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ORIGINAL RESEARCH

Angiotensin Axis Blockade, Hypotension, and Acute Kidney Injury in Elective Major Orthopedic Surgery

Erik Nielson, MD[1], Eileen Hennrikus, MD, FACP[2*], Erik Lehman, MS[3], Berend Mets, MB, PhD, FRCA[4]

[1]Department of Anesthesiology, Pennsylvania State University College of Medicine and Milton S. Hershey Medical Center, Hershey, Pennsylvania; [2]Department of Internal Medicine, Pennsylvania State University College of Medicine and Milton S Hershey Medical Center, Hershey, Pennsylvania; [3]Department of Public Health Sciences, Penn State Hershey College of Medicine, Hershey, Pennsylvania; [4]Department of Anesthesiology, Pennsylvania State University College of Medicine and Milton S Hershey Medical Center, Hershey, Pennsylvania.

BACKGROUND: Patients presenting for surgery with angiotensin axis blockade (AAB) from therapy with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers experience an increased incidence of perioperative hypotension. Acute kidney injury (AKI) in patients receiving preoperative AAB has been demonstrated after lung, vascular, and cardiac surgery. However, there is little literature evaluating the hypotensive and renal effects of preoperative AAB and major orthopedic surgery.

METHODS: We performed a retrospective chart review of 1154 patients who underwent spinal fusion, total knee arthroplasty, or total hip arthroplasty during the 2010 calendar year in our academic medical center.

RESULTS: A total of 922 patients met inclusion criteria, 343 (37%) received preoperative AAB. Postinduction hypotension (systolic blood pressure $\leq$80 mm Hg for 5 minutes) was significantly higher in patients receiving AAB when compared to those not so treated (12.2% vs 6.7%; odds ratio [OR]: 1.93, $P = 0.005$). Of the 922 patients, 798 had documented measurements of both preoperative and postoperative creatinine. Postoperative AKI was significantly higher in patients receiving AAB therapy (8.3% vs 1.7%; OR: 5.40, $P < 0.001$), remaining significant after adjusting for covariates including hypotension (OR: 2.60, $P = 0.042$). Developing AKI resulted in a significantly higher mean length of stay (5.76 vs 3.28 days, $P < 0.001$) but no difference in 2-year mortality.

CONCLUSIONS: Patients undergoing major elective orthopedic surgery who receive preoperative AAB therapy,have an associated increased risk of postinduction hypotension and postoperative acute kidney injury resulting in a greater hospital length of stay. *Journal of Hospital Medicine* 2014;9:283–288. © 2014 Society of Hospital Medicine

Patients presenting for surgery with angiotensin axis blockade (AAB) from therapy with either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) experience an increased incidence of perioperative hypotension.[1–4] Debate continues as to whether this hypotension results in any significant clinical sequelae. Some authors found that the use of an ACEI decreased the incidence of acute kidney injury (AKI),[5] mortality, and septicemia in cardiac and vascular surgical patients.[6] However, others found that in vascular and cardiac surgery there is increased mortality[7] as well as increased incidence of postoperative AKI.[8–10] A retrospective study of 10,000 coronary artery bypass graft patients found that ACEI was associated with increased inotropic support, AKI, mortality, and new onset atrial fibrillation.[11] In a meta-analysis of 69,000 cardiothoracic surgery patients, the use of ACEIs/ARBs was associated with an increase in AKI and mortality.[12] AKI has also been demonstrated after lung resection surgery in patients receiving preoperative therapy with an ARB.[13]

Studies on noncardiac general surgery patients demonstrate that the use of AAB results in postinduction hypotension, but they fail to show an increased incidence in postoperative AKI.[14,15] We propose, however, that major orthopedic surgery patients are a specific surgical cohort, like cardiac, vascular, and lung, who can develop operative hypotension and postoperative AKI when AAB is taken on the morning of surgery. To address this question we performed a retrospective study of 1154 patients undergoing either spinal fusion, total knee arthroplasty (TKA), or total hip arthroplasty (THA) during the 2010 calendar year in our academic medical center. We measured the incidence of postanesthesia induction hypotension, intraoperative hypotension, and postoperative AKI as it relates to the administration of AAB preoperatively.

MATERIALS AND METHODS

This study was a retrospective, observational investigation at a single, large academic hospital. The study design for chart review was approved by the institutional review board prior to data collection. Informed patient consent was not required for this retrospective study.

*Address for correspondence and reprint requests: Eileen Hennrikus, MD, Department of Internal Medicine, Pennsylvania State University College of Medicine and Milton S Hershey Medical Center, 500 University Drive, MC H034, Hershey, PA 17033; Telephone: 717-531-8161; Fax: 717-531-7726; E-mail: ehennrikus@hmc.psu.edu

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Patient Selection

We retrospectively reviewed the computerized chart and operating room electronic medical records of all patients who underwent elective major orthopedic surgery in the 2010 calendar year. We chose vertebral spine fusion, TKA, and THA as the 3 surgeries to represent major elective orthopedic surgery. Electronic query of the hospital database identified 1154 patients having undergone these surgeries in the year 2010. Nine hundred twenty-two patients met inclusion criteria: ≥21 years old and evaluated in the preanesthesia clinic with documented vital signs and clearly defined preoperative medication recommendations. The policy in the preanesthesia clinic was to recommend taking the ACEI and ARB on the morning of surgery. All 922 patients were included in the analysis of the outcomes for induction hypotension and intraoperative hypotension. Of the 922 patients, 798 had the documented preoperative and postoperative creatinine values needed to define AKI. Therefore, only these 798 patients were included in the AKI outcome analysis. During the time of the study it was the practice at our medical center that all such surgeries were performed under general anesthesia.

Data Collection

Preanesthesia records were reviewed for patient demographics including age, body mass index (BMI), baseline blood pressure, diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HTN), and congestive heart failure (CHF), as well as for therapy with ACEI or ARB, diuretics, β-blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and calcium channel blockers (CCB). The 4 statistically and clinically significant comorbidities were looked at individually as well as added together for a total sum of weighted comorbidity risk factors. The Anesthesia Electronic Record (Surginet Anesthesia, Kansas City, MO) was reviewed for each corresponding patient to determine the general anesthesia induction agent used and to assess the postinduction and intraoperative systolic blood pressures. Blood pressure was determined using an automated blood pressure cuff and automatically recorded at intervals of 5 minutes or less. Further, ephedrine, phenylephrine and vasopressin doses, estimated blood loss, blood transfusion requirements, and intravenous fluid administration (colloid and crystalloid) were noted. Preoperative (<30 days) and postoperative (within 24 hours after surgery) serum creatinine and hematocrit values were also recorded.

Outcome Measures

The primary outcome measures studied were:

1. Postinduction hypotension (systolic blood pressure [SBP] ≤80 mm Hg for ≥ 5 minutes) occurring within 30 minutes after anesthesia induction but before surgical incision.[16]
2. Intraoperative hypotension (SBP ≤80 mm Hg for ≥10 minutes) occurring after surgical incision.[16]
3. Postoperative AKI defined as an increase in serum creatinine ≥0.3 mg/dL or an increase of 50% from preoperative creatinine (Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury)[17] within 24 hours postoperatively.

The secondary outcome measures were:

1. Hospital length of stay (LOS).
2. Two-year mortality associated with the development of AKI.

Statistical Analysis

Categorical variables were summarized with frequencies and percentages, whereas continuous variables were summarized with means, standard deviations, medians, and quartiles. A χ^2 test or a Wilcoxon rank sum test was used to determine differences in preoperative and intraoperative characteristics between those patients with AAB and those patients without AAB. Logistic regression was used to determine the association between the main outcome variables (hypotension at anesthetic induction, hypotension during the operative procedure, and postoperative AKI) and the primary independent variable, AAB, as well as other preoperative and intraoperative characteristics. The significance and magnitude of the associations were quantified with percentages and odds ratios. Exact logistic regression was used as necessary when expected cell counts were too small for the usual asymptotic logistic regression to be valid. The statistically significant ($P < 0.05$) variables resulting from this bivariate analysis as well as important clinically significant variables with known associations with the outcome variables were included as covariates in a multivariable logistic regression model for each outcome variable with AAB. By adjusting for these covariates, any potential and unwanted variation resulting from differences between the AAB groups in other preoperative or postoperative characteristics is removed from the association between each outcome variable and AAB. Variance inflation factor and tolerance statistics were used to test for multicollinearity between all independent variables before including them in the final models. The Hosmer and Lemeshow goodness-of-fit test was used to assess the fit of the final models. Logistic regression was used to test the association of AKI with mortality, whereas a Wilcoxon rank sum test was used to test the difference in mean/median LOS between AKI and non-AKI groups.

RESULTS

Preoperative, Surgical, and Anesthesia Data

A total of 922 patients met inclusion criteria, of which 343 (37%) were receiving AAB with either an ACEI

or ARB preoperatively. Preoperative characteristics are documented in Table 1. Patients receiving AAB were older (63.0 ± 10.8 vs 57.3 ± 13.9 years) and had a higher BMI (34.6 ± 7.3 vs 31.9 ± 7.7) than patients not receiving this therapy. They were also more likely to be receiving diuretics, β-blockers, and CCBs as well as have DM, CHF, CAD, and HTN. These characteristics were included as covariates in a multivariable logistic regression model so that any confounding resulting differences caused by these variables were removed from the association between each outcome variable and AAB use. There was no difference in baseline SBP or diastolic blood pressures. There was no difference in the use of NSAIDs. Patients receiving AAB underwent a higher percentage of TKAs (56.0% vs 44.2%) and lower percentage of spine fusions (16.6% vs 24.4%) and THAs (27.4% vs 31.4%). Propofol was the most commonly used general anesthetic induction agent (78%). Anesthetic induction agent usage was not different across the groups.

Estimated blood loss for the procedures was similar between the 2 groups (301.2 ± 340 vs 356.9 ± 482.7 mL) and similar colloid and packed red cell administration occurred. However, patients receiving AAB were administered less crystalloid infusion (2584.4 ± 1401.6 vs 2765.2 ± 1487.2 mL, $P = 0.036$) and received less phenylephrine but higher ephedrine and vasopressin dosages as a group. Patients in both groups had similar preoperative and postoperative hematocrit concentrations. Average preoperative serum creatinine was higher in the AAB group than in the non-AAB group (0.96 ± 0.41 vs 0.85 ± 0.23, $P < 0.001$) and remained so postoperatively (0.96 ± 0.42 vs 0.81 ± 0.23, $P < 0.001$).

TABLE 1. Perioperative Characteristics and Outcome Variables by AAB

	AAB (N = 343)	Non-AAB (N = 579)	*P* Value*
Patient demographics			
Age (y), mean ± SD	63.0 ± 10.8	57.3 ± 13.9	<0.001
BMI (kg/m^2), mean ± SD	34.6 ± 7.3	31.8 ± 7.7	<0.001
Baseline systolic BP (mm Hg), mean ± SD	135.0 ± 16.8	130.8 ± 19.8	0.339
Baseline diastolic BP (mm Hg), mean ± SD	74.5 ± 14.5	75.3 ± 11.8	0.798
Medications			
Diuretic, %	53.6	18.5	<0.001
β-Blocker, %	39.4	22.4	<0.001
Calcium channel blocker, %	23.3	9.9	<0.001
Nonsteroidal anti-inflammatory drug, %	36.1	35.7	0.901
Comorbidities			
Diabetes mellitus, %	32.9	9.5	<0.001
Congestive heart failure, %	2.9	0.4	0.001
Coronary artery disease, %	20.1	9.5	<0.001
Hypertension, %	95.3	36.8	<0.001
Total comorbidities, mean ± SD	1.5 ± 0.7	0.5 ± 0.7	<0.001
Procedure type			
Spinal fusions, %	16.6	24.4	0.001
Total knee arthroplasty, %	56.0	44.2	0.001
Total hip arthroplasty, %	27.4	31.4	0.001
Induction agents			
Etomidate, %	14.9	11.9	0.199
Propofol, %	77.6	78.3	0.801
Methohexital, %	7.3	9.2	0.329
Other (gas, ketamine), %	0.3	1.2	0.270
Hematocrit			
Preoperative (%), mean ± SD	40.5 ± 3.7	40.2 ± 3.8	0.150
Postoperative (%), mean ± SD	34.0 ± 4.6	33.7 ± 4.3	0.511
% Change, mean ± SD	−15.3 ± 8.5	−16.8 ± 8.9	0.036
Creatinine			
Preoperative (mg/dL), mean ± SD	0.96 ± 0.41	0.85 ± 0.23	<0.001
Postoperative (mg/dL), mean ± SD	0.96 ± 0.42	0.81 ± 0.23	<0.001
% change, mean ± SD	1.48 ± 29.22	−4.14 ± 14.18	0.235
Fluids			
Estimated blood loss (mL), mean ± SD	301.2 ± 340.0	356.9 ± 482.7	0.125
Crystalloid (mL), mean ± SD	2584.4 ± 1401.6	2765.2 ± 1487.2	0.036
Colloid (mL), mean ± SD	124.3 ± 322.4	151.0 ± 553.5	0.810
Packed red blood cells (mL), mean ± SD	78.5 ± 323.1	99.5 ± 452.0	0.613
Vasopressors			
Ephedrine (mg), mean ± SD	11.7 ± 15.0	8.0 ± 13.0	<0.001
Phenylephrine (μg), mean ± SD	615.7 ± 2210.9	687.1 ± 3905.3	0.002
Vasopressin (U), mean ± SD	0.35 ± 1.90	0.08 ± 0.90	<0.001
Outcomes			
Induction hypotension, %	12.2	1.93	0.005
Intraoperative hypotension, %	26.0	20.9	0.078
Acute kidney injury, %	8.3	1.7	<0.001

NOTE: **Abbreviations:** AAB, angiotensin axis blockade; BMI, body mass index; BP, blood pressure; SD, standard deviation. *P values from an analysis using logistic regression (%) or Wilcoxon rank sum test (mean ± SD).

Primary and Secondary Outcome Measures

Postinduction Hypotension

Therapy with AAB was associated with a greater incidence of postinduction hypotension (12.2% vs 6.7%, $P = 0.005$). Using a multivariate logistic regression model adjusting for the effects of age, BMI, antihypertensive medications, comorbidities, and anesthetic induction agents, the use of AAB had a greater odds ratio (OR) of 1.93 (95% confidence interval [CI]: 1.10-3.41, $P = 0.023$) for developing postinduction hypotension (Table 2). A higher BMI had a lower OR for postinduction hypotension.

Postincision (Intraoperative) Hypotension

The incidence of postincision, intraoperative hypotension in patients receiving AAB (26.0%) was not statistically different ($P = 0.078$) from those not receiving these agents (20.9%). Multivariate logistic regression demonstrated that preoperative hypertension (OR: 1.73, 95% CI: 1.05-2.85, $P = 0.031$) and THA were each independent risk factors for intraoperative hypotension. The other comorbidities of DM, CHF, CAD, and the individual antihypertensive agents were not found to have a strong influence on the outcome of intraoperative hypotension. The odds ratio of developing intraoperative hypotension during the procedure in patients receiving AAB was not statistically significant (OR: 1.30, 95% CI: 0.85-1.97, $P = 0.226$) from those not receiving this therapy preoperatively (Table 2).

TABLE 2. Multivariable Models for Outcome Variables by AAB

Comparison	Hypotension at Induction, OR (95% CI), *P* Value	Intraoperative Hypotension, OR (95% CI), *P* Value	Acute Kidney Injury, OR (95% CI), *P* Value
AAB vs none, unadjusted	1.93 (1.22–3.06), 0.005	1.33 (0.97–1.82), 0.078	5.40 (2.41–12.06), <0.001
AAB vs none, adjusted for covariates	1.93 (1.10–3.41), 0.023	1.30 (0.85–1.97), 0.226	2.68 (1.08–6.69), 0.034
AAB vs none, adjusted for covariates + hypotension at induction	N/A	N/A	2.51 (1.0–6.32), 0.051
AAB vs none, adjusted for covariates + intraoperative hypotension	N/A	N/A	2.66 (1.06–6.64), 0.037
AAB vs none, adjusted for covariates + any hypotension	N/A	N/A	2.60 (1.04–6.51), 0.042

NOTE: **Abbreviations:** AAB, angiotensin axis blockade; CI, confidence interval; N/A, not applicable when hypotension is a primary outcome; OR, odds ratio. *OR and *P* values from an analysis using logistic regression. Covariates include age, body mass index, medications, total comorbidities, procedure type, induction agents, hematocrit % change from preoperative to postoperative, preoperative creatinine, estimated blood loss, and crystalloid depending on the outcome modelled Any hypotension defined as hypotension at induction or intraoperative hypotension.

AKI

There was a significantly higher incidence of AKI (26/313 [8.3%] vs 8/485 [1.7%], $P < 0.001$) in patients receiving preoperative AAB. No patients required renal replacement therapy. Of those patients who developed postoperative AKI, 73% of the AAB group and 75% of the non-AAB group had a normal glomerular filtration rate (GFR) (mL/min/1.73 m^2, GFR >90 prior to surgery. Of both the AAB and non-AAB groups, 20% to 25% were in stage 2 (GFR 60–89) chronic kidney disease (CKD)[18] preoperatively. Only 2 patients in the AAB group began in stage 3 (GFR 30–59) CKD. Fifty percent of both groups went from stage 1 kidney function to stage 3. For all others who developed AKI, the GFR rose by a single stage.

Multivariate logistic regression, controlling for statistically significant and clinically significant variables, demonstrated that AAB administered preoperatively was independently associated with a greater OR of 2.68 (95% CI: 1.08-6.69, $P = 0.034$) for developing AKI postoperatively than if AAB was not taken (Table 2). Higher BMI was a further independent risk factor for postoperative AKI; a 5-unit increase in BMI revealed an OR of 1.58 (95% CI: 1.25-1.99, $P < 0.001$) for experiencing postoperative AKI. Although the AAB group had statistically significantly more comorbidities, in the final analysis only the presence of CAD trended to an association with the development of AKI (OR: 2.37, 95% CI: 1.00–5.60, $P = 0.050$).

We wished to determine whether the increased risk of AKI associated with AAB therapy was explained by the associated postinduction or postincision, intraoperative hypotension experienced by the patients or independent of these effects. To do so we accounted for the development of either postinduction or intraoperative hypotension as a possible confounder in the multivariate analysis for the development of AKI (Table 2). Postinduction hypotension alone was not statistically associated with AKI (OR 2.04, 95% CI: 0.70-6.0, $P = 0.193$). However, intraoperative hypotension was found to be an independent risk factor for the development of AKI (OR: 2.62, 95% CI: 1.17-5.84, $P = 0.019$). When eliminating the effect of this intraoperative hypotension as a confounder, patients on AAB therapy continued to have a 2.66 OR for the development of AKI postoperatively (95% CI: 1.06-6.64, $P = 0.037$), independent of the development of intraoperative hypotension. When eliminating the effect of both postinduction and intraoperative hypotension ("all hypotension" Table 2), AAB therapy continued to have a statistically significant independent effect (OR: 2.60, 95% CI: 1.04–6.51, $P = 0.042$) on developing postoperative AKI.

As secondary outcome measures, we looked at the development of AKI and its relationship to hospital LOS and mortality. The development of AKI was associated with a significantly greater mean length of hospital stay (5.76 days vs 3.28 days, $P < 0.001$). Although 2-year mortality was higher, 5.9% in the AKI group compared to 2.4% in the non-AAB group, it was not statistically significant ($P = 0.211$).

DISCUSSION

In this retrospective review of 922 patients presenting for major orthopedic surgery, we found that 343(37%) were receiving therapy with either ACEIs or ARBs. In such patients, we demonstrated a higher incidence of postinduction hypotension and an increased incidence of AKI. We further demonstrated that the development of AKI associated with AAB therapy was independent of hypotension occurring either postinduction or intraoperatively after incision.

Postinduction hypotension in patients receiving AAB was demonstrated to be 12.2% compared to 7.7% in patients not receiving this therapy. Hypotension after general anesthesia induction in patients receiving AAB is widely reported,[1,14,15] and ranges from 22% to 100%[19,20] based on varying definitions of what constitutes hypotension. We chose an absolute value of a systolic blood pressure of ≤80 mm Hg occurring for ≥5 minutes as constituting significant hypotension.[16] Monk et al. reported an increased one year post–non-cardiac surgery mortality risk of 1.036 times per minute of intraoperative hypotension,

defining hypotension as a systolic blood pressure of <80 mm Hg.[21]

We further demonstrated that AAB therapy resulted in an 8.3% incidence of AKI versus 1.7% in non-AAB patients ($P < 0.001$). AKI was defined as an increase in serum creatinine of ≥0.3 mg/dL or a 50% increase in creatinine when pre- and postoperative values were compared.[17] A number of other investigators have identified AKI associated with AAB use in patients undergoing cardiac,[6,11] vascular,[7,10] and lung[13] surgery. Similarly, in the present study, in orthopedic patients, AAB remained a significant risk factor for developing AKI (OR: 2.68, $P = 0.034$) independent of patient comorbidities and adjunct therapy (Table 2).

ACEIs and ARBs are prescribed to treat HTN, CHF, and improve renal function in diabetic and proteinuric nephropathy.[22] AAB therapy is prescribed for nephropathy because these medications decrease glomerular pressure by selective inhibition of angiotensin II mediated vasoconstriction of the efferent glomerular arteriole.[23] Normally, this is beneficial to patients and is associated with a decrease in serum creatinine concentration. However, during hypotension, when there is decreased renal perfusion, further decreases in intraglomerular pressure may occur, precipitating renal failure.[23] In addition, other factors may contribute to the development of AKI, as AAB has both tissue and systemic effects that extend beyond simply dilating the efferent glomerular arteriole. These include effects on the sympathetic nervous system, oxidative stress, and altering the release and synthesis of vasodilators such as bradykinin, nitric oxide, and prostacyclins[24] as well as effects through the release of aldosterone and arginine-vasopressin.[25] These other factors might help explain the present study's findings that, when eliminating the effect of both postinduction and intraoperative hypotension, AAB therapy continued to have a statistically significant independent effect (OR: 2.60, 95% CI: 1.04–6.51, $P = 0.042$) on developing postoperative AKI.

Although we demonstrated an association of AAB therapy with the development of hypotension after induction, we demonstrated only a trend in the development of postincisional, intraoperative hypotension ($P = 0.078$). We defined intraoperative hypotension as a systolic BP <80 mm Hg for ≥10 minutes occurring after skin incision.[16] One must take into consideration, however, that a significant number of AAB patients were hypotensive during induction and received higher doses of ephedrine and vasopressin during the operative period. These patients may have been rescued from intraoperative hypotension by receiving vasopressor treatment at the outset. We did find that intraoperative hypotension was a significant, independent risk factor for AKI (OR: 2.62, $P = 0.019$).

We looked further at the consequences of developing AKI. Patients who developed AKI had a significant greater mean length of hospital stay (5.76 days vs 3.28 days, $P < 0.001$), which is consistent with other investigators' findings.[25–27] Although 2-year mortality was higher at 5.88% in the AKI group compared to 2.38% in the non-AAB group, this was not statistically significant ($P = 0.211$). Other studies have shown that the development of AKI results in greater mortality.[26,28]

The American College of Physicians (ACP) recommendations as of 2013 regarding the use of ACEIs and ARBs preoperatively is: "uncertain, continue with caution, avoid hypovolemia. Potential for hypotension with induction of anesthesia and increased vasoconstrictor requirements and decreased responsiveness to pressors."[29] The ACP acknowledges that preoperative ACEIs and ARBs have the potential for postinduction hypotension and increased requirements for vasopressors. We have implemented recommendations at our preoperative anesthesia clinic to hold ACEIs and ARBs on the morning of surgery in patients with controlled blood pressure scheduled for spine fusion, and hip and knee arthroplasties. In accordance with ACP guidelines, other antihypertensives such as β-blockers, calcium channel blockers, nitrates, and sympatholytics should be continued preoperatively and can be used perioperatively.

Limitations of the Study

There are several limitations to our study. This was a retrospective analysis over a fixed time period in one academic institution. Further, because of the retrospective nature, anesthesia and intraoperative (fluid and vasoconstrictor) management was not standardized. The definition of hypotension (SBP ≤80 mm Hg for ≥5 minutes after induction and ≥10 minutes after incision) may have been too stringent, so that more subtle decreases in blood pressure that could have impacted AKI might not have been captured to show statistical significance. Thus, our finding, that the development of AKI associated with preoperative AAB therapy may be independent of the occurrence of hypotension, must be interpreted with this in mind.

CONCLUSIONS

Patients who receive preoperative ACEI or ARB therapy and undergo major orthopedic surgery such as spinal fusion, and hip or knee arthroplasties experience a higher incidence of postinduction hypotension and AKI than those not receiving such therapy. The development of AKI in such patients is associated with a significantly prolonged length of hospital stay. Our findings suggest an association between preoperative ACEI/ARB use and moderate kidney injury following major orthopedic surgeries. However, a prospective, multicentered, randomized trial needs to be performed to confirm that withdrawal of AAB therapy preoperatively will decrease the incidence of AKI in patients undergoing major orthopedic

procedures under general anesthesia. Future studies also need to determine the optimal time duration of withholding AAB therapy and the consequences on cardiac outcomes.

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