Preoperative Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Is Associated with Increased Risk for Acute Kidney Injury after Cardiovascular Surgery

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Background and objectives: Acute kidney injury (AKI) occurs commonly after cardiac surgery. Most patients who undergo cardiac surgery receive long-term treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB). The aim of this study was to determine whether long-term use of ACEI/ARB is associated with an increased incidence of AKI after cardiac surgery.

Design, setting, participants, & measurements: This was a retrospective cohort study of 1358 adult patients who underwent cardiac surgery between January 1, 2001, and December 31, 2005, in two tertiary care hospitals in Buffalo, NY. The incidence of AKI was determined after cardiac surgery. Clinical data were collected using a standardized form that included comorbid condition, use of ACEI/ARB, and intraoperative and postoperative complications.

Results: Overall, 40.2% of patients developed AKI. Preoperative variables that were significantly associated with development of AKI included increasing age; nonwhite race; combined valve surgery and coronary artery bypass grafting compared with coronary artery bypass grafting alone; American Society of Anesthesiologists (ASA) Risk Score category 4/5 compared with 2 to 3; presence of diabetes, congestive heart failure, or neurologic disease at baseline; use of ACEI/ARB; and emergency surgery. Intra- and postoperative factors that were associated with postoperative AKI were hypotension during surgery, use of vasopressors, and postoperative hypotension. Multiple regression logistic model confirmed an independent and significant association of AKI and preoperative use of ACEI/ARB. This was confirmed using a bivariate-probit and propensity score model that adjusts for confounding by indication of use and selection bias.

Conclusions: Preoperative use of ACEI/ARB is associated with a 27.6% higher risk for AKI postoperatively. Stopping ACEI or ARB before cardiac surgery may reduce the incidence of AKI.

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Acute kidney injury (AKI) occurs in up to 30% of patients who undergo cardiac surgery, and approximately 1% of patients will require dialysis (1–4). AKI after cardiac surgery is associated with a more complicated hospital course and increased risk for death (5,6). Various factors are found to be associated with the development of AKI after surgery. Preoperative correlates include advanced age, baseline renal dysfunction, female gender, chronic obstructive pulmonary disease, diabetes, peripheral vascular disease, congestive heart failure, left ventricular ejection fraction <35%, cardiogenic shock, need for emergency surgery, and left main coronary artery disease. Intraoperative correlates include duration of surgery, cardiopulmonary bypass, and aortic cross-clamping (1).

Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are used commonly in many clinical settings. Although use of ACEI increases survival in patients with congestive heart failure (CHF) and retards the progression of renal disease, its use has been associated with the development of AKI in settings where maintenance of glomerular filtration requires efferent arteriolar constriction, which is blocked by ACEI or angiotensin II receptor antagonists (7,8). ACEI/ARB have been associated with AKI in different clinical situations such as diabetes and CHF and in patients with diarrhea and vomiting (9–11). We hypothesized that long-term preoperative ACE inhibition is associated with the development of AKI after cardiac surgery.

Materials and Methods

The study population was drawn from patients who underwent cardiac surgery at two tertiary care hospitals affiliated with the State University of New York at Buffalo: Buffalo Veterans Administration

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Medical Center and Erie County Medical Center. A list of patients who had undergone surgery between January 1, 2001, and December 31, 2005, was generated through the hospital record system. This research protocol was approved by the Buffalo Veterans Administration Medical Center and the State University of New York at Buffalo institutional review boards.

Clinical data were collected using a standardized form. Baseline data collection included demographics (age, gender, race, weight, height, body mass index, smoking history), comorbid conditions including CHF (shortness or breath or weakness with concomitant decreased ejection fraction on two-dimensional echocardiography, chronic obstructive lung disease (based on pulmonary function test), peripheral vascular disease (intermittent claudication, arterial Doppler or surgery for peripheral vascular disease), cerebrovascular accidents (transient ischemic attack/stroke), malignancy, hepatobiliary disease (persistent elevation of aspartate aminotransferase/alanine aminotransferase, liver biopsy), gastrointestinal disease (history of gastrointestinal bleed), hypertension, diabetes, neurologic disease (disease other than stroke), and depression/psychosis. Intraoperative data collection included the on/off pump status, BP, use of vasopressors, and urine output. Postoperatively, serial serum creatinine levels, BP, intravenous fluid, urine output, use of vasopressors, and dialysis requirement were recorded. Preoperative use of ACEI, ARB, and nonsteroidal anti-inflammatory drugs was also recorded from the admission note, pharmacy orders. All patients had received ACEI/ARB before surgery.

Definitions

AKI was defined using the modified RIFLE (risk, injury, failure, loss, ESRD) classification: Stage 1, increase in serum creatinine of ≥0.3 mg/dl or an increase of 50 to 200% from baseline (peak creatinine postoperatively minus preoperative creatinine); stage 2, increase in serum creatinine of 200 to 300%; and stage 3, increase in serum creatinine >300% or serum creatinine level >4 mg/dl (12,13). We did not use urine output in defining AKI.

Race was categorized as white, black, or other. Type of surgery was defined as elective or emergency as per surgical attending note.

Anesthesia risk was determined from preoperative anesthesia records and stratified into five categories. American Society of Anesthesiologists (ASA) Risk Score 1 was defined as a healthy individual; ASA 2, patient with mild systemic disease; ASA 3, patient with severe systemic disease; ASA 4, patient with severe systemic disease with constant threat to life; ASA 5, moribund patient who is not expected to survive without surgery (14).

Statistical Analysis

There were too few patients in stages 2 and 3 AKI; therefore, analysis was done for AKI *versus* no AKI. Similarly, preanesthesia risk factor was grouped as category 3 or less and 4 and 5 combined because there were very few patients with ASA of 2 and 5 and no patient with ASA 1. Race classification was also changed to white and nonwhite because there were very few patients in the "other" category.

Descriptive statistics and/or frequency distributions were compiled for age; gender; body mass index (BMI); preoperative use of ACEI/ARB and nonsteroidal anti-inflammatory drugs; presence of CHF, hypertension, diabetes, chronic obstructive pulmonary disease, liver disease, or neurologic disease; intraoperative fluid intake; use of vasopressors; and postoperative hypotension or vasopressor use. Data are shown as means ± SD or percentage. The patients who developed AKI and those who did not develop AKI were compared on all of these parameters. Similarly, patients who were using ACEI/ARB and those who were not using ACEI/ARB were compared. The *t* test was used to test the differences in the mean values of continuous variables, whereas the tests of differences in proportions were based on χ^2 test or Fisher exact test.

To demonstrate the influence of ACEI/ARB on AKI in patients who had undergone coronary artery bypass grafting (CABG), we constructed a naive logistic model that included ACEI/ARB and other covariates:

$$\mathrm{AKI_i} = \alpha_i + \delta'_{1i}X_{1i} + \beta_{1i}\,\mathrm{ACEI_i} + \varepsilon_i \quad (1)$$

where β_{1i} is of interest, X_{1i} is a vector of covariates besides $\mathrm{ACEI_i}$ with coefficients δ'_{1i}, and ε_i is the error term representing unobserved determinants of $\mathrm{AKI_i}$. A crucial assumption here is that $\mathrm{ACEI_i}$ and ε_i are independent.

Because this was a retrospective study, differences between patients who used ACEI/ARB and those who did not use ACEI/ARB in the outcome of interest (AKI) may be subject to bias; that is, differences in the occurrence of AKI between the two groups may reflect underlying characteristics that may also have contributed to the use of ACEI/ARB and were not measured and controlled for in our naive logistic model (15–19). Therefore, we also used a joint model of ACEI/ARB and AKI. In constructing this model, we used hypertension at baseline as an instrument. This suggests that hypertension affects the use of ACEI/ARB but not the occurrence of AKI directly. In this model, we retained equation 1 but dropped the assumption that $\mathrm{ACEI_i}$ and ε_i are independent. Instead, we added an equation that we think drives the use of $\mathrm{ACEI_i}$:

$$\mathrm{ACEI_i^*} = \gamma_i + \delta'_{2i}X_{2i} + \beta_{2i}\,\mathrm{Hypertension_i} + \eta_i \quad (2)$$

where X_{2i} is a vector of covariates (some of which may be common with X_{1i}) with coefficients δ'_{2i}, and η_i is an error term.

ACEI use was determined by

$$\mathrm{AECI_i} = \begin{cases} 1 & \text{if } \mathrm{ACEI_i^*} > 0 \\ 0 & \text{if } \mathrm{ACEI_i^*} \le 0 \end{cases}$$

Note that only $\mathrm{ACEI_i}$ was observed and not $\mathrm{AECI_i^*}$. The error terms η_i and ε_i were assumed to have bivariate normal distribution such that

$$\begin{pmatrix} \varepsilon_i \\ \eta_i \end{pmatrix} \sim \mathrm{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix} \right)$$

that is, the means of η_i and ε_i are normalized to 0, and the variances are assumed to be 1. ρ is the correlation coefficient between η_i and ε_i.

The implication that hypertension affects the use of ACEI/ARB but not the occurrence of AKI directly, although it cannot be directly tested, may possibly be inferred. In several analyses of renal insufficiency, baseline hypertension was not in the set of predictors (20–23), although, in one of them (23), systolic BP ≥ 160 with CABG was important in predicting renal failure. In one study that focused on risk for postoperative dialysis (24), it was significant, whereas, in another research study on renal insufficiency (25), it was barely significant ($P = 0.049$). The different objectives of these studies and the different definitions used for renal failure make it difficult to draw a definite conclusion, although it seems that hypertension does not play a major role in predicting AKI, which is the focus of our analysis.

The naive logistic regression model was constructed in steps. First, we tested individual logistic regressions of risk for AKI using variables that had a univariate association with the AKI outcome with $P \le 0.2$. All of the variables that had $P \le 0.2$ in these individual logistic regressions were candidates for inclusion in the final logistic model along with variables that were selected *a priori* (age, gender, race). The initial model contained ACEI/ARB and demographic variables. Next, we included diabetes and CHF. Finally, we added intraoperative hypoten-

sion to the model. In all models, odds ratio (OR) with 95% confidence interval were calculated. We also estimated a propensity score model using several covariates. We then used the propensity score to match patients (based on nearest neighbor algorithm) who were on ACE/ARB with those who were not. After matching, we estimated the logistic model for AKI with several covariates. Patients with missing data for any of the covariates entered in the model were excluded. No attempt was made to impute data. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test (26). Collinearity was checked using tolerance and variable inflation factor. We also use the propensity score as a proxy for an index of disease, albeit a nonlinear one, because it is estimated using baseline hypertension, diabetes at baseline, and CHF as covariates.

We then constructed several logistic models for predicting AKI and compared them with the base model, which did not include the propensity score. This model included all of the other covariates and is designated as model 1. The model that excludes one or more variables that are included in another model is called the nested model of the latter. Comparison between these nested models can be achieved by using the differences in the χ^2 values and differences in the degrees of freedom. For example, if a model includes propensity score (along with other covariates) and a second model excludes only the propensity score variable, then differences in the χ^2 values between the two models with one degree of freedom (because only one variable is dropped) can be tested for significance.

- Model 1: The base model includes ACEI/ARB, diabetes, CHF, and baseline hypertension
- Model 2: ACEI/ARB, diabetes, CHF, baseline hypertension, and propensity score
- Model 3: ACEI/ARB and propensity score (excludes diabetes, CHF, baseline hypertension)
- Model 4: Diabetes, CHF, baseline hypertension and propensity score (excludes ACEI/ARB)
- Model 5: Propensity score (excludes ACEI/ARB, diabetes, CHF, and baseline hypertension)
- Model 6: Diabetes, CHF, baseline hypertension (excludes ACEI/ARB and propensity score)

Kaplan-Meier estimates and survival function for mortality were created by AKI *versus* no AKI. Unadjusted and adjusted hazard ratios were obtained from Cox model. The naive logistic model was estimated with SAS 9.1 (SAS Institute, Cary, NC) and the bivariate probit model with LIMDEP 9.0 (Econometric Software Inc., Plainview, NY).

Results

A total of 1358 patients who were older than 18 yr and underwent cardiac surgery at two major hospitals in Western New York between January 1, 2001, and December 31, 2005, were the subjects of study. The mean age of the patients was 65.9 ± 11.9 yrs (median age 67 yrs). The majority (85.6%) of the patients were white. Mean body mass index was 29.4; 79.2% were male, 33.7% had diabetes, and 80% had hypertension; 19.8% had CHF, and 17.8% had chronic obstructive pulmonary disease. More than half (52%) were on ACEI/ARB preoperatively. A total of 189 (14%) patients had AKI even at the time of discharge. At 3 mo, the serum creatinine was available for 525 patients, 18% of which fulfilled the criteria for AKI.

Characteristics for ACEI/ARB use and no ACEI/ARB use before cardiac surgery are shown in Table 1. Significantly more patients with diabetes, ASA risk 4/5, hypertension, CHF, and neurologic disease at baseline received ACEI preoperatively.

Table 1. Univariate analysis of factors associated with ACEI/ARB use[a]

Variable	Patients not Using ACEI/ARB	Patients Using ACEI/ARB	*P*
Age (yr)	65.9 (12.1)	65.9 (10.7)	0.9000
Female gender	133 (20.40%)	150 (21.22%)	0.7107
BMI	28.8	29.9	0.0006
White race	563 (86.35%)	613 (90.10%)	0.8482
Elective/urgent surgery	600 (92.02%)	637 (90.24%)	0.2486
Risk category (ASA 4/5)	179 (27.45%)	244 (34.51%)	0.0050
Diabetes	147 (22.55%)	311 (43.99%)	<0.0001
Surgery type (CABG)	564 (86.50%)	619 (87.55%)	0.5647
Hypertension	454 (69.63%)	638 (90.24%)	<0.0001
CHF	83 (12.73%)	185 (26.17%)	<0.0001
COPD	107 (16.41%)	136 (19.24%)	0.1745
Liver disease	30 (4.60%)	22 (3.11%)	0.1527
GI comorbidity	115 (17.64%)	126 (17.82%)	0.9294
Neurologic disease	112 (17.18%)	154 (21.78%)	0.0326
Arthritis	165 (25.35%)	198 (28.01%)	0.2685
Use of NSAID	69 (10.58%)	75 (10.61%)	0.9879
On pump	457 (70.20%)	481 (68.30%)	0.4500
Intraoperative hypotension	270 (41.41%)	337 (47.67%)	0.0205
Postoperative hypotension	86 (13.19%)	92 (13.01%)	0.9228
AKI (present)	179 (36.70%)	212 (43.40%)	0.0006

[a]ASA, American Society of Anesthesiologists Risk Score; ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drugs.

There was no significant difference in age and baseline serum creatinine between patients who received ACEI and patients who did not receive ACEI. Various multiple logistic regression models were built. Presence of CHF, diabetes, and hypertension was associated with increased odds for use of ACEI.

Overall, 40.2% developed AKI. There were very few patients in stages 2 ($n = 7$) and 3 ($n = 2$) AKI; therefore, analysis was done comparing two groups: Group A, no postoperative AKI, and group B, postoperative AKI.

In the univariate analysis and in the individual logistic regressions, preoperative variables that were significantly associated with development of AKI included increasing age; nonwhite race; combined valve surgery and CABG compared with CABG alone; ASA category 4/5 compared with 2 to 3; presence of diabetes, CHF, or neurologic disease at baseline; use of ACEI/ARB; and emergency surgery. Intra- and postoperative factors that were significantly associated with postoperative AKI were hypotension during surgery, use of vasopressors, and postoperative hypotension (Table 2). Multiple regression logistic model and propensity score model confirmed a significant association between AKI and preoperative use of ACEI/ARB (Table 3).

The results from the simple logistic regression are complemented by the bivariate probit model with selection controlled for (Table 4). We see a much more pronounced effect of ACEI/ARB. Also, in the selection model, the correlation coefficient ρ is significant, indicating the presence of selection bias. The same three variables, baseline hypertension, CHF, and diabetes, were significant predictors of ACEI use in the bivariate probit model as well. It is interesting that the variables that predict the use of ACEI, namely CHF, baseline hypertension, and diabetes, did not enter the equation for AKI significantly. Propensity score models confirm the independent association of ACEI/ARB and AKI (Table 5). Comparison between a base model with and without propensity score provides additional support that ACEI/ARB are significantly associated with acute kidney injury (Table 5).

LIMDEP allows us to calculate the marginal effect of AKI for use of ACEI holding all of the other variables constant at their mean values. Calculated this way, use of preoperative ACEI increases the risk for AKI by 27.6%. Twenty-four (4.4%) patients had died at 90 d postoperatively among those who developed AKI, compared with 1.6% among those without AKI (adjusted hazard ratio 2.4; 95% confidence interval 1.2 to 4.8).

Discussion

The incidence of AKI after cardiac surgery was 40.2%. In univariate analysis, factors that were significantly associated with development of AKI included increasing age; black race; combined valve surgery and CABG compared with CABG alone; ASA category 4/5 compared with 1 to 3; presence of diabetes, CHF, or neurologic disease at baseline; use of ACEI/ARB; emergency surgery, on-pump surgery; hypotension during surgery; use of vasopressors; and postoperative hypotension. Preoperative use of ACEI/ARB was significantly associated with an increased risk for AKI postoperatively in different multiple logistic regression models. The bivariate probit and propensity score methods confirmed the results from the naive logistic regression model.

ACEI/ARB are one of the most frequently used classes of antihypertensive drugs. They are also used in the management of CHF and diabetic and nondiabetic nephropathies. Although

Table 2. Factors associated with AKI: Univariate analysis

Variable	Group 1 (No AKI)	Group 2 (AKI)	*P*
Age (yr)	63.8 (11.4)	69.1 (10.7)	<0001
Female gender	170 (21.0%)	113 (20.7%)	0.9200
BMI	29.2	29.7	0.2900
White race	696 (92.6%)	480 (87.9%)	0.2200
Elective/urgent surgery	753 (92.6%)	484 (88.6%)	0.0100
Risk category (ASA 4/5)	208 (25.6%)	215 (39.4%)	<0.0001
Diabetes	234 (28.8%)	224 (41.0%)	<0.0001
On-pump surgery	516 (63.6%)	422 (77.6%)	<0.0001
Surgery type (CABG)	742 (91.3%)	441 (80.7%)	<0.0001
Hypertension	622 (76.5%)	470 (86.0%)	0.0005
CHF	122 (15.1%)	146 (26.7%)	<0.0001
COPD	128 (15.7%)	115 (21.1%)	0.0100
Liver disease	33 (4.1%)	19 (3.5%)	0.5800
GI comorbidity	135 (16.6%)	106 (19.4%)	0.1800
Neurologic diseases	146 (17.9%)	120 (22.0%)	0.0700
Arthritis	209 (25.7%)	154 (28.2%)	0.2100
Use of NSAID	93 (11.4%)	51 (9.3%)	0.3100
ACEI/ARB	386 (48.5%)	321 (58.8%)	0.0001
Intraoperative hypotension	319 (39.2%)	288 (52.8%)	<0.0001
Postoperative hypotension	86 (10.6%)	92 (16.8%)	0.00082

Table 3. Multiple regression models showing association of ACEI/ARB with AKI[a]

Variable	Point Estimate	95% CI
Model 1: Logistic model for AKI by ACEI/ARB[b]		
demographics	1.51	1.200 to 1.910
demographics + diabetes	1.39	1.100 to 1.760
demographic + diabetes + CHF	1.28	1.010 to 1.640
Model 2: All variables that were significant in univariate model + demographics, NSAID		
ACEI/ARB	1.35	1.050 to 1.730
age	1.04	1.030 to 1.060
NSAID (not used)	0.77	0.530 to 1.140
diabetes	1.66	1.290 to 2.130
CABG + valve replacement	2.24	1.590 to 3.160
emergency surgery	1.49	0.990 to 2.230
CHF	1.42	1.050 to 1.910
intraoperative hypotension	1.36	1.060 to 1.740
on pump	1.89	1.440 to 2.480
intraoperative IVF (L)	1.06	1.004 to 1.130
Model 3: Logistic model after matching on propensity score		
ACEI/ARB	1.41	1.070 to 1.850
age	1.04	1.030 to 1.050
NSAID	0.80	0.490 to 1.290
diabetes	1.66	1.290 to 2.130
CABG + valve replacement	1.69	1.230 to 2.590
emergency surgery	1.21	0.750 to 1.940
CHF	1.34	0.930 to 1.940
intraoperative hypotension	1.42	1.060 to 1.880
on pump	1.89	1.380 to 2.590
intraoperative IVF (L)	1.05	0.980 to 1.130

[a]CI, confidence interval; IVF, intravenous fluid.
[b]Demographics included age, race, gender, and BMI.

Table 4. Bivariate probit model for ACEI/ARB and AKI

Variable	Coefficient	*P*
ACEI/ARB		
hypertension	0.77040000	<0.0001
diabetes	0.49620000	<0.0001
CHF	0.46590000	<0.0001
type of surgery (CABG or CABG+)	0.18010000	0.0862
neurologic diseases	0.14760000	0.0942
AKI		
intercept	−0.36442757	0.0581
ACEI/ARB	0.89614838	0.0007
age	0.00149361	0.0014
diabetes	0.10842955	0.2990
CHF	0.10699360	0.3266
CABG	−0.54771289	0.0000
elective/urgent	−0.23503286	0.0440
intraoperative hypotension	0.21368280	0.0024
IVF (L)	0.02818111	0.0912
on/off pump	−0.00012434	0.8549
NSAID	−0.15864714	0.1393
ρ	−0.47115189	0.0069

Table 5. Comparison between base models and models with propensity score

Model	Key Variables Included/Excluded	LR χ^2 (df)	Comparison	Difference in LR χ^2 (df)	$P > \chi^2$	Significant Key Variables	Inference
1	ACEI/ARB, diabetes, CHF, and hypertension	184.4894 ($df = 11$)	–	–	–	ACEI/ARB, diabetes, and CHF	–
2	ACEI/ARB, diabetes, CHF, hypertension, and propensity score	184.7427 ($df = 12$)	2 *versus* 1	0.2533 ($df = 1$)	0.61480	ACEI/ARB	Possible high collinearity between propensity score and diabetes, CHF, and hypertension because diabetes and CHF are significant in the base model. Addition of all four variables (diabetes, CHF, hypertension, and propensity score) adds no value to the model.
3	ACEI/ARB and propensity score (excludes diabetes, CHF, and hypertension)	180.9792 ($df = 9$)	2 *versus* 3	3.7635 ($df = 3$)	0.05238	ACEI/ARB and propensity score	Confirms high collinearity between propensity score and diabetes, CHF, and hypertension. Addition of diabetes, CHF, and hypertension adds no value to the model when propensity score is already present. Supports the notion that propensity score may be used as a proxy for a disease index for these diseases.
4	Diabetes, CHF, hypertension, and propensity score (excludes ACEI/ARB)	179.2128 ($df = 11$)	2 *versus* 4	5.5299 ($df = 1$)	0.01869	None	ACEI/ARB has independent effect on AKI. Addition of ACEI/ARB significantly contributes to the model.
5	Propensity score (excludes ACEI/ARB, diabetes, CHF, and baseline hypertension)	175.4759 ($df = 8$)	3 *versus* 5	5.5033 ($df = 1$)	0.01898	Propensity score	ACEI/ARB has independent effect on AKI. Addition of ACEI/ARB significantly contributes to the model.
			4 *versus* 5	3.7369 ($df = 3$)	0.05322		Confirms high collinearity between propensity score and diabetes, CHF, and hypertension. Addition of diabetes, CHF, and baseline hypertension adds no value to the model when propensity score is already present. Supports the notion that propensity score may be used as a proxy for a disease index for these diseases.
6	Diabetes, CHF, hypertension (excludes ACEI/ARB and propensity score)	178.7873 ($df = 10$)	1 *versus* 6	5.7021 ($df = 1$)		Diabetes, CHF, and hypertension	ACEI/ARB has independent effect on AKI.

ACEI therapy usually improves renal blood flow and sodium excretion rates in CHF and reduces the rate of progressive renal injury in chronic kidney disease, its use can also be associated with a syndrome of "functional renal insufficiency" and/or hyperkalemia. Typically, this form of AKI develops shortly after initiation of ACEI use but can be observed after months or years of therapy, even in the absence of previous ill effects. AKI is most likely to occur when renal perfusion pressure cannot be sustained because of substantial decreases in mean arterial pressure or when the GFR is highly angiotensin II dependent.

The association of ACEI therapy with AKI after cardiac surgery has been controversial. In the early 1990s, the benefits of ACEI in heart failure were extrapolated to improved clinical outcome of patients who were undergoing cardiovascular surgery. Colson *et al.* (27) and Licker *et al.* (28) studied the effect of acute administration of ACEI prophylactically in cardiopulmonary bypass and aortic surgery patients, respectively, and showed that creatinine clearance was maintained for a short period of time among patients who received ACEI compared with patients who received placebo (in whom creatinine clearance was decreased). This effect of ACEI/ARB on kidney function may be different in patients who have been exposed to ACEI/ARB long term. Indeed, Rady *et al.* (29) studied the effect of long-term use of ACEI on the incidence of acute organ damage including AKI (defined as postoperative serum creatinine ≥3.8 mg/dl or doubling of serum creatinine when baseline serum creatinine was >1.9 mg/dl.). They did not find a significant association of use of ACEI and AKI in patients with normal or low left ventricular systolic function; however, that study did not analyze the association of ACEI and postoperative stage 1 or 2 AKI. Our study showed a significant association of long-term use of ACEI/ARB and postcardiac surgery AKI (primarily stage 1 AKI). Similar results were also shown after abdominal aorta surgery. Cittanova *et al.* (30) studied preoperative risk factors and the risk for AKI (defined as decrease in creatinine clearance by >20% by day 7) after elective aortic surgery. Long-term inhibition of ACE was the only factor that was significantly associated with postoperative AKI. ACEI in combination with aprotonin but not alone was shown to be associated with increased risk for AKI after cardiac surgery (31); however, the definition was different from the modified RIFLE classification. More than half of patients who developed AKI required dialysis, and 48% of patient died, suggesting that those were patients with either stage 2 or stage 3 AKI. Our study predominantly includes patients with stage 1 AKI.

Several studies have examined the risk factors that are associated with AKI after cardiac surgery. Unfortunately, most patient-related factors are irreversible. We looked at use of ACEI/ARB (which can be stopped before surgery) and its association with AKI after cardiac surgery. As expected physiologically, use of these medications was associated with increased risk for AKI after cardiac surgery. When our models were adjusted for known predisposing factors, a significant association persisted. Furthermore, bivariate models and propensity score analysis using different methods, including disease index, confirm the association of ACEI/ARB with AKI. In addition, the AKI models with and without baseline hypertension, diabetes at baseline, and CHF reveal an interesting pattern: When they are included, the propensity score is insignificant, but when they are excluded, the propensity score is significant. This confirms the utility of propensity score as a proxy for an index of the three diseases, but in both models, the estimated coefficients of ACEI/ARB and their significance levels are nearly the same, indicating that even in the presence of a proxy for an index of baseline hypertension, diabetes, and CHF, patients who are treated with ACEI/ARB are more likely to have AKI after surgery than those who are not treated with ACEI/ARB.

There are no definitive data demonstrating that ACEI/ARB should be stopped before surgery; however there are opinions published on this topic. Lazar (32) opined that use of ACEI can benefit patients who undergo surgery by minimizing perioperative ischemia and reducing long-term cardiovascular events. Devbhandari *et al.* (33) surveyed the opinion of UK cardiovascular surgeons on the continuation of ACEI before cardiac surgery. They found that 35% believed that ACEI should be withheld before surgery, and 65% did not think that ACEI should be withheld. It is clear that there is no consensus on its perioperative use in cardiovascular surgery. Results of our study showed a significant association of preoperative use of ACEI/ARB with AKI, raising the question of whether these medications should be stopped before cardiac surgery.

Our study has several important limitations. Even with various logistic models, we cannot truly evaluate the effect of ACEI/ARB, as we could in a prospective, randomized trial. Although propensity score can adjust for confounding by indication, this may not eliminate residual unobserved factors. The bivariate model does account for selection bias. Furthermore, the data were collected from two major hospitals in one region; therefore, results may not be generalizable to the entire United States.

Conclusions

We determined that preoperative ACEI/ARB use was associated with an increased incidence of AKI after cardiac surgery. Because it has been shown that even a small rise in serum creatinine is associated with increased risk for death in these patients, one should consider stopping ACEI/ARB before cardiac surgery. Further randomized, controlled trials are needed to confirm our results.

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Disclosures

None.

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