooks RM, Faraci FM, et al: Role of angiotensin II in endothelial dysfunction induced by lipopolysaccharide in mice. *Am J Physiol Heart Circ Physiol* 293:H3726-H3731, 2007
29. Boldt J, Papsdorf M, Kumle B, et al: Influence of angiotensin-converting enzyme inhibitor enalaprilat on endothelial-derived substances in the critically ill. *Crit Care Med* 26:1663-1670, 1998
30. Hagiwara S, Iwasaka H, Hidaka S, et al: Antagonist of the type-1 ANG II receptor prevents against LPS-induced septic shock in rats. *Intensive Care Med* 35:1471-1478, 2009
31. Reynvoe E, Blot SI, vandiick DM, et al: Epidemiology of infection in critically ill patients with acute renal failure. *Crit Care Med* 37: 2203-2209, 2009
32. Mets B: Management of hypotension associated with angiotensin-axis blockade and general anesthesia administration. *J Cardiothorac Vasc Anesth* . [Epub ahead of print], 2012
33. Drenger B, Fontes ML, Miao Y, et al: Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass: Effects on in-hospital morbidity and mortality. *Circulation* 126:261-269, 2012
34. Auron M, Harte B, Kumar A, et al: Renin-angiotensin system antagonists in the perioperative setting: Clinical consequences and recommendations for practice. *Postgrad Med J* 87:472-481, 2011
35. Singh N, Patel P, Wyckoff T, et al: Progress in perioperative medicine: Focus on statins. *J Cardiothorac Vasc Anesth* 24:892-896, 2010
36. Augoustides JG: Integrating outcome benefit into anesthetic design: The promise of steroids and statins. *J Cardiothorac Vasc Anesth* 25: 880-884, 2011