Preoperative Angiotensin-Converting Enzyme Inhibitors and Acute Kidney Injury After Coronary Artery Bypass Grafting

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Background. **Angiotensin-converting enzyme (ACE) inhibitors confer renal protection in different clinical settings. No final conclusions are available on the renal benefits of ACE inhibitors after coronary artery bypass grafting (CABG). Because ACE inhibitors decrease glomerular perfusion pressure, they may exacerbate kidney injury during cardiopulmonary bypass (CPB)-related hypoperfusion. We evaluated the effect of preoperative ACE inhibitors on acute kidney injury (AKI) after CABG.**

Methods. **A propensity score–based analysis of 536 patients undergoing CABG on CPB was performed, among which 281 received ACE inhibitors preoperatively. Patients with preoperative end-stage renal failure requiring dialysis were excluded. Postoperative AKI was defined as 50% or more decrease in the glomerular filtration rate from preoperative or postoperative mechanical renal support.**

Results. **After CABG, AKI developed in 49 patients (9.1%), and 23 (4.2%) required dialysis. The incidence of AKI was 6.4% in patients who received preoperative ACE inhibitors and 12.2% in patients who did not (p = 0.02). The incidence of AKI requiring dialysis was 2.4% in the treatment group and 6.3% in controls (p = 0.03). After adjusting for propensity score and covariates, preoperative ACE inhibitors were found to reduce the incidence of postoperative AKI (odds ratio, 0.48; 95% confidence interval, 0.23 to 0.77; p = 0.04). Other independent predictors were age, preoperative glomerular filtration rate, left ventricular ejection fraction of less than 0.35, preoperative use of intraaortic balloon pump, emergency operation, and CPB time.**

Conclusions. **Preoperative ACE inhibitors are associated with a reduced rate of AKI after on-pump CABG surgery.**

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Coronary artery bypass grafting (CABG) remains one of the most common surgical procedures, with more than 300,000 operations performed annually in the United States [1]. A major complication remains acute kidney injury (AKI), which occurs in up to 30% of patients, depending on its definition [2]. AKI requiring dialysis is a well-known morbidity and mortality risk factor. Recent studies, however, demonstrated that milder degrees of renal dysfunction are associated with an increased mortality risk as well [3, 4]. In addition, the rate of postoperative AKI is likely to increase because patients undergoing operations are increasingly older and have more comorbidities. Therefore, there is a considerable interest in determining strategies that may prevent the development of renal injury in the setting of CABG.

Angiotensin-converting enzyme (ACE) inhibitor therapy has been shown to confer renal protection in different clinical settings [5, 6]. However, no final conclusions are available on the renal benefits of ACE inhibitors in CABG patients [7]. On the other hand, it is still believed that preoperative ACE inhibitor therapy may exacerbate kidney injury during hypoperfusion related to cardiopulmonary bypass (CPB) [2]. This hypothesis is based on previous observations that ACE inhibitor therapy may cause a reversible decline in renal function in several clinical conditions associated with decreased renal perfusion, such as bilateral renal artery stenosis, severe congestive heart failure, or volume depletion [8, 9]. However, no previous study has demonstrated a deleterious effect of ACE inhibitors on renal function after CABG.

In the present study, we aimed to evaluate the impact of preoperative ACE inhibitor therapy on the incidence of postoperative AKI after CABG on CPB using a risk-adjusted approach.

Patients and Methods

This study was reviewed and approved by the Institutional Review Board of the University of Rome, and a waiver of consent was granted.

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Patient Population

We analyzed 536 consecutive patients with a median age of 67 years (range, 38 to 88;interquartile range, 59 to 73) who were undergoing isolated CABG at our institution between May 2004 and January 2008. The following characteristics were matched: (1) procedures on CPB, (2) no preoperative renal failure requiring dialysis, (3) no preoperative treatment with angiotensin II type 1 receptor antagonists, and (4) no treatment with ACE inhibitors lasting less than 2 weeks preoperatively. This cutoff was used because the effect of ACE inhibitors on glomerular filtration rate reduction is generally achieved after 2 weeks of oral treatment [8, 9].

All patients who had received 2 or more weeks of ACE inhibitors until the day of operation were included in the ACE inhibitors group. They were compared with the remaining patients who had not received ongoing ACE inhibitor therapy preoperatively.

Data Collection

Data were prospectively collected and recorded in an electronic database by physicians. The primary outcome—AKI after CABG—was a composite event. This was defined in two ways: (1) postoperative renal failure requiring dialysis before discharge or death, or (2) 50% or more decline in the glomerular filtration rate (GFR) relative to baseline but not requiring dialysis. The four-variable Modified Diet and Renal Disease equation was used to estimate GFR [10]. The rationale for using the 50% in GFR reduction, as assessed by the Modified Diet and Renal Disease equation to estimate GFR, was based on its strong association with operative mortality after surgical revascularization [4]. Preoperative and daily in-hospital postoperative serum creatinine assessments according to institutional routine were evaluated to identify preoperative and peak in-hospital postoperative values.

Operative mortality was defined as all deaths that occurred during the hospital stay or after hospital discharge but within 30 days postoperatively.

Statistical Analysis

Continuous variables are shown as median with interquartile range (IQR). All categoric data were displayed as percentages. Comparisons were made with Mann-Whitney rank-sum tests and χ^2 tests as appropriate. A post hoc χ^2 test analysis was performed to achieve the study power to detect significant differences for the outcome of interest.

Initially, univariate logistic regression analysis was performed to identify significant predictors of AKI after operation. Those variables identified to have a value of $p < 0.05$ in the univariate analysis were considered as candidates for multivariable analysis, which was performed in a stepwise fashion to identify independent predictors of AKI.

A propensity score–adjusted analysis was performed to reduce the effect of preoperative variability between the groups [11]. A logistic regression analysis was performed with the received drug (ACE inhibitors) as the dependent variable and preoperative confounding factors as independent variables. The predicted probability of receiving ACE inhibitors preoperatively represented the propensity score for each patient. The propensity score was subsequently regressed as an independent covariate in the multivariate logistic regression analysis, using all relevant observations.

Potential preoperative confounding factors considered in this analysis were selected on the basis of a literature review and clinical plausibility. These variables included

Table 1. Patient Demographics, Clinical Data, and Procedural Characteristics

	Preoperative ACE Inhibitors		
Variables	Yes (n = 281)	No (n = 255)	*p* Value
Demographics			
Age, median (IQR) years	68 (59–72)	67 (59–73)	0.96
Female, %	17.6	14.4	0.44
BMI, median (IQR) kg/m^2	26 (24–29)	26 (24–29)	0.7
Clinical risk factors			
Pre-op GFR, median (IQR)[a]	67 (56–79)	67 (54–81)	0.76
Diabetes mellitus, %	40.0	39.4	0.96
COPD, %	12.2	21.1	0.01
Hypertension, %	92.2	76.2	<0.0001
Peripheral vascular disease, %	19.2	14.0	0.15
Congestive heart failure, %	10.2	14.0	0.22
LVEF < 0.35, %	6.9	7.7	0.8
Prior CABG, %	16.3	10.5	0.08
Prior MI ≤ 30 days, %	35.5	48.7	0.003
Pre-op IABP, %	3.6	6.7	0.18
Emergency operation, %	12.2	18.6	0.07
Pre-op medications			
β-Blockers, %	62.4	23.3	<0.0001
Diuretics, %	24.9	27.5	0.58
Procedural characteristics			
Distal anastomoses/pt, median (IQR) No.	3 (2–3)	3 (2–3)	0.14
Internal mammary artery usage, %	100	100	1
Aortic cross-clamp time, median (IQR) min	78 (74–82)	84 (77–87)	0.19
CPB time, median (IQR) min	104 (84–126)	105 (88–124)	0.65

[a] Calculated as mL/min/1.73 m^2.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; GFR = glomerular filtration rate; IABP = intraaortic balloon pump; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

(1) demographics characteristics such as age, gender, and body mass index (BMI); (2) clinical risk factors such as preoperative GFR, diabetes mellitus, chronic obstructive pulmonary disease requiring treatment, hypertension, peripheral vascular disease, congestive heart failure, left ventricular ejection fraction of less than 0.35, prior CABG, prior myocardial infarction within 30 days, preoperative use of an intraaortic balloon pump (IABP), and emergency surgery; and (3) procedural characteristics such as number of distal anastomoses, rate of internal mammary artery usage, CPB time, and aortic cross-clamp time. We included in the analysis preoperative medications such as β-blockers and diuretics in addition to ACE inhibitors.

Models fit analysis was evaluated with the Hosmer-Lemeshow goodness-of-fit statistic. The C statistic was reported as a measure of predictive power. Odds ratios (OR) and their associated 95% confidence intervals (CI) were estimated. In all tests, values of $p < 0.05$ were considered significant. Statistical analysis was done with SPSS 11 software (SPSS, Chicago, IL) and G*Power 3.0.5 for Windows (Microsoft, Bellingham, WA).

Table 2. Univariate Logistic Regression Analysis for Risk Factors Associated With Acute Kidney Injury

Variables	Unadjusted Odds Ratio	95% CI	*p* Value
Age[a]	1.10	1.05–1.15	0.00001
Female sex	2.5	1.26–5.18	0.008
BMI[b]	1.02	0.94–1.11	0.58
Pre-op GFR[c]	0.95	0.94–0.97	0.000001
Diabetes mellitus	1.65	0.88–3.10	0.11
COPD	1.07	0.45–2.50	0.87
Hypertension	0.93	0.31–2.74	0.89
Peripheral vascular disease	0.96	0.41–2.25	0.93
Congestive heart failure	2.22	0.98–4.97	0.051
LVEF < 0.35	2.89	1.17–7.09	0.02
Prior CABG	1.45	0.17–12.14	0.72
Prior MI ≤ 30 days	2.31	1.17–4.54	0.01
Pre-op IABP	6.94	2.85–16.89	0.00001
Emergency operation	3.12	1.50–6.49	0.002
Pre-op ACE inhibitors	0.48	0.25–0.94	0.03
Pre-op β-blockers	0.96	0.51–1.80	0.91
Pre-op diuretics	1.26	0.60–2.67	0.53
No. of distal anastomoses	0.65	0.44–1.29	0.08
Rate of IMA usage	0.98	0.89–1.12	0.65
Aortic cross-clamp time[d]	1.002	0.99–1.01	0.63
CPB time[d]	1.01	1.001–1.19	0.02

[a] Per 1-year increase. [b] Per 1-kg/m^2 increase. [c] Per 1-mL/min/1.73 m^2 decrease. [d] Per 1-minute increase.

ACE = angiotensin converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; GFR = glomerular filtration rate; IABP = intraaortic balloon pump; IMA = internal mammary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Table 3. Multivariate Logistic Regression Analysis[a,b] for Risk Factors Associated With Acute Kidney Injury Adjusted for Propensity Score[c] to Receive Angiotensin Converting Enzyme Inhibitor Therapy Preoperatively

Variables	Adjusted Odds Ratio	95% CI	*p* Value
Age[d]	1.08	1.03–1.13	0.0007
Preoperative GFR[e]	0.97	0.95–0.98	0.002
LVEF < 0.35	3.1	1.08–9.06	0.03
Pre-op IABP	8.1	2.75–24.20	0.0001
Emergency surgery	2.5	1.14–5.90	0.02
Pre-op ACE inhibitors	0.48	0.23–0.77	0.04
CPB time[f]	1.009	1.00–1.019	0.04

[a] Model χ^2, 51.4; $p < 0.0001$; C statistic, 0.78. [b] Hosmer-Lemeshow χ^2, 9.28; $p = 0.14$. [c] C statistic for propensity score, 0.69; $p = 0.0001$. [d] Per 1-year increase. [e] Per 1-mL/min/1.73 m^2 decrease. [f] Per 1-minute increase.

ACE = angiotensin-converting enzyme; CI = confidence interval; CPB = cardiopulmonary bypass; GFR = glomerular filtration rate; IABP = intraaortic balloon pump; LVEF = left ventricular ejection fraction.

Results

Demographic, Clinical Data, and Procedural Characteristics

A total of 281 patients (52%) received ACE inhibitor therapy preoperatively, and 255 patients (48%) did not. Demographic, clinical data, and procedural characteristics are reported in Table 1.

Age, gender distribution, and preoperative GFR were similar between groups. Patients receiving ACE inhibitors preoperatively were more likely to have hypertension and to receive preoperative β-blockers. Patients who did not receive preoperative ACE inhibitor therapy were more likely to have chronic obstructive pulmonary disease and prior myocardial infarction within 30 days.

Procedural characteristics, including the number of distal anastomoses, rates of internal mammary artery usage, CPB time, and aortic cross-clamp time, were similar in both groups.

Renal Outcomes

After CABG, AKI developed in 49 patients (9.1%), and 23 (4.2%) of these required dialysis. The median postoperative length of intensive care unit (ICU) stay in survivors with AKI was 5.5 days (range, 3.0 to 11.5 days) compared with 2.0 days (range, 1.0 to 3.0 days) for patients without AKI ($p < 0.0001$). The median postoperative length of ICU stay in survivors with AKI who required dialysis was 9.0 days (range, 6.75 to 26.75 days) compared with 2.0 days (range, 1.0 to 3.0 days) for patients who did not require postoperative dialysis ($p < 0.0001$). The incidence of AKI in patients who received preoperative ACE inhibitors was 6.4% compared with 12.2% for patients who did not receive ACE inhibitors ($p = 0.02$), and the incidence of AKI requiring dialysis was 2.4% and 6.3%, respectively ($p = 0.03$). Post hoc power analysis for χ^2 tests showed an acceptable study power to detect significant difference for the incidence of AKI (1-β, 0.99; critical χ^2, 11.070; effect size w, 0.23) for an $\alpha = 0.05$.

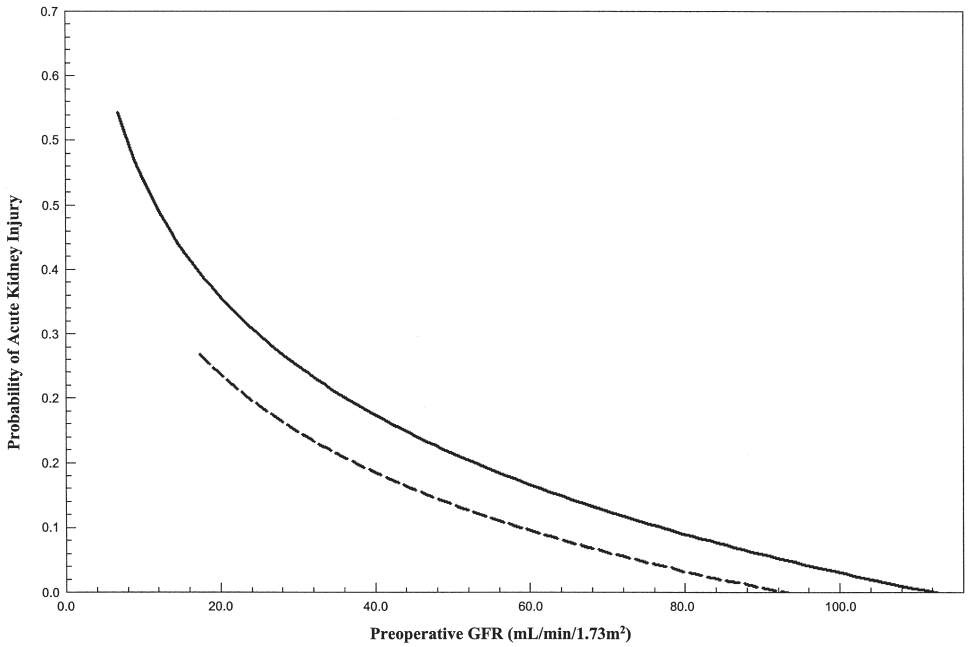

Fig 1. Prediction curves[a] for acute kidney injury (AKI) for patients who received angiotensin-converting enzyme (ACE) inhibitors[b] (dashed line) and patients who did not receive ACE inhibitors preoperatively[c] (solid line). The comparative predictive curves for AKI in two groups showed that a beneficial effect of preoperative ACE inhibitors was achieved for all preoperative value of glomerular filtration rate (GFR). ([a]Model definition: $Y = a + b \times \log(x)$. [b]Adjusted coefficient of multiple regression $R_a^2 = 0.50$; [c]Adjusted coefficient of multiple regression $R_a^2 = 0.36$.)

Independent Risk Factors for AKI

The unadjusted univariate analysis showed that risk factors related with AKI were age, female sex, preoperative GFR, left ventricular ejection fraction of less than 0.35, prior myocardial infarction within 30 days, preoperative use of IABP, emergency operation, preoperative ACE inhibitor therapy, and CPB time (Table 2).

Multivariate analysis was adjusted for propensity score to assess independent risk factors for AKI. The propensity score for preoperative ACE inhibitor therapy achieved an acceptable discrimination between the two group (C statistic, 0.69; 95% CI, 0.65 to 0.73; $p = 0.0001$).

After adjusting for propensity score and covariates, preoperative ACE inhibitors were found to have a protective effect on the incidence of AKI after CABG (OR, 0.48; 95% CI, 0.23 to 0.77; $p = 0.042$). Other independent predictors of AKI were age (OR, 1.08 per 1 year; 95% CI, 1.03 to 1.13; $p = 0.0007$), preoperative GFR (OR, 0.97 per 1 mL/min/1.73 m^2 decrease; 95% CI, 0.95 to 0.98; $p = 0.002$), left ventricular ejection fraction of less than 0.35 (OR, 3.1; 95% CI, 1.08 to 9.68; $p = 0.03$), preoperative use of IABP (OR, 8.16; 95% CI, 2.75 to 24.20; $p = 0.0001$), emergency operation (OR, 2.5; 95% CI, 1.14 to 5.90; $p = 0.02$), and CPB time (OR, 1.009; 95% CI, 1.0001 to 1.019; $p = 0.04$; Table 3).

The multivariate model significantly predicted the occurrence of AKI (model χ^2, 51.4; $p < 0.0001$). The discriminatory ability of the logistic model was acceptable (C statistic, 0.78; 95% CI, 0.74 to 0.82; $p = 0.0001$). The model was well calibrated among deciles of observed and expected risk (Hosmer-Lemeshow χ^2, 9.28; $p = 0.14$).

The comparative predictive curves for AKI in two groups (Fig 1) showed that a beneficial effect of preoperative ACE inhibitors was achieved for all preoperative values of GFR.

Operative Mortality

Overall, the operative mortality rate was 17 of 536 (3.1%). The operative mortality rate was 24.5% for patients with AKI compared with 0.8% for patients without AKI ($p < 0.0001$) and 39.1% for patients who required postoperative dialysis compared with 1.5% for those who did not ($p < 0.0001$). Operative mortality was 2.8% for patients who received preoperative ACE inhibitor therapy and 3.5% for patients who did not ($p = 0.80$).

Comment

Acute kidney injury after CABG remains a challenging problem. Despite the progress in surgical techniques and intensive care, few gains have been reached in the prevention and treatment of AKI, and patients who present with postoperative renal dysfunction continue to have an extremely poor outcome [2, 3]. In this regard, because ACE inhibitor therapy was found to be a promising tool in renal protection in different clinical settings [5, 6], it could be even useful in CABG procedures. However no final conclusions are available on the usefulness of preoperative ACE inhibitor therapy on renal outcome in CABG patients [7].

On the other hand, it is widely believed that preoperative ACE inhibitors may impair the autoregulation of renal blood flow during CPB, thus exacerbating CPB-related renal hypoperfusion and injury [2, 12]. This hypothesis was derived from previous observations that showed that ACE inhibitor therapy may cause a reversible decline in renal function in several clinical conditions associated with decreased renal perfusion, such as bilateral renal artery stenosis, severe congestive heart failure, or volume depletion [8, 9]. Because an increasing number of patients who receive ACE inhibitor therapy are pre-

senting for operations, the definition of ACE inhibitor impact on postoperative renal dysfunction should add important benefits to CABG outcomes.

This analysis found that preoperative ACE inhibitors continued to the day of operation are associated with a significantly lower risk of postoperative AKI compared with no preoperative ACE inhibition treatment. We observed a 47.5% relative reduction and a 5.8% absolute reduction of AKI rates, defined as a composite event of renal failure requiring dialysis or a 50% or more decline in GFR postoperatively. The improvement in renal outcome persisted after statistical adjustment, which included the propensity to have received preoperative ACE inhibitors.

Rady and colleagues [13] previously failed to find a significant effect of preoperative ACE inhibitors on postoperative renal dysfunction on a large series of cardiac surgical patients. However, we must point out that their study population was heterogeneous, including also thoracic aortic surgical patients. Most remarkably, postoperative renal dysfunction was arbitrarily defined as a postoperative serum creatinine level of 3.8 mg/dL or more, with a very low reported rate of 2.7% postoperatively. Gamoso and colleagues [14] did not show any significant association between long-term ACE inhibitors use and renal dysfunction after surgical revascularization. However, the off-pump patients included in their study may be a relevant confounding factor because ACE inhibitors may have an extremely different impact if CPB is eliminated. In addition, the high rate of missing values (37%) reported for ACE inhibitors use raises concerns in interpreting the data.

Our results, on the other hand, are supported by several studies demonstrating an increased renin-angiotensin system activity during CPB, which has a prominent role in hypoperfusion-related renal injury [15, 16]. The intraoperative administration of enalaprilat, an intravenous ACE inhibitor, improves renal perfusion by contrasting the renin-angiotensin system activity [15, 16]. In addition, enalaprilat increases cardiac output in patients with left ventricular dysfunction after weaning from CPB, thus improving renal perfusion [15, 16].

The reduction of AKI rate that we observed in patients receiving preoperative ACE inhibitors may therefore be related to the protective effect of ACE inhibition on renal perfusion intraoperatively. Moreover, preoperative ACE inhibitor therapy in the surgical population might be associated with a higher preoperative renal function reserve, making these patients less susceptible to renal injury during further CPB.

Some reports have warned of episodes of profound hypotension in patients receiving long-term treatment with ACE inhibitors [17], but others have not supported this suggestion [18]. We did not observe any adverse event in patients who were receiving ACE inhibitors, including hypotension on induction of anaesthesia or an increase in vasoconstrictor requirements after CPB.

Other independent risk factors for AKI identified in the present analysis were consistent with other reports [3, 19–25]. We found postoperative AKI was strongly related with age, preoperative renal function, and prolonged CPB time [15, 19]. Our results confirmed that variables related to perioperative hemodynamic instability, such as impaired left ventricular ejection fraction, preoperative use of an IABP, and emergency operation, are related to postoperative renal failure [19–25]. Such conditions are highly predictive of low cardiac output syndrome, which is one of the most important determinants for postoperative renal dysfunction [12]. We failed to find that diabetes was an independent determinant of AKI. The effect of diabetes on AKI after operation has been controversial [19–24]. Some studies have shown an increased risk of AKI among patients with diabetes, but others failed to demonstrate it. These differences might be due to the prevalence of diabetic patients among populations of interest and the predominant type of diabetes (ie, diet-controlled, noninsulin-dependent, or insulin-dependent diabetes).

This study has several major limitations. It was retrospective in design, and preoperative ACE inhibitor therapy was not randomized; therefore, our results may be influenced by treatment bias. We performed statistical adjustment, including the use of propensity scores, in an attempt to account for the nonrandomized nature of preoperative ACE inhibitor therapy. However, our propensity analysis for the use of ACE inhibitors was only modestly predictive, which is perhaps not surprising because almost half of the patients received ACE inhibitors.

Our analysis was restricted to patients undergoing isolated CABG operations on CPB; therefore, our results may not be applicable to overall cardiac surgical population.

In conclusion, the present propensity score–adjusted analysis showed that preoperative ACE inhibitors are associated with a significant improvement in renal outcomes after CABG. These results suggest that ACE inhibitor therapy until the day of operation should be recommended.

No clinical evidence supports a deleterious effect of ACE inhibitor treatment on kidney function after operation. However, an appropriately powered, randomized, controlled trial evaluating the optimal management of preoperative ACE inhibitor therapy before CABG operations would be useful to confirm our results.

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INVITED COMMENTARY

Management guidelines for the perioperative angiotensin-converting enzyme inhibitors (ACEIs) are increasingly needed, as their use becomes more prevalent in patients presenting for cardiac surgery, and studies report experimental evidence for protective effects with short-term therapy with these agents. The ACEIs have their actions on the renin-angiotensin system (RAS), a signaling pathway that mediates systemic vasoconstriction, but has an equally important role in the local regulation of renal microcirculatory flow. Paradoxically, RAS blockade can have both renoprotective properties and the disconcerting ability to precipitate acute renal failure. The ACEIs (such as captopril) are clinically useful to slow the advance of chronic renal disease and in animals to provide protection against ischemic acute kidney injury. However, when RAS activation is critical to sustain renal blood flow (such as with renal artery stenosis or volume depletion) the ACEIs are detrimental. One study in cardiac surgical patients even noted a synergistic association of combining ACEIs with aprotinin in adding to renal risk. Specific circumstances and practices aside, previous clinical studies of acute kidney injury and perioperative ACE inhibition in surgical populations provide evidence of a confusing relationship with positive, neutral, and negative associations being reported.

In the retrospective assessment of 536 aortocoronary bypass procedures presented in this issue, Benedetto and colleagues [1] takes another stab at disentangling the numerous effects possible from acute and chronic ACEI therapy on the kidney in cardiac surgical patients. Notable challenges in drawing valid conclusions from the current study include the relatively high rate of new dialysis in the study population and the potential for selection bias in the characteristics of patients receiving ACEIs. The investigators appropriately used a propensity score-based multivariable analysis to minimize bias and found an association between perioperative ACEI therapy and an approximate 50% reduction in the likelihood of acute kidney injury, after accounting for other known renal risk factors. When added to the larger body of literature in this area, this study is interesting and further expands our insight into the relationship of preoperative ACEIs and postoperative outcome, but as a single study added to an accumulating collection of conflicting evidence (see the

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