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Perioperative Renin–Angiotensin System Inhibitors Improve Major Outcomes of Heart Failure Patients Undergoing Cardiac Surgery

A Propensity-Adjusted Cohort Study

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Objective: The aim of this study was to study the association of perioperative administration of renin angiotensin system inhibitors (RASi) and clinical outcomes of patients with heart failure (HF) undergoing cardiac surgery.

Summary Background Data: It is controversial whether the perioperative RASi should be administered in HF patients undergoing cardiac surgery.

Methods: A total of 2338 patients with HF and undergoing CABG and/or valve surgeries at multiple hospitals from 2001 to 2015 were identified from STS database. After adjustment using propensity score and instrumental variable, logistic regression was conducted to analyze the influence of preoperative continuation of RASi (PreRASi) on short-term in-hospital outcomes. Independent risk factors of 30-day mortality, major adverse cardiovascular events (MACE), and renal failure were analyzed by use of stepwise logistic regression. The effects of pre- and postoperative use of RASi (PostRASi) on long-term mortality were analyzed using survival analyses. Stepwise Cox regression was conducted to analyze the independent risk factors of 6-year mortality. The relationships of HF status and surgery type with perioperative RASi, as well as PreRASi-PostRASi, were also evaluated by subgroup analyses.

Results: PreRASi was associated with lower incidences of 30-day mortality [$P < 0.0001$, odds ratio (OR): 0.556, 95% confidence interval (CI) 0.405−0.763], stroke ($P = 0.035$, OR: 0.585, 95% CI: 0.355−0.962), renal failure ($P = 0.007$, OR: 0.663, 95% CI: 0.493–0.894). Both PreRASi ($P = 0.0137$) and PostRASi ($P = 0.007$) reduced 6-year mortality compared with the No-RASi groups.

Conclusions: Pre- and postoperative use of RASi was associated with better outcomes for the patients who have HF and undergo CABG and/or valve surgeries. Preoperative continuation and postoperative restoration are warranted in these patients.

Keywords: cardiac surgery, heart failure, mortality, prognosis, RASi

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Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), and direct renin inhibitors collectively known as renin angiotensin system inhibitors (RASi) are the first-line antihypertensive agents and have been well documented to reduce the risk of cardiovascular events and all-cause mortality in patients with hypertension.[1,2] Furthermore, RASi are protective against heart failure (HF), myocardial infarction (MI), renal dysfunction, and diabetic retinopathy independent of its effects on blood pressure.[3] Thus, RASi have become one of the most commonly used medications in the setting of hypertension and cardiovascular diseases. Many studies support continuing RASi therapy before surgery because discontinuation of RASi was associated with increased risk of postoperative acute HF, hypertension, and ischemic events.[4–6] Preclinical and clinical studies have shown that RASi hold promise as cardiovascular protective agents for patients undergoing surgery.[7] However, preoperative continuation of RASi has repeatedly been implicated in hypotension and vasoconstrictor requirement during surgery. Additionally, preoperative continuation of RASi has been associated with increased postoperative incidence of acute kidney injury (AKI), use of inotropic support, new onset of postoperative atrial fibrillation and all-cause mortality.[8–10] The debate surrounding perioperative management of RASi has created critical inconsistency among professional medical society guidelines and has resulted in significant variability in clinical practice.[11,12]

A recent prospective cohort study consisting of 14,687 patients provides strong evidence supporting the discontinuation of RASi before noncardiac surgery because of the risks of death and postoperative cardiovascular events.[13] The number of professional medical societies favoring preoperative discontinuation of RASi have increased in recent years, with only the European Society of Anesthesiology and the French Society of Anesthesiology still recommending continuing RASi before surgery.[14] However, whether preoperative RASi should be discontinued in patients with HF undergoing cardiac surgery still needs to be evaluated.

Heart failure is commonly present in patients undergoing cardiac surgery, and surgical patients with HF are more prone to

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postoperative readmission, morbidity, and mortality.[15–17] Thus far, there is a critical lack of evidence on the effect of continuation or discontinuation of RASi on clinical outcomes in HF patients undergoing cardiac surgery. Here, we hypothesize that the benefits of preoperative continuation of RASi in surgical patients with HF may outweigh the risks.

METHODS

Study Design and Data Acquisition

We conducted a retrospective cohort study of 2338 patients with HF and on chronic RASi therapy identified from an initial group of 8800 consecutive patients undergoing coronary artery bypass grafting (CABG) and/or valve surgery from three US academic medical centers between 2001 and 2015. The data were from the participating institutions' Society of Thoracic Surgeons (STS) database. This study was approved by local Institutional Review Boards (IRB), and individual consent was waived in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations and the waiver criteria.

Variable Measurements

Preoperative characteristics include age, sex, body mass index (BMI), diabetes, hypertension, smoking, cerebrovascular disease, peripheral arterial disease (PAD), chronic lung disease, prior MI, family history of coronary artery disease (CAD), and use of beta blockers, aspirin, and lipid lowering medications. The treatments include preoperative continuation of RASi (PreRASi) and postoperative use of RASi (PostRASi). Postoperative short-term outcomes were obtained from institutional STS database and patients' medical records, which include stroke, cardiac arrest, renal failure, 30-day mortality, MACE, transient ischemic attack (TIA), heart block, dialysis requirement, and coma in the in-hospital period. The specific definitions of the major characteristics are listed in Table S1, http:// links.lww.com/SLA/D702. The long-term mortality data were retrieved from medical records of the participating hospitals and Social Security Death Index.

Statistical Analysis

Continuous and categorical variables are reported as mean ± standard deviation (SD) or percentages. Statistical analysis was performed using SAS (ver. 9.4, SAS Institute Inc., Cary, NC). Multivariable logistic regression was used to derive a propensity score for the tested treatment, including PreRASi and PostRASi, respectively, of all patients, which reflected the probability that a patient would continue using preoperative RASi and discharge prescription of RASi. When compared the difference in outcomes between the patients who received and not received PreRASi, the inverse probability weighting (IPW) approach based on the propensity scores was then applied to adjust for differences in baseline characteristics between the 2 groups, also termed as treatment selection bias.[18] Standard mean difference was applied to evaluate the effect of the application of IPW adjustment. In addition, multivariable stepwise logistic regression was performed to evaluate the potential independent risk factors of postoperative outcomes including 30-day mortality, MACE, and renal failure.

We further conducted instrumental variable (IV) analyses to adjust for measured and unmeasured potential confounders. We used the site PreRASi rate of the hospital as the IV. The IV approach depends on the assumption that the hospital PreRASi rate was highly related to the application of PreRASi, and the IV was not associated with the tested short-term outcomes. Or, the IV is allowed to associate with the outcome through its correlation with the treatment. This method has been widely used in observational studies to strengthen causal inference. A 2-stage regression was conducted using STATA software. First, a logistic regression with PreRASi as the dependent variable and site PreRASi rate as the independent variable. Second, the prediction of PreRASi from the step-one regression was used as the proxy variable of PreRASi to test its causal association with the outcomes.

Survival curves were estimated by use of the Kaplan-Meier method. For each group with or without preoperative RASi, the survival curves represented the expected proportion of survival if the treatment of interest (continue or discontinue preoperative RASi) were applied to all study patients. Using estimated rates of survival among patients undergoing cardiac surgery with or without preoperative and postoperative RASi, we calculated relative risk at the time points of interest and used bootstrap methods to obtain their 95% confidence intervals (CI), adjusting for multiplicity and false discovery to assess the effects of PreRASi on survival for 1 to 6 years, respectively. The stepwise regression based on Cox proportional hazards model was conducted to screen the independent factors of 6-year mortality.

To test the potential interaction of the effects of perioperative RASi with the type of surgery and HF status, we also conducted the aforementioned analyses in patients undergoing CABG and valve surgery alone, as well as in patients without record of HF. We also tested the potential effects of PreRASi and PostRASi on the long-term mortality by a survival analysis in which the whole sample was subgrouped by PreRASi × PostRASi.

RESULTS

Of the initial 8800 study subjects, 2341 patients were identified with HF and 1064 patients without HF undergoing CABG and/or valve surgeries. Details of the procedures of the study sample screening are presented in Figures S1, http://links.lww.com/SLA/ D693 and S2, http://links.lww.com/SLA/D694.

The characteristics of the HF patients used for developing propensity score are summarized in Table S2, http://links.lww.com/SLA/D703 and S3, http://links.lww.com/SLA/D704. Patients in the PreRASi group had lower ejection fraction (EF), were more likely to have diabetes ($P = 0.0002$), hypertension ($P < 0.0001$), and more take beta-blockers ($P < 0.0001$), aspirin ($P = 0.0002$), and lipid-lowering medications ($P < 0.0001$). These unbalanced baseline characteristics between the 2 groups were successfully adjusted as evidenced by that all adjusted P values > 0.05 and that all standardized differences $< 10\%$, which percentage is suggested as the acceptable upper threshold for favoring successful adjustment.[19,20] Thus, these initially unbalanced characteristics would have likely introduced treatment selection bias and influenced the clinical outcomes of interest. Besides, EF of the PreRASi group (44.30 ± 15.14) was significantly lower ($P = 5.58 \times 10^{-6}$) than that of the No-PreRASi group (47.18 ± 15.35). The variables used in the propensity analyses for PostRASi are listed in Table S3, http://links.lww.com/SLA/D704. The EF in the PostRASi group (42.68 ± 16.03) was significantly lower ($P = 7.91 \times 10^{-14}$) than that of the No-PostRASi group (48.18 ± 14.47). As evidenced by all P values > 0.05 and all standard mean differences $< 10\%$, success balance was also achieved between No-PostRASi and PostRASi groups.

The results of statistical analyses of PreRASi on short-term outcomes in HF patients are shown in Figure 1, along with the corresponding estimates of effect size. After correction using

Characteristics	PreRASi		*p* value	OR (95% CI)
	Yes, n = 1,081	No, n = 1,257		
MI	7 (0.65%)	7 (0.56%)	0.777	1.164 (0.407 - 3.329)
Heart block	36 (3.33%)	23 (1.83%)	***0.023***	1.848 (1.088 - 3.139)
MACE	104 (9.62%)	122 (9.71%)	0.945	0.990 (0.752 - 1.304)
30-day mortality	62 (5.74%)	124 (9.86%)	***< 0.0001***	0.556 (0.405 - 0.763)
Coma	657 (60.78%)	713 (56.72%)	0.057	1.175 (0.996 - 1.386)
Stroke	24 (2.22%)	47 (3.74%)	***0.035***	0.585 (0.355 - 0.962)
Cardiac arrest	40 (3.70%)	47 (3.74%)	0.961	0.989 (0.644 - 1.520)
Dialysis requirement	40 (3.70%)	68 (5.41%)	0.051	0.672 (0.451 - 1.002)
Renal failure	75 (6.94%)	127 (10.10%)	***0.007***	0.663 (0.493 - 0.894)
Readmission	115 (10.64%)	114 (9.07%)	0.204	1.194 (0.909 - 1.568)

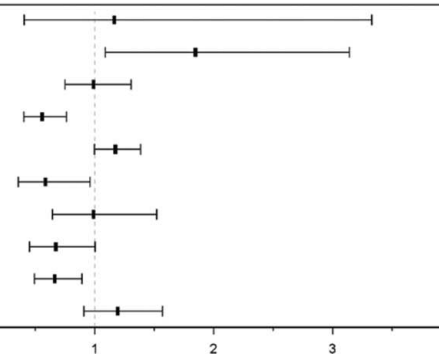
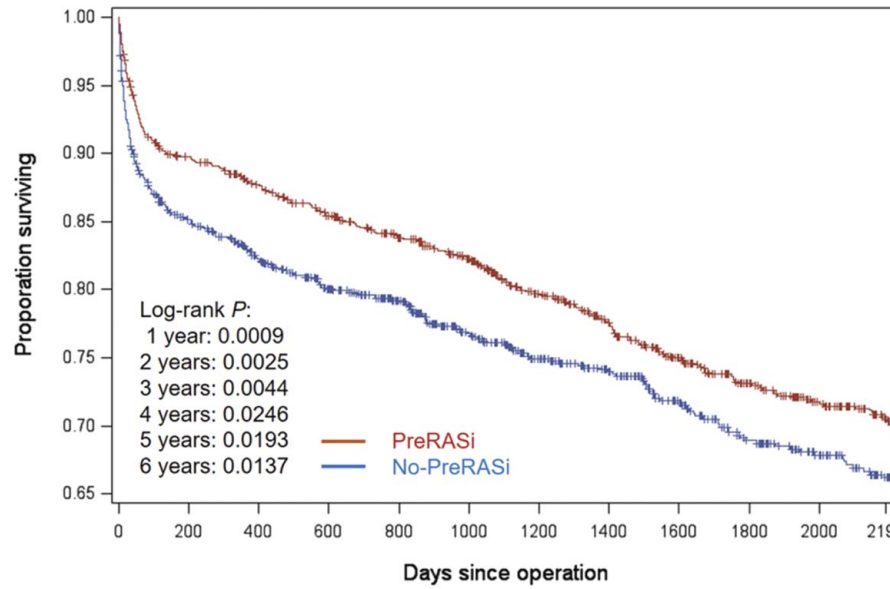


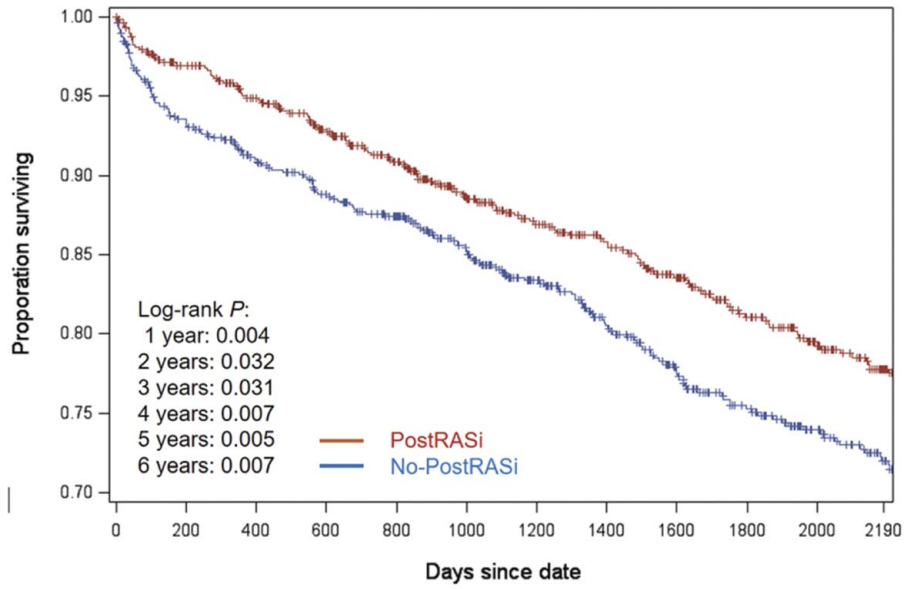
FIGURE 1. Effects of PreRASi on short-term outcomes in HF patients. In the right figure, x-axis represents odds ratio (OR). y-axis represents the corresponding clinical outcomes. OR <1 means preoperative continuation of RASi brings favorable effect on the clinical outcome with decreased risk. The vertical lines in blue represent the estimates of OR, with the extending horizontal bars representing their 95% confidence intervals. Propensity score and instrumental variable were applied to adjust for measured and unmeasured confounders. The significant *P* values (P < 0.05) are in italic bold.

IPW method and IV analyses, we found that PreRASi was associated with reduction of risk of 30-day mortality (5.74% vs 9.86%, OR: 0.556, 95% CI: 0.405–0.763, P < 0.001), stroke (2.22% vs 3.74%, OR: 0.585,95% CI: 0.355–0.962, *P* = 0.035), and renal failure (6.94% vs 10.10%, OR: 0.663, 95% CI: 0.493-0.894, P = 0.007) compared to No-PreRASi group. However, we also observed that PreRASi therapy was associated with increased risks of heart block (3.33% vs 1.83%, OR: 1.848, 95% CI: 1.088–3.139, *P* = 0.023). There was no significant difference in the risks of postoperative MI, MACE, coma, cardiac arrest,



	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years
Mortality% with PreRASi = Yes (95% CI)	12.06 (11.89-12.23)	15.83 (15.65-16.02)	19.32 (19.14-19.50)	23.67 (23.49-23.85)	27.17 (26.99-27.36)	29.57 (29.38-29.76)
Mortality% with PreRASi = No (95% CI)	17.04 (16.87-17.21)	20.59 (20.41-20.77)	24.07 (23.89-24.25)	26.51 (26.32-26.69)	31.32 (31.11-31.52)	33.87 (33.66-34.08)
Hazard Ratio of PreRASi = Yes versus No	0.73 (0.58-0.91)	0.77 (0.63-0.95)	0.80 (0.66-0.97)	0.86 (0.72-1.02)	0.86 (0.72-1.02)	0.85 (0.72-1.01)
Log-Rank *p* value	***0.0009***	***0.0025***	***0.0044***	***0.0246***	***0.0193***	***0.0137***

FIGURE 2. Survival curve of 6-year by PreRASi in HF patients. The x-axis is day number since operation. The significant *P* values (*P* < 0.05) are in italic bold.



	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years
Mortality% with PostRASi = Yes (95% CI)	5.05 (4.81-5.29)	8.70 (8.47-8.94)	12.30 (12.04-12.56)	14.92 (14.65-15.18)	19.05 (18.77-19.33)	22.43 (22.13-22.72)
Mortality% with PostRASi = No (95% CI)	8.71 (8.48-8.94)	12.47 (12.23-12.71)	16.06 (15.81-16.31)	20.23 (19.98-20.47)	25.14 (24.88-25.40)	28.07 (27.80-28.35)
Hazard Ratio of PostRASi = Yes versus No	0.54 (0.37-0.79)	0.68 (0.50-0.92)	0.72 (0.55-0.94)	0.69 (0.54-0.89)	0.69 (0.55-0.87)	0.71 (0.57-0.89)
Log-Rank *p* value	***0.004***	***0.032***	***0.031***	***0.007***	***0.005***	***0.007***

FIGURE 3. Survival curve of 6-year in HF patients. Because our PostRASi was defined as prescription of RASi at discharge, to avoid immortal time bias, the in-hospital dead patients was excluded from the analysis, and the *x*-axis is day number since discharge. The significant P values ($P < 0.05$) are in italic bold.

dialysis requirement, or readmission between the 2 groups. In contrast, in the supplemental analyses in patients without HF (Table S4, http://links.lww.com/SLA/D705), PreRASi only provided protection against renal failure ($P = 0.026$).

The mean follow-up time for long-term outcomes was 5.34 years. The estimates of cumulative survival, relative risk of death,, and survival curves, as well as the P values for testing the equality of mortality between these 2 groups in HF patients, are shown in Figure 2 for PreRASi versus No-PreRASi and Figure 3 for PostRASi versus No-PostRASi. Both PreRASi ($P = 0.0137$) and PostRASi ($P = 0.007$) reduced 6-year mortality compared with the corresponding no-RASi groups. Please keep in mind that the inhospital mortality was excluded from the analysis to avoid immortal time bias because the PostRASi was defined as patients receiving discharge prescriptions of RASi.

Multivariable stepwise logistic regression was performed to screen for independent risk factors of 30-day mortality, MACE, and renal failure. For 30-day mortality (Table 1), we observed that RASi ($P = 0.0011$), male sex ($P = 0.0268$), and increased BMI ($p < 0.0001$) had protective effects; increased preexisting PAD ($P < 0.0001$), cardiopulmonary bypass (CPB) time
($P < 0.0001$) and older age ($P = 0.0004$) correlated with higher risk. For MACE (Table 2), analysis showed that use of aspirin provided protection ($P = 0.0351$); preexisting PAD ($P = 0.0064$), as well as increased initial ICU time ($P < 0.0001$) and age ($P = 0.0017$) significantly increase the risk. As shown in Table S5, http://links.lww.com/SLA/D706, the risk of renal failure was significantly decreased by PreRASi ($P = 0.011$) and increased with preexisting diabetes ($P = 0.0036$), as well as increased time

TABLE 1. Independent Factors of 30-Day Mortality

	30-Day Mortality			
Characteristics	**Yes (N = 186)**	**No (N = 2152)**	***P***	**OR (95% CI)**
PreRASi	62 (33.33%)	1019 (47.35%)	0.0011	0.584 (0.422–0.807)
PAD	50 (26.88%)	321 (14.92%)	<0.0001	2.218 (1.554–3.164)
Male sex	100 (53.76%)	1352 (62.83%)	0.0268	0.704 (0.516–0.960)
Body mass index	26.62 ± 6.88	29.64 ± 17.42	< 0.0001	0.571 (0.432–0.756)
CPB time	131.33 ± 54.41	119.02 ± 30.67	< 0.0001	1.262 (1.141–1.397)
Age	71.26 ± 13.51	67.04 ± 13.11	0.0004	1.578 (1.228–2.028)

The significant P values are $P < 0.05$.

TABLE 2. Independent Factors of Major Adverse Cardiovascular Events

Characteristics	MACE		P	OR (95% CI)
	Yes (N = 221)	No (N = 2,117)		
Aspirin	139 (61.50%)	1412 (66.86%)	0.0351	0.733 (0.549–0.978)
PAD	51 (22.57%)	320 (15.15%)	0.0064	1.607 (1.143–2.259)
Initial ICU Time	239.76 ± 299.40	136.31 ± 206.70	< 0.0001	1.647 (1.377–1.970)
Age	69.41 ± 13.88	67.15 ± 13.09	0.017	1.306 (1.049–1.627)

The significant P values are $P < 0.05$.

of CPB ($P = 0.0074$) and initial ICU stay ($P < 0.0001$). As shown in Table 3, high BMI ($P = 0.0242$), as well as use of lipid lowering medications ($P = 0.0346$) and aspirin ($P = 0.0008$) were independent protective factors of 6-year mortality, whereas older age ($P < 0.0001$), diabetes ($P = 0.0009$), PAD ($P < 0.0001$), chronic lung disease ($P < 0.0001$), and prior MI ($P = 0.0006$) being independent risk factors.

In the subgroup analyses by surgery type for the effect of PreRASi on short-term outcomes (Table S6, http://links.lww.com/ SLA/D707 for CABG and Table S7, http://links.lww.com/ SLA/ D708 for valve surgery), the effect of PreRASi on 6-year mortality (Figure S3, http://links.lww.com/SLA/D695 for CABG and S4, http:// links.lww.com/SLA/D696 for valve surgery), and the effect of PostRASi on 6-year mortality (Figure S5, http:// links.lww.com/SLA/D697 for CABG and S6, http://links.lww.com/SLA/D698 for valve surgery), we found both homogeneity and heterogeneity existing between the subgroups by the surgery type. Specifically, PreRASi protected against 30-day mortality in both CAB ($P = 0.008$) and valve ($P = 0.006$) subgroups, protected against renal failure in CAB patients ($P = 0.014$), whereas increased risks of heart block ($P = 0.007$) and coma ($P = 0.039$) in valve patients. We also found protective effect of PreRASi against long-term mortality mainly in valve-surgery patients. In contrast, PostRASi exerted stronger protection in CAB patients.

We further conducted interaction survival analyses of PreRASi and PostRASi by subgrouping the whole cohort into 4 according to perioperative RASi application: Pre-Post, NoPre-Post, Pre-NoPost, and NoPre-Post. As shown in Figure S7, http://links.lww.com/SLA/ D699, Pre-Post and NoPre-Post RASi are associated with much better outcome than Pre-NoPost and NoPre-NoPost groups.

We also tested whether the long-term protective effects of PreRASi and PostRASi persisted in patients without HF. The results are presented in Figures S8, http://links.lww.com/SLA/ D700 and S9, http://links.lww.com/SLA/D701. As shown, neither PreRASi nor PostRASi exhibited protection against all-cause mortality (all $P \geq 0.05$).

TABLE 3. Effects of Baseline Characteristics On 6-Year Mortality

Characteristics	P	Hazard Ratio (95% CI)
PreRASi	0.087	0.87 (0.74–1.02)
Age, y	***<0.0001***	1.03 (1.02–1.04)
Body mass index	***0.0242***	0.99 (0.97–1.00)
Male sex	0.1726	0.89 (0.76–1.05)
Diabetes	***0.0009***	1.32 (1.12–1.56)
Hypertension	0.342	1.11 (0.90–1.36)
Cerebrovascular disease	0.0604	1.19 (0.99–1.43)
PAD	***<0.0001***	1.53 (1.26–1.86)
Chronic lung disease	***<0.0001***	1.41 (1.19–1.67)
Previous MI	***0.0006***	1.34 (1.14–1.59)
Lipid lowering medicine	***0.0346***	1.21 (1.01–1.44)
Aspirin	***0.0008***	0.75 (0.63–0.89)

The significant P values ($P < 0.05$) are in italic bold.

DISCUSSION

In this retrospective cohort study in patients with HF undergoing CABG and/or valve surgeries, we found that PreRASi exerted protection on 30-day mortality, stroke, and renal failure after propensity score adjustment and instrumental variable analyses. Both PreRASi and PostRASi were associated with lower 6-year mortality compared to No-RASi groups in this cohort.

Preoperative RASi management is a complicated issue related to the patient's clinical and physiological characteristics, type of surgery, duration and dose of RASi use, and preoperative continuation versus discontinuation of RASi.[3] Therefore, performing subgroup analysis in patients with important preoperative clinical characteristics may be more relevant, especially in the patients with HF which is already predisposed to increased postoperative complications and higher mortality.

A randomized study suggested that continuous infusion of the ACEi enalaprilat before initiation of CPB may help to protect the heart against ischemia/reperfusion injury.[21] Preclinical study using animal HF model demonstrated that using ACEi in patients with cardioplegia improved postischemic heart function and coronary perfusion, as well as increased the level of high-energy phosphate in myocardial cells.[22] The authors suggested that the cardioprotective effect of ACEi may be related to the decreases in oxygen consumption of the remodeled myocardium which may help to explain the observed favorable effects of Pre- and PostRASi on postoperative outcomes in this study.

Cardiopulmonary bypass has been reported to cause an increase in plasminogen activator inhibitor-1 (PAI-1) in the early postoperative period, and the increased PAI-1 activity was associated with early vein graft occlusion after CABG.[23,24] Preoperative ACEi attenuates the increase in PAI-1 after CABG and thus may play a role in reducing the risk of graft thrombosis.[25] It was reported that patients undergoing CABG pretreated with captopril starting 2 days before surgery had better preserved renal plasma flow and glomerular filtration rate (GFR) during CPB compared with placebo.[26] Moreover, patients undergoing abdominal aorta surgery pretreated with a single dose of enalapril before anesthesia induction had a significantly greater creatinine clearance on the first postoperative day compared with the placebo group.[27]

In a large sample comprising 240,978 patients who underwent inpatient surgery, the authors found that nonresumption of ACEi was independently associated with increased 30-day mortality compared to the restarted group.[28] Our findings in this study also favor the restarting RASi after surgery since PostRASi even provided stronger evidence and longer protection against mortality compared with PreRASi. Unfortunately, data show that about 25% patients fail to resume

ACEi medications after surgery.[28] Therefore, for patients who may have stopped RASi drugs before surgery, it is important to make sure to restart RASi after surgery. Based on the findings of this study, this is especially important for patients with HF who are already at greater risk of postoperative mortality and complications.

In this study, patients in the PreRASi group had significantly more comorbidities, including diabetes and hypertension, compared to patients in No-PreRASi group. Also, we found that EF of the PreRASi group was significantly lower than that of the No-PreRASi group. This implies that despite the lack of precise guidelines and evidence-based support, there is still a tendency in clinical practice to continue RASi before surgery in high-risk patients. At the same time, EF of the PostRASi group was also significantly lower than that of the No-PostRASi group. Lower EF in PreRASi and PostRASi groups further strengthens the advantage of pre- and postoperative use of RASi.

At present, there are limited studies examining the effect of discontinuing versus continuing RASi on postoperative clinical outcomes in patients with HF undergoing cardiac surgery. Pichette et al recommended withholding RASi 3 days before cardiac surgery in patients with HF because preoperative continuation was associated with an increased risk of postoperative AKI and dialysis requirement.[29] This recommendation was made based on 2 studies that in patients with HF who underwent heart transplantation[30] or implantation of left ventricular assist devices (LVAD).[31] However, it is important to keep in mind that those studies were in the heart transplantation or LVAD implantation patients with end-stage HF which is distinct from the patient population in this study cohort. Moreover, 61% of the patients who developed AKI requiring renal replacement therapy were taking both an ACEi and an ARB preoperatively in the heart transplant study. The authors suggested that the detrimental effects of ACEi and ARB on renal function could be related specifically to combination therapy. In the LVAD study, the use of ACEi or ARB contributed to a decrease in GFR 1 month after LVAD implantation for patients with admission GFRs < 60 mL/min/ 1.73 m^2. The difference in surgical procedures and patient population may at least partially explain the inconsistent findings between these 2 studies and this study here regarding renal effects.

As shown in Figures 2 and 3, PreRASi and PostRASi showed consistent protection against mortality compared with the No-Pre-RASi and No-PostRASi groups, respectively. This protective effect is in line with our previously findings in the entire patient sample, without controlling for whether the patient has HF or not.[32] Comparing the results of the survival analyses between these two studies, we found smaller hazard ratios for the protective effect of PreRASi on postoperative mortality. This implies that PreRASi exerts more significant protection against mortality in patients with HF, which was further supported by the findings that neither PreRASi nor PostRASi provided protection against 6-year mortality in patients without HF history (Figure S8, http://links.lww.com/SLA/D700, S9, http://links.lww.com/SLA/D701).

In this study, use of aspirin and lipid lowering medications showed independent protection on 6-year mortality, strengthening the importance of prescription of these medications in cardiac surgical patients with HF. Unsurprisingly, age was an important independent risk factor for most of the observed adverse events including 30-day mortality, MACE, and 6-year mortality. Another interesting finding was that higher BMI had a protective effect on postoperative 30-day mortality (average BMI of the nonsurvivors was 26.62 vs 29.64 for survivors). Although obesity is an important risk factor for cardiovascular disease, the negative correlation between obesity and short-term mortality in surgical or nonsurgical patients is not uncommon, known as the "obesity paradox." Our previous study demonstrated that extreme obesity and underweight were significantly associated with major adverse clinical outcomes in patients undergoing cardiac surgery. However, there was an obesity paradox observed in short-term mortality. A recent reported retrospective study and meta-analysis showed that although there was a positive correlation between BMI and risk of most postoperative complications, BMI and in-hospital all-cause mortality after cardiac surgery still showed negative correlation.[33] In the risk score developed by Andersson et al for predicting 30-day mortality in HF patients undergoing noncardiac surgery, postoperative 30-day mortality decreases gradually along with a gradual increase in BMI.[34] These findings are in agreement with the findings in this study, although the underlying mechanisms are still largely unclear.

Our study did demonstrate an unfavorable effect of preoperative continuation of RASi on risk of postoperative heart block. The explanation of this observation is challenging. From a statistical perspective, the prevalence of postoperative heart block in our study is very low (3.33% in PreRASi group and 1.83% in No-PreRASi group). This may limit the robustness of the statistical inference. Although we speculate the increased risk of heart block might be partially attributable to potential hypotension induced by RASi, there is no direct evidence to support this. However, indirect evidence, such as myocardial ischemia, has been suggested to cause heart block.[35] Further studies are still warranted to clarify the effect of PreRASi on heart block in the HF population.

In the interaction survival analyses of PreRASi and PostRASi, the 2 subgroups with PostRASi provided much better protection against mortality than the 2 No-PostRASi subgroups did (Figure S7, http://links.lww.com/SLA/D699). On the contrary, it seems that the 2 subgroups with PreRASi did not provided better mortality protection than the 2 No-PreRASi subgroups did. However, this result needs to be interpreted with caution. To avoid immortal time bias brought by in-hospital death, the in-hospital dead patients were excluded from this analysis. So actually, what this plot indicates is that in the patients who could live through discharge, PostRASi provides more powerful protection against mortality over PreRASi does. At the same time, we did not observe mortality protection of PreRASi or PostRASi in patients without HF (Figures S8, http://links.lww.com/ SLA/D700 and S9, http://links.lww.com/SLA/D701). This finding suggestions we should take into consideration the differences between patients with and without HF to optimize the use of perioperative RASi medications.

The primary limitation of this study is that this is not a randomized study, although we utilized propensity scores and conducted IV analyses to minimize bias and control for confounders. In the setting of a large sample size, these methods can provide robust analysis and reliable results. We selected the method of IPW due to its reported advantages over matching and stratification methods.[36] Another limitation may be that we did not differentiate ARB with ACEi drugs in our database. ACEi and ARBs are often clinically considered interchangeable. However, these 2 drug classes have different mechanisms of inhibition and thus differ in their clinical effects.[37,38]

In summary, the results of this study favor the pre- and postoperative use of RASi in patients with heart failure undergoing CABG and/or valve surgeries. Further studies, especially large-scale randomized controlled trials, are warranted to

provide more definitive evidence on this issue. The risk factors for postoperative 30-day mortality, MACE, and renal failure from this study can be used for risk reduction and prognostication in heart failure patients undergoing CABG and/or valve surgeries.

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