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ORIGINAL RESEARCH

Impact of Renin-Angiotensin System Blockers on Mortality in Veterans Undergoing Cardiac Surgery

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BACKGROUND: Renin-angiotensin system blockers (RASBs) have well-validated benefit in patients with hypertension, coronary artery disease, and left ventricular systolic dysfunction. Their use in the perioperative period, however, has been controversial, including in patients undergoing cardiac surgery, who often have a strong indication for their use. In the current study, we explore the impact of RASB use with 30-day and 1-year mortality after cardiac surgery.

METHODS AND RESULTS: The Veterans Affairs Surgical Quality Improvement Program and Corporate Data Warehouse were data sources for this retrospective cohort study. A total of 37 197 veterans undergoing elective coronary artery bypass grafting and or valve repair or replacement over a 10-year period met inclusion criteria and were stratified into 4 groups by preoperative exposure (preoperative exposure versus no preoperative exposure) and postoperative continuing exposure (current exposure versus no current exposure) to RASBs. After adjusting for all baseline covariates, the preoperative exposure/current exposure group had lower 30-day and 1-year mortality than the preoperative exposure/no current exposure (30-day hazard ratio [HR], 0.25; 95% CI, 0.19–0.33 [*P*<0.001] and 1-year HR, 0.40; 95% CI, 0.33–0.48 [*P*<0.001] or no preoperative exposure/no current exposure (30-day HR, 0.44; 95% CI, 0.32–0.60 [*P*<0.001] and 1-year HR, 0.72; 95% CI, 0.62–0.84 [*P*<0.001] groups. The no preoperative exposure/current exposure group had significantly lower 30-day (HR, 0.31; 95% CI, 0.14–0.71 [*P*=0.006]) and 1-year (HR, 0.64; 95% CI, 0.53–0.77 [*P*<0.001]) mortality than the no preoperative exposure/no current exposure group.

CONCLUSIONS: Continuation of preoperative RASBs and initiation before discharge is associated with decreased mortality in veterans undergoing cardiac surgery. Given these findings, continuation of preoperative RASBs or initiation in the early postoperative period should be considered in patients undergoing cardiac surgery.

Key Words: ACEI ■ ARB ■ cardiac surgery ■ mortality

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) together are the most commonly prescribed class of antihypertensives in the United States, and it is estimated that ≈18% of adults use these drugs.[1] Given the wealth of data supporting their benefits beyond hypertension control, multiple professional guidelines strongly endorse their use in patients with coronary artery disease (CAD), systolic heart failure, and diabetes mellitus.[2–4] Despite this, considerable controversy exists regarding their use in the preoperative and early postoperative period because of concerns of adverse outcomes such as hypotension, stroke, and kidney injury.[5–11] Even among patients undergoing cardiac surgery (compared with noncardiac surgery), where the majority of patients may have a strong indication for this class of medication and greater likelihood of long-term benefit, findings have been mixed.[12–17] Among patients undergoing coronary artery bypass grafting (CABG), postoperative continuation of preoperative ACEI/ARB prescription is supported in the guidelines, as is de novo prescription for ACEIs/ARBs in patients

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective study of 37 197 veterans undergoing cardiac surgery (85% coronary artery bypass grafting with or without valve repair/replacement), ≈38% were not taking renin-angiotensin system blockers (RASBs) preoperatively and 25% never received RASBs during 1-year follow-up.
- Continuation of preoperative RASB or initiation early in the postoperative period was associated with lower all-cause mortality at 30 days and 1 year following surgery compared with discontinuation or noninitiation.
- This favorable impact was similar among patients with chronic kidney disease stages I to III and evident even in patients undergoing isolated valve surgery.

What Are the Clinical Implications?

- RASBs remain underutilized in patients undergoing cardiac surgery despite proven benefits in those with coronary artery disease and those with valve disease and left ventricular dysfunction, diabetes mellitus, or chronic kidney disease.
- Continuation of preoperative RASBs or initiation in the postoperative period before discharge (for patients not taking them preoperatively) should be considered for most patients undergoing coronary artery bypass grafting and/or valve repair or replacement surgery.

Nonstandard Abbreviations and Acronyms

BCMA	Barcode Medication Administration
CDW	Corporate Data Warehouse
CE	current exposure
CICSP	Continuous Improvement in Cardiac Surgery Program
NCE	no current exposure
NPE	no preoperative exposure
PE	reoperative exposure
RASB	renin-angiotensin system blocker
VA	Veterans Affairs
VASQIP	Veterans Affairs Surgical Quality Improvement Program
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure

with left ventricular (LV) dysfunction, diabetes mellitus, or chronic kidney disease (CKD).[18–20] In patients without LV dysfunction, diabetes mellitus, or CKD, the guidelines diverge, with some recommending for[19] and others recommending against[18] (Kulik) postoperative initiation of these agents. Notably, the evidence base supporting the benefits of commonly prescribed therapies for CAD in patients who undergo CABG is relatively less robust and comes from much smaller studies[15,21–23] compared with patients treated with medical therapy or percutaneous coronary intervention. Furthermore, it has been clearly shown that patients with CABG are less than half as likely to receive ACEIs/ARBs compared with those undergoing percutaneous coronary intervention, indicating that there is a gap between practice and evidence in patients post-CABG.[21,24,25] Currently, CABG is the most common cardiac surgery performed in the United States and accounts for 60% of all cardiac surgeries (≈8% are combined with valve surgery), while isolated valve repair or replacement accounts for ≈15% of cardiac surgeries.[26] In contrast to guidelines in patients undergoing CABG, guidelines on valvular heart disease make no recommendation regarding postoperative use of ACEIs or ARBs.[27] A small number of trials, however, have demonstrated greater LV mass regression, decreased heart failure, and improved survival with ACEIs and ARBs in patients undergoing valve surgery.[28–30] Thus, while there is significant evidence supporting the long-term benefits of renin-angiotensin system blockers (RASBs) in patients undergoing cardiac surgery, their short-term impact on mortality remains unclear and their use remains less than optimal. In this study, we explore the impact of RASB use on 30-day and 1-year mortality in veterans undergoing cardiac surgery.

METHODS

This study was approved by the Veterans Affairs (VA) Nebraska-Western Iowa Healthcare System Subcommittee on Human Subjects Research. Informed consent was waived. A deidentified, anonymized version of the data that support the findings of this study will be made available by the corresponding author upon reasonable request.

Data Source

The study population was derived from the Veterans Affairs Surgical Quality Improvement Program (VASQIP), known originally as the Continuous Improvement in Cardiac Surgery Program (CICSP). VASQIP contains prospectively collected demographic, clinical, and operative data on all cardiac surgeries within the Veterans Healthcare Administration (VHA) system since 1987.[31] The study population was linked via scrambled social security number to the VHA's Corporate Data Warehouse (CDW) that accommodates analysis of the decades of administrative, demographic, and clinical data contained in the VHA's integrated healthcare

information system. Complete descriptions of CICSP,[32] VASQIP,[33] and CDW[34] have been previously published.

Veteran Selection

From the VASQIP database, 46 115 encounters were identified with a primary CABG (Current Procedural Terminology [CPT] codes: 33510–33548) or primary valve repair or replacement surgery (CPT codes: 33400–33496) occurring between January 1, 2005, and December 31, 2014 (Figure 1). We excluded veterans who had repeat CABG or valve surgery during the study period, as well as veterans with severe (estimated glomerular filtration rate, 15–29 mL/min per 1.73m^2) or end-stage (estimated glomerular filtration rate, <15 mL/min per 1.73m^2) CKD, preoperative acute kidney injury or renal replacement therapy, concomitant aorta or other great vessel surgery, or concomitant implantation of a circulatory support device other than intra-aortic balloon pump. Veterans with missing preoperative creatinine values and those missing a unique veteran or VA facility indicator were excluded.

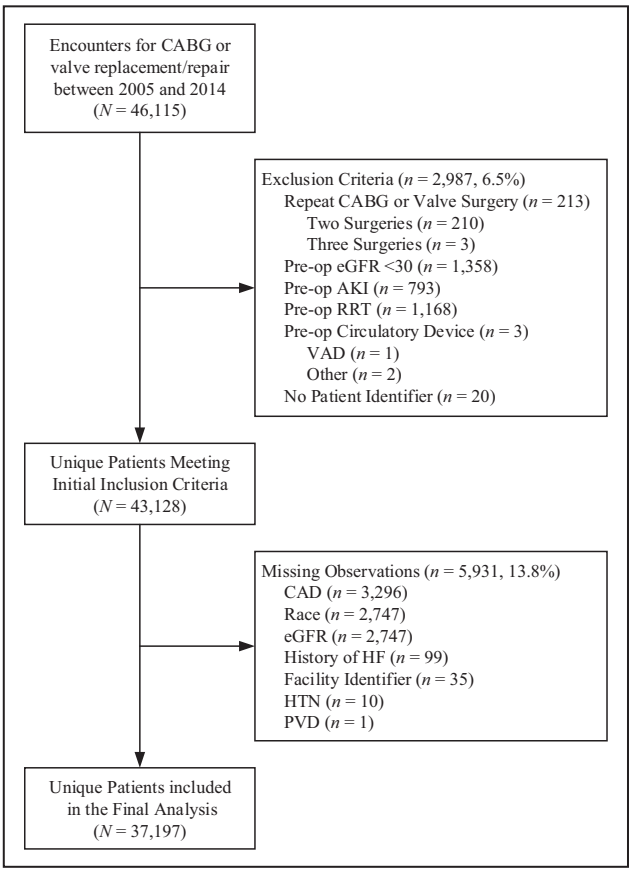

Figure 1. Study flow diagram.
AKI indicates acute kidney injury; CABG, coronary artery bypass grafting; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; Pre-op, preoperative; PVD, peripheral vascular disease; RRT, renal replacement therapy; and VAD, ventricular assist device.

RASB Exposure

Preoperative and postoperative RASB prescriptions were identified using inpatient dispensary data (via the Barcode Medication Administration [BCMA]) and using outpatient prescriptions filled at any VA pharmacy. Single or combination RASBs were included (Table S1). Veterans who filled an outpatient RASB prescription with enough days of supply to overlap their surgery date (maximum days of supply was 90 days), as well as veterans who received any BCMA-documented RASBs during their surgical stay between admission date and surgery date, were considered to be taking preoperative RASBs. Postoperative RASB use and exposure is described in detail in the Statistical Analysis section below. The study population was then divided into 4 groups based on preoperative and postoperative exposure. Conceptually, these can be thought of as "continuation" (taking RASBs preoperatively and continued postoperatively), "withdrawal" (taking RASBs preoperatively but not after surgery), "addition" (not taking RASBs preoperatively but initiated on RASBs after surgery), and "never" (not taking RASBs preoperatively or after surgery). However, because patients could have their RASB initiated at different points after surgery, and because a patient could have his/her RASB stopped and/or added/resumed multiple times during the 30- and 365-day follow-up period, the 4 groups were not constant across the follow-up period. To more accurately reflect the analysis, the groups were thus divided by preoperative exposure (PE) versus no preoperative exposure (NPE), and postoperative exposure was defined as current exposure (CE) or no current exposure (NCE) at the day level by the real-time RASB status of the veterans on the day of an event. The 4 resulting groups are labeled as PE/CE, PE/NCE, NPE/CE, and NPE/NCE.

Outcomes and Covariates

Outcomes of interest were all-cause mortality at 30 days and 1 year following surgery. Covariates were chosen a priori based on known clinical association with the outcomes and included age at surgery, race/ethnicity (White, Black, or other [American Indian, Asian or Pacific Islander, Hispanic, and Other or Unknown]), biological sex, history of heart failure, history of stroke, preoperative CKD, type of surgery (CABG, valve, or both), and presence of diabetes mellitus, hypertension, CAD, and/or peripheral vascular disease.

Statistical Analysis

The association between mortality and RASB use was estimated using marginal multivariable Cox proportional hazards models.[35] Marginal models were required to account for the clustering of veterans within

VA facilities. As such, reported hazard ratios (HRs) represent the (population) average effect among VA facilities. We identified postoperative daily RASB exposure for each veteran for 30 days and 365 days post-surgery using inpatient dispensary data during the index surgical stay and any subsequent inpatient stays, as well as fill dates and days of supply for prescriptions filled at outpatient VA pharmacies. For subsequent outpatient refills, we accounted for days of supply remaining based on the previous refill's days of supply. Collecting RASB exposure at the day level allowed us to partition exposure status into time intervals during which the veteran was either exposed or not exposed, from which we transformed the data into counting-process format that allowed multiple start and stop intervals for each veteran corresponding to each veteran's own RASB exposure (Table S2).[36,37] Here, we assumed that a filled outpatient prescription was taken as prescribed for the duration of the days of supply. The counting-process format serves to reduce the immortal time bias[38] by allowing more accurate RASB exposure compared with the more traditional binary RASB exposure status variable—that assumes RASB exposure is constant during the entire length of follow-up—or a cumulative RASB exposure variable.

Continuous variables are presented as mean±SD, whereas categorical variables are presented as frequency and percent. Given that RASB exposure was time dependent, baseline demographic and clinical characteristics were stratified by any RASB exposure within 30 days and 365 days of surgery. Because veterans could be exposed and unexposed to RASB during the study period, the sample sizes varied over time and no statistical tests were conducted for baseline characteristics. The functional form of continuous covariates was evaluated using smoothed Martingale residuals and LOESS smoothing. The proportionality of hazards assumption was evaluated graphically for each categorical covariate using log-negative–log survival curves and statistically using weighted Schoenfeld residuals modeled against follow-up time. We calculated E values for all final models.[39] Briefly, the E value quantifies how large of an HR would be needed for an unmeasured confounding variable to explain away the association between RASB exposure group and mortality. For HRs >1, the E value is calculated as: $HR + \sqrt{HR^* (HR - 1)}$; note that for HRs <1, the reciprocal of the HR was used in the formula. All statistical analyses were conducted using the SAS Grid (SAS Institute Inc) within the VA Informatics and Computing Infrastructure (VINCI)[40] environment; 2-sided $P<0.05$ was used to indicate statistical significance.

RESULTS

Between 2005 and 2014, VASQIP reported data on a total of 46 115 patients who underwent elective CABG and or valve repair or replacement surgery. Of these, 37 197 patients within 41 VA facilities were included in our analysis (median number of patients per VA facility: 852; interquartile range, 664–1091) based on predefined inclusion and exclusion criteria as shown in Figure 1. Patient categorization by RASB use is shown in Table 1. Baseline characteristics of the 4 groups are presented in Tables 2 and 3. As is expected with a VA study, most patients were men and of White race (>98% and >87%, respectively). In general, the PE/CE group had a small but statistically significantly higher baseline prevalence of diabetes mellitus, hypertension, CAD, and stroke, and lower baseline estimated glomerular filtration rate compared with the NPE/NCE group. In contrast, the NPE/NCE group more often consisted of White patients, had slightly higher baseline estimated glomerular filtration rate, and less often underwent isolated CABG compared with the PE/CE group. Isolated valve surgery was significantly more frequent in the NPE/CE and NPE/NCE groups compared with the others. The demographic differences between groups were similar whether they were categorized by RASB use at 1 month (Table 2) or 1 year (Table 3). Lisinopril was the most commonly prescribed ACEI and accounted for >75% of the RASB prescriptions, while losartan was the most commonly prescribed ARB and accounted for 9% of RASB prescriptions (Table S1).

Table 1. Group Definitions

Group	Preoperative RASB	Postoperative RASB	Sample Size	
			30 d	365 d
PE/CE	Yes	Yes	20 221	21 529
PE/NCE	Yes	No	2767	1459
NPE/CE	No	Yes	4497	7184
NPE/NCE	No	No	9712	7025

Sample sizes are based on complete data for time-to-event, outcomes, age, race, biological sex, history of heart failure, chronic kidney disease, diabetes mellitus, hypertension, coronary artery disease, peripheral vascular disease, coronary artery bypass grafting/valve surgery, preoperative stroke, and facility indicator. CE indicates current exposure; NCE, no current exposure; NPE, no preoperative exposure; PE, preoperative exposure; and RASB, renin-angiotensin system blocker.

Table 2. Baseline Characteristics Based on Postoperative RASB Exposure Within 30 Days

	PE/CE (n=20 221)	PE/NCE (n=2767)	NPE/CE (n=4497)	NPE/NCE (n=9712)	*P* Value
Age, y	64.9±8.5	65.1±9.2	64.5±8.9	64.8±8.9	<0.001
Race/Ethnicity					
White	86.6	87.1	87.6	89.7	<0.001
Black	11.4	10.9	11.7	8.2	
Other*	2.0	2.0	2.4	2.1	
Men	98.9	98.6	98.7	98.5	0.067
History of HF	76.4	79.5	74.5	75.6	<0.001
eGFR, mL/min per 1.73m^2	74.4±18.6	74.6±19.3	75.4±18.1	76.5±18.4	<0.001
≥90	23.8	24.9	24.3	27.1	<0.001
60–89	52.1	51.4	54.5	53.0	
30–59	24.0	23.8	21.3	19.9	
Diabetes mellitus	51.4	40.7	38.9	27.0	<0.001
Hypertension	96.5	93.0	89.6	81.9	<0.001
CAD	89.2	92.5	80.1	82.3	<0.001
PVD	22.7	22.4	22.0	17.6	<0.001
History of stroke	4.9	4.7	4.1	3.7	<0.001
Surgery type					
CABG	74.3	76.0	60.8	65.5	<0.001
Valve	13.1	9.5	23.1	20.5	
CABG and valve	12.6	14.5	16.1	14.0	

Data are presented as mean±SD for continuous variables and as percent for categorical variables. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CE, current exposure; eGFR, estimated glomerular filtration rate; HF, heart failure; NCE, no current exposure; NPE, no preoperative exposure; PE, preoperative exposure; PVD, peripheral vascular disease; and RASB, renin-angiotensin system blocker.

* Other includes American Indian, Asian or Pacific Islander, Hispanic, and Other or Unknown.

Unadjusted 30-day mortality (Figure 2 and Table 4) was lowest in the PE/CE ("continuation") group at 0.6%, followed by the NPE/CE ("addition") group at 0.7%. In contrast, 30-day mortality was significantly higher in the NPE/NCE ("never") and PE/NCE ("withdrawal") groups at 1.9% and 10.4%, respectively. After adjusting for all baseline covariates (Table 4 and Figure 3A), the PE/CE group had a 75% (HR, 0.25; 95% CI, 0.19–0.33 [*P*<0.001]) and 56% (HR, 0.44; 95% CI, 0.32–0.60 [*P*<0.001]) lower risk of 30-day mortality compared with the PE/NCE and NPE/NCE groups, respectively. There was no significant mortality difference between the PE/CE and NPE/CE groups (HR, 1.39; 95% CI, 0.65–2.96 [*P*=0.4]). Furthermore, in comparison to the NPE/NCE group, risk of 30-day mortality was 69% lower (HR, 0.31; 95% CI, 0.14–0.71 [*P*=0.006]) in the NPE/CE group.

Unadjusted 1-year mortality (Figure 2 and Table 4) was lowest in the NPE/CE ("addition") group at 3.3%, followed by the PE/CE ("continuation") group at 3.8%. In contrast, 1-year mortality was significantly higher in the NPE/CE ("never") and PE/NCE ("withdrawal") groups at 5% and 27.1%, respectively. After adjusting for all baseline covariates (Table 4 and Figure 3B), the PE/CE group had a 60% (HR, 0.40; 95% CI, 0.33–0.48 [*P*<0.001]) and 28% (HR, 0.72; 95% CI, 0.62–0.84 [*P*<0.001]) lower risk of 1-year mortality compared with the PE/NCE and NPE/NCE groups, respectively. There was no significant mortality difference between the PE/CE and NPE/CE groups (HR, 1.13; 95% CI, 0.93–1.37 [*P*=0.21]). Furthermore, in comparison to the NPE/NCE group, risk of 1-year mortality was 36% lower (HR, 0.64; 95% CI, 0.53–0.77 [*P*=0.006]) in the NPE/CE group.

We also performed a number of sensitivity analyses to test the robustness of our findings. The results were consistent when analyses were restricted only to patients undergoing CABG who clearly had an indication for RASB. On landmark analyses (Table S3), exclusion of mortality in the first month did not change the directionality or significance of 1-year mortality. Approximately 13.8% of the study sample had missing variables, which was primarily race. The distribution of these patients was similar among the 4 categories. We performed a repeat analysis by using multiple imputation for missing data, and imputed results were similar to our main analysis (Table S4). Finally, we explored the impact of CKD stages on the associations between mortality and the various RASB groups. There was no significant interaction of CKD stages on any of the mortality effects (*P* values for all interactions were nonsignificant). These results indicate that the between-group differences

Table 3. Baseline Characteristics Based on Postoperative RASB Exposure Within 365 Days

	PE/CE (n=21 529)	PE/NCE (n=1459)	NPE/CE (n=7184)	NPE/NCE (n=7025)	*P* Value
Age, y	64.9±8.5	65.7±9.3	65.1±8.7	64.9±9.1	0.002
Race					
White	86.6	88.3	87.6	90.6	<0.001
Black	11.4	10.1	10.1	7.5	
Other*	2.0	1.6	2.3	2.0	
Men	98.9	98.6	98.7	98.4	0.035
History of HF	76.7	78.8	75.5	75.1	0.002
eGFR, mL/min per 1.73m^2	74.4±18.7	74.9±19.3	75.5±18.4	76.7±18.2	<0.001
≥90	23.9	25.2	25.1	27.3	<0.001
60–89	52.1	50.9	53.6	53.4	
30–59	24.0	23.9	21.3	19.3	
Diabetes mellitus	51.1	34.5	38.1	23.2	<0.001
Hypertension	96.3	91.8	89.1	79.5	<0.001
CAD	89.4	92.3	82.9	80.2	<.001
PVD	22.7	22.6	21.4	16.5	<0.001
History of stroke	4.8	4.9	3.9	3.8	<0.001
Surgery type					
CABG	74.5	75.1	64.4	63.7	<0.001
Valve	12.8	10.4	20.0	22.6	
CABG and valve	12.7	14.6	15.6	13.7	

Data are presented as mean±SD for continuous variables and as percent for categorical variables. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CE, current exposure; eGFR, estimated glomerular filtration rate; HF, heart failure; NCE, no current exposure; NPE, no preoperative exposure; PE, preoperative exposure; PVD, peripheral vascular disease; and RASB, renin-angiotensin system blocker.

* Other includes American Indian, Asian or Pacific Islander, Hispanic, and Other/Unknown.

presented for both the 30- and 365-day mortality outcome are statistically similar for patients regardless of CKD stages (Table S5).

DISCUSSION

The main finding of our study is that in patients undergoing elective cardiac surgery continuing preoperative RASB or initiating RASB in the postoperative period is associated with lower all-cause mortality at 30 days and 1 year. Furthermore, discontinuation of preoperative RASB is a marker of high risk and is associated with the highest 30-day and 1-year mortality. Significant controversy exists regarding perioperative continuation and early postoperative use of RASBs in patients undergoing elective surgeries in general and cardiac surgeries in particular. A number of studies have suggested that in patients taking RASBs, preoperative continuation is associated with adverse events such as hypotension and need for vasoactive medication.[8,9,41] On the contrary, in 2 large studies in veterans taking preoperative ARBs undergoing noncardiac surgery, Lee et al[40] and Mudumbai et al[42] showed that nonresumption of the ARB within 2 to 14 days of surgery was associated with excess 30-day mortality. It is therefore not surprising that the practice patterns with respect to withholding or continuation of RASB preoperatively and reinitiation of RASBs postoperatively are variable and inconsistent.[43]

A majority of the aforementioned studies assessed the impact of perioperative RASB use in patients undergoing noncardiac surgery where patients are likely to receive RASBs for hypertension. In contrast, the likelihood of taking and benefiting from RASBs is significantly greater in patients undergoing cardiac surgery, where a majority of patients have CAD and or LV dysfunction. Additionally, there is evidence that RASBs, particularly ARBs can prevent microvascular dysfunction and ischemia and reperfusion-mediated injury in acute settings,[41] which could be cardioprotective in patients undergoing cardiac surgery. In contrast, given the higher operative risks of cardiac surgery (compared with noncardiac surgery), the likelihood of perioperative hypotension and adverse outcomes with perioperative RASBs may be higher in this group of patients. A prior large systematic review and meta-analysis of 13 studies (3 randomized controlled trials and 10 observational) and >30 000 patients demonstrated that the risk of perioperative hypotension and

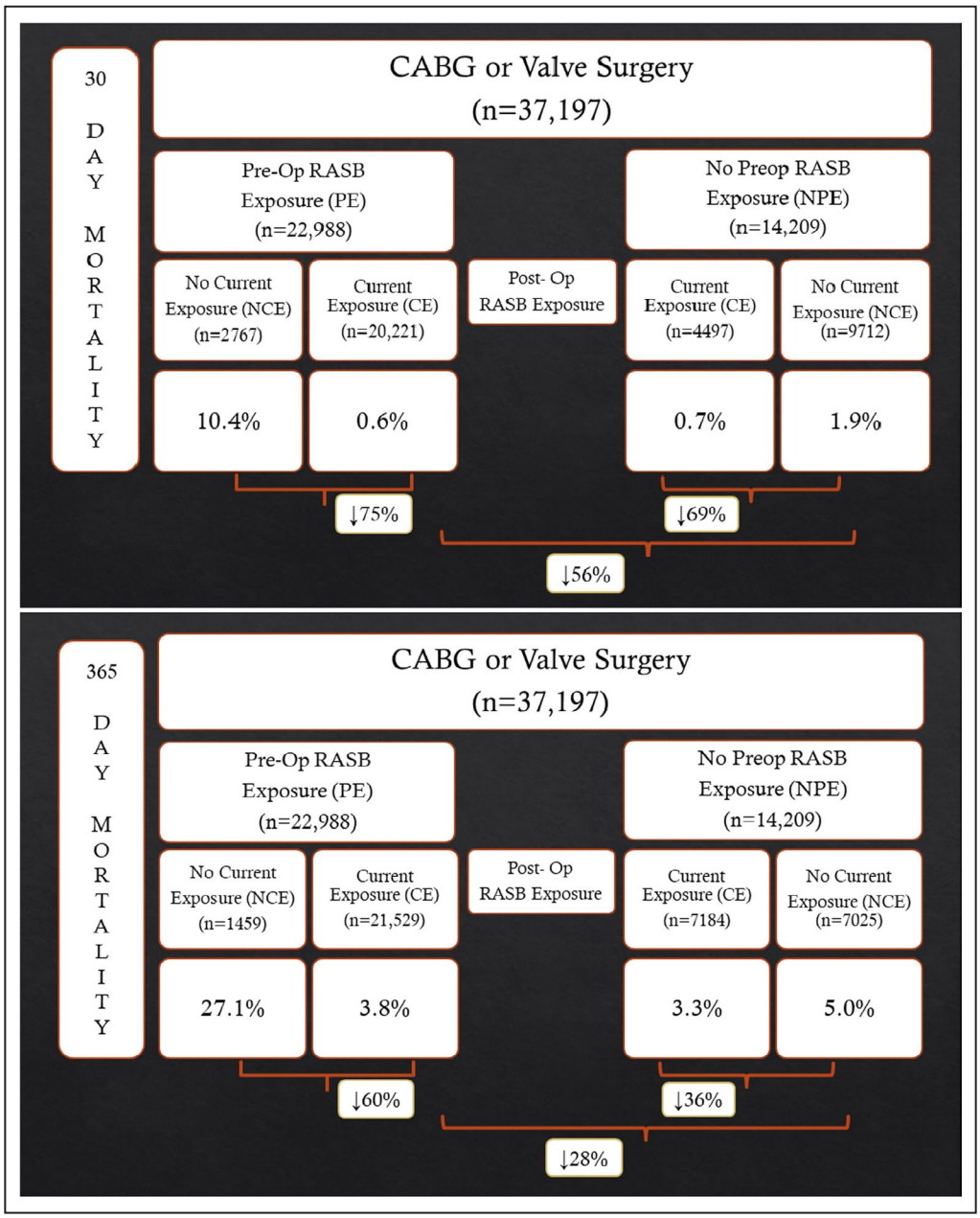

Figure 2. Unadjusted mortality by study group.
CABG indicates coronary artery bypass grafting; Post-op, postoperative; Pre-op, preoperative; and RASB, renin-angiotensin system blocker.

myocardial infarction was higher in those who received preoperative RASBs.[44]

Our study shows that patients who continue preoperative RASBs and those initiated on RASBs postoperatively have better survival at 30 days that persists up to 1 year after the surgery. Our study findings are similar to 2 other observational studies that stratified patients undergoing cardiac surgery into 4 distinct groups and demonstrated that patients who continued or were started on RASBs had significantly better postoperative survival.[45,46] Our study extends these findings to the veteran population and provides evidence for sustained benefits beyond the initial postoperative period. Furthermore, on landmark analyses, exclusion of mortality in the first month did not change the directionality or strength of our findings, suggesting that benefit from exposure was accrued continually. The mortality in the withdrawal group was significantly higher than the other 3 groups despite risk adjustment. This is likely a result of residual bias as this group includes a high-risk population. Several factors such

Table 4. Outcomes

	Outcome Rate, %	Adjusted HR (95% CI)	*P* Value	E Value	
				HR	CI
All-cause mortality at 30 d					
PE/CE vs PE/NCE	0.6 vs 10.4	0.25 (0.19–0.33)	<0.001	7.46	5.51
PE/CE vs NPE/CE	0.6 vs 0.7	1.39 (0.65–2.96)	0.394	2.12	1.00
PE/CE vs NPE/NCE	0.6 vs 1.9	0.44 (0.32–0.60)	<0.001	3.97	2.72
NPE/CE vs NPE/NCE	0.7 vs 1.9	0.31 (0.14–0.71)	0.006	5.91	2.17
All-cause mortality at 365 d					
PE/CE vs PE/NCE	3.8 vs 27.1	0.40 (0.33–0.48)	<0.001	4.44	3.59
PE/CE vs NPE/CE	3.8 vs 3.3	1.13 (0.93–1.37)	0.206	1.51	1.00
PE/CE vs NPE/NCE	3.8 vs 5.0	0.72 (0.62–0.84)	<0.001	2.12	1.67
NPE/CE vs NPE/NCE	3.3 vs 5.0	0.64 (0.53–0.77)	<0.001	2.50	1.92

The reference group is provided after the "vs." As such, an HR <1 indicates that the risk of a given outcome was lower for the first group listed. For example, the HR of 0.25 for all-cause mortality between the continuous and withdrawal groups indicated that patients who continued taking RASBs after surgery averaged a 75% lower risk of death compared with patients for whom the RASB was withdrawn after surgery. CE indicates current exposure; HR, hazard ratio; NCE, no current exposure; NPE, no preoperative exposure; PE, preoperative exposure; and RASB, renin-angiotensin system blocker.

as significant hypotension, shock, need for pressors or ventricular support devices, blood loss requiring multiple transfusions, and acute kidney injury could lead to the postoperative RASB discontinuation and all of the confounders could not be captured given the retrospective nature of our study. However, our finding of a high mortality rate in the postoperative RASB discontinuation group has been consistently demonstrated in other similar studies and serves as a marker for high risk.[45,46] Certain key variables such as LV ejection fraction were not available in this data set and could not be accounted for. Given the known association of LV dysfunction with excess mortality, such an indication bias should have demonstrated a higher mortality rate in patients taking RASBs and a lower mortality rate in veterans who were never started on RASBs who are more likely to have normal LV systolic function. Despite this, veterans who were not taking RASBs had a higher mortality rate, suggesting that the association between RASB use and lower mortality rate may be a true benefit of this class of drugs rather than selection bias. Furthermore, the large E values noted in our analysis (1.51–7.46) suggest that considerable unmeasured confounding would be needed to negate the observed association between RASB use and better survival, strengthening the argument that this is likely a true effect.[39]

Finally, while our study and the weight of evidence from prior research clearly demonstrate the long-term benefits of RASBs in patients undergoing cardiac surgery, the appropriate timing and protocol for initiation or resumption of these medications remains unclear given the concerns for short-term adverse events (intraoperative and early postoperative). While some experts have reported the safety[47] of clear institutional protocols, which can help avoid many of these short-term adverse events, yet providing the long-term cardiovascular benefits, these are not widely tested. This lacuna in evidence is clearly a reason for the variable practice patterns.[43] While a few studies have clearly demonstrated that a strategy of continuation of preoperative RASB is safe compared with routine discontinuation,[48] such evidence is lacking regarding the postoperative approaches with no validated protocols that have been tested in a prospective well-designed study. Factors such as intraoperative events, postoperative hemodynamics, and patient risk and comorbidities should all be considerations that dictate the timing and dose of the RASB initiation or resumption. Therefore, a protocolized approach that can be individualized is necessary for minimizing short-term adverse effects and maximizing long-term benefits of RASBs in these patients. Given the retrospective nature of our study, these various factors could not be assessed, and future research is necessary.

Limitations

Our study has several limitations because of its retrospective and observational nature. The high mortality in the RASB withdrawal group is likely attributable to residual confounding that was not captured in this study. Despite this residual confounding, our results and observations from prior studies[45,46] suggest that this group of patients has a high postoperative mortality rate. Additionally, the determination of RASBs following discharge was made based on outpatient pharmacy data. The proportion of patients having had surgery at a VHA facility but filling prescriptions at a non-VHA pharmacy is not known, and such patients' RASB use would not have been captured.[49]

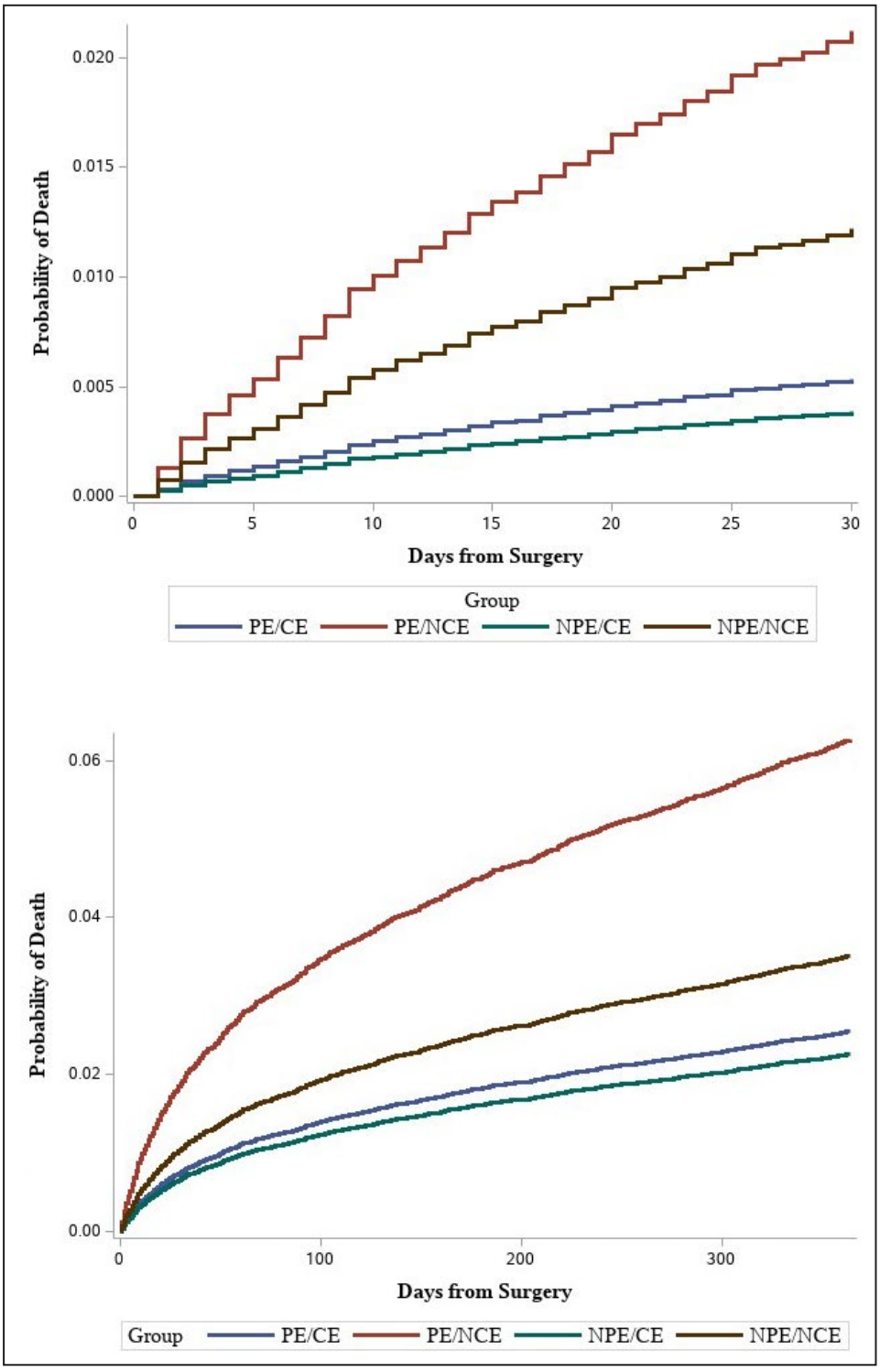

Figure 3. Cumulative incidence for all-cause mortality.
A, Thirty-day mortality; (**B**) 365-day mortality. Predicted incidences are from the adjusted model for the average patient. CE indicates current exposure; NCE, no current exposure; NPE, no preoperative exposure; and PE, preoperative exposure.

While pharmacy refills would not necessarily mean compliance, our study is much more comprehensive in classifying RASB exposure compared with prior studies because of our ability to integrate pharmacy refill data. Our analysis was adjusted for major indications for RASB use such as diabetes mellitus and

CKD but not LV ejection fraction, which is a major predictor of mortality. However, as previously mentioned, such an indication bias should have demonstrated a lower and not excess mortality in veterans who did not receive RASBs, further adding strength to our findings. Our data spans the period of 2005 to 2015, during and after which guidelines and clinical practice with respect to RASB use after cardiac surgery has evolved, and it is likely that RASB use patterns are now different in 2021. We did not have data on cardiac versus noncardiac causes of death and used all-cause mortality as our primary end point. While knowledge of cause of death is important in planning interventions, it is known that even noncardiac deaths after procedures may be related to the procedure itself and should not be discounted.[50] Our study included 5938 isolated valve surgeries. This is a large number of patients but only 16% of our overall study population, and the observed associations may, therefore, be less robust for isolated valve surgery than for CABG. Our analysis assumed an instantaneous effect, while, in reality, the impact on mortality of initiating or discontinuing these medications takes some time to manifest.[51–57] As with any VA study, our study population was predominantly comprised of men and those of White race, and as such our findings may not be directly applicable to a more diverse patient sample without independent validation. Despite these limitations, our study is the first to assess the impact of RASB use on cardiac outcomes in veterans undergoing cardiac surgery. We used well-validated VA data sets that linked clinical, surgical, pharmacy, and survival data, which provided a comprehensive estimate of RASB exposure and its relation to mortality. We also categorized RASB use based on cumulative time (using pharmacy refill data) rather than binary (which is too simplistic), ensuring a more robust assessment of the exposure. Finally, our findings were consistent in multiple sensitivity analyses, clearly demonstrating the strength of the association between RASB exposure and lower mortality in postcardiac surgery patients.

CONCLUSIONS

Continuation of preoperative RASBs and initiation of RASBs before discharge is associated with decreased 30-day and 1-year mortality in veterans undergoing cardiac surgery. Given the findings of our study and prior investigators, continuation of preoperative RASBs or initiation in the early postoperative period should be considered in most patients undergoing cardiac surgery.

ARTICLE INFORMATION

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None.

Supplementary Material

Table S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Frequency of the various RASBs used.

		Post-op Use	
	Pre-op Use (*n* = 22,988)	30-day (*n* = 24,718)	365-day (*n* = 28,713)
Lisinopril	74.6	74.2	75.0
Losartan	9.1	8.6	8.5
Lisinopril/Hydrochlorothiazide	3.5	2.4	2.5
Valsartan	3.1	2.5	2.6
Enalapril	3.0	2.6	2.6
Fosinopril	2.6	2.1	2.1
Captopril	2.2	4.4	3.9
Benazepril	1.2	1.3	1.3
Irbesartan	0.3	0.2	0.2
Ramipril	0.2	0.2	0.2
Candesartan	0.1	0.1	<0.1
Losartan/Hydrochlorothiazide	<0.1	<0.1	<0.1
Benazepril/Hydrochlorothiazide	<0.1	<0.1	<0.1
Enalaprilat	<0.1	1.1	1.0
Valsartan/Hydrochlorothiazide	<0.1	<0.1	<0.1
Quinapril	<0.1	<0.1	<0.1
Aliskiren	<0.1	<0.1	<0.1
Irbesartan/Hydrochlorothiazide	<0.1	<0.1	<0.1
Olmesartan	<0.1	<0.1	<0.1
Telmisartan	<0.1	<0.1	<0.1

Data presented as percent.

RASB, renin angiotensin system blocking agent; pre-op, preoperative; post-op, postoperative.

Table S2. RASB Use Characteristics.

	Total Cohort	PE/CE	PE/NCE	NPE/CE	NPE/NCE
RASB Use at Time of Surgery	61.8	100	100	0.0	0.0
Any Post-operative RASB	77.2	100	0.0	100	0.0
			30-day Outcomes		
Sample Size	37,197	20,221	2,767	4,497	9,712
Days of Post-Surgery RASB Use	22 [12-25]	23 [17-26]	-	7 [3-16]	-
Proportion* of Post-Surgery RASB Use	0.7 [0.4-0.8]	0.8 [0.6-0.9]	-	0.2 [0.1-0.5]	-
			365-day Outcomes		
Sample Size	37,197	21,529	1,459	7,184	7,025
Days of Post-Surgery RASB Use	241 [92-312]	258 [115-319]	-	180 [37-280]	-
Proportion* of Post-Surgery RASB Use	0.7 [0.3-0.9]	0.7 [0.4-0.9]	-	0.5 [0.1-0.8]	-

Data presented as percent or median [interquartile range]

* Proportion of RASB use was calculated by dividing the number of days exposed to drug by the number of days in the follow-up period (i.e. 30 or 365).

RASB, renin angiotensin system blocking agent; PE, preoperative exposure; CE, current exposure; NCE, no current exposure; NPE, no preoperative exposure.

Table S3. Landmark analysis.

	Adjusted Hazard Ratio (95% CI)	*p*
All-Cause Mortality		
PE/CE vs. PE/NCE	0.46 (0.38-0.55)	<.001
PE/CE vs. NPE/CE	1.15 (0.96-1.39)	0.133
PE/CE vs. NPE/NCE	0.87 (0.73-1.03)	<.109
NPE/CE vs. NPE/NCE	0.75 (0.62-0.91)	0.004

This analysis excludes data for initial 30-days post-op.

CI, confidence interval; PE, preoperative exposure; CE, current exposure; NCE, no current exposure; NPE, no preoperative exposure.

Table S4. Imputed analysis accounting for missing data.

	Adjusted Hazard Ratio (95% CI)	*p*
30-day All-Cause Mortality		
PE/CE vs. PE/NCE	0.24 (0.19-0.31)	<.001
PE/CE vs. NPE/CE	1.39 (0.75-2.58)	0.290
PE/CE vs. NPE/NCE	0.47 (0.36-0.62)	<.001
NPE/CE vs. NPE/NCE	0.34 (0.18-0.65)	0.001
365-day All-Cause Mortality		
PE/CE vs. PE/NCE	0.40 (0.34-0.46)	<.001
PE/CE vs. NPE/CE	1.12 (0.91-1.39)	0.291
PE/CE vs. NPE/NCE	0.72 (0.62-0.83)	<.001
NPE/CE vs. NPE/NCE	0.64 (0.52-0.78)	<.001

5,931 (13.8%) of the eligible 43,128 patients were missing one or more of the variables identified for inclusion in the multivariable models.

CI, confidence interval; PE, preoperative exposure; CE, current exposure; NCE, no current exposure; NPE, no preoperative exposure.

Table S5. Between-group differences in 30- and 365-day mortality by CKD stage.

30-day All-Cause Mortality	aOR (95% CI)	*p*-Values		
		Simple Main Effect	Within-Comparison Interaction	Overall Interaction
PE/CE vs. PE/NCE				
CKD Stage 1	0.30 (0.20-0.45)	<.001		
CKD Stage 2	0.21 (0.13-0.32)	<.001	0.285	
CKD Stage 3	0.27 (0.18-0.41)	<.001		
PE/CE vs. NPE/CE				
CKD Stage 1	2.33 (0.32-16.67)	0.409		
CKD Stage 2	0.81 (0.29-2.30)	0.697	0.343	
CKD Stage 3	3.37 (0.58-19.60)	0.177		
PE/CE vs. NPE/NCE				0.303
CKD Stage 1	0.63 (0.37-1.07)	0.089		
CKD Stage 2	0.43 (0.27-0.68)	<.001	0.304	
CKD Stage 3	0.67 (0.23-0.60)	<.001		
NPE/CE vs. NPE/NCE				
CKD Stage 1	0.28 (0.04-1.86)	0.186		
CKD Stage 2	0.53 (0.18-1.60)	0.259	0.393	
CKD Stage 3	0.11 (0.02-0.80)	0.029		

365-day All-Cause Mortality	aOR (95% CI)	*p*-Values		
		Simple Main Effect	Within-Comparison Interaction	Overall Interaction
PE/CE vs. PE/NCE				
CKD Stage 1	0.40 (0.28-0.55)	<.001		
CKD Stage 2	0.40 (0.32-0.50)	<.001	0.993	
CKD Stage 3	0.40 (0.31-0.51)	<.001		
PE/CE vs. NPE/CE				
CKD Stage 1	1.10 (0.67-1.80)	0.719		
CKD Stage 2	1.03 (0.77-1.39)	0.829	0.665	
CKD Stage 3	1.33 (0.89-2.00)	0.166		
PE/CE vs. NPE/NCE				0.504
CKD Stage 1	0.64 (0.48-0.85)	0.002		
CKD Stage 2	0.81 (0.66-0.98)	0.030	0.208	
CKD Stage 3	0.67 (0.54-0.84)	<.001		
NPE/CE vs. NPE/NCE				
CKD Stage 1	0.58 (0.35-0.99)	0.044		
CKD Stage 2	0.78 (0.56-1.09)	0.146	0.258	
CKD Stage 3	0.50 (0.36-0.70)	<.001		

CKD, chronic kidney disease; aOR, adjusted odds ratio; PE, preoperative exposure; CE, current exposure; NCE, no current exposure; NPE, no preoperative exposure.