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Chronic Use of Angiotensin Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers is Not Associated With Stroke After Noncardiac Surgery: A Retrospective Cohort Analysis

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Background: Inhibition of the renin-angiotensin-aldosterone pathways reduces blood pressure and proliferation of vascular smooth muscles and may therefore reduce the risk of stroke. We tested the hypothesis that patients taking angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for at least 6 months have fewer postoperative strokes after non-neurological, noncarotid, and noncardiac surgeries than those who do not.

Methods: We considered adults who had noncardiac surgery at the Cleveland Clinic between January 2005 and December 2017. After excluding neurological and carotid surgeries, we assessed the confounder-adjusted association between chronic use of ACEIs/ARBs (during 6 preoperative months) and the incidence of postoperative stroke using logistic regression models.

Results: Postoperative strokes occurred in 0.26% (27/10,449) of patients who were chronic ACEI/ARBs users and in 0.18% (112/62,771) of those who were not. There was no significant association between ACEI/ARB use and postoperative stroke, with an adjusted odds ratio of 1.15 (95% confidence interval [CI]: 0.91-1.44; $P = 0.24$). Secondarily, there was no association between exposures to ACEIs and postoperative stroke, versus no such exposure (adjusted odds ratio 0.88, 95% CI: 0.65-1.19; $P = 0.33$). Similarly, there was no association between exposure to ARBs and postoperative stroke, versus no such exposure (adjusted odds ratio 1.05, 95% CI: 0.75-1.48; $P = 0.75$).

Conclusion: We did not detect an effect of chronic ACEI/ARB use on postoperative strokes in patients who had non-neurological, noncarotid and noncardiac surgery; however, power was extremely limited.

Key Words: anesthesia, angiotensin receptor antagonists, angiotensin receptor blocker, postoperative cognitive complications, ischemic stroke, postoperative complications

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Postoperative strokes are rare. For example, the incidence of clinically apparent perioperative stroke is reportedly around 0.7% after hemicolectomy, 0.2% after hip replacement, and 0.6% after lobectomy or segmental lung resection.[1] Unsurprisingly, the incidence is greater in older patients and up to 90% of perioperative strokes occur in patients with a previous stroke history.[1,2] Perioperative strokes are devastating; roughly a third of the patients die within 1 month and another third are permanently incapacitated.[3] Mortality from perioperative stroke exceeds that from nonoperative stroke.[4]

Endothelial dysfunction may contribute to perioperative stroke. The neuroendocrine response to surgery provokes a cascade of inflammatory mediators and cytokines that triggers inflammatory responses in vessels, which makes them vulnerable to thrombosis.[5,6] Hyperactivity of the renin-angiotensin-aldosterone system is thought to contribute to the pathogenesis of stroke via its vasoconstrictor effects on cerebral vasculature and oxidative effects on brain parenchyma.[7,8] Inhibition of the renin-angiotensin-aldosterone pathways blunts the neuroendocrine response to surgery and enhances fibrinolysis, stabilizes plaque, decreases the risk of plaque rupture, and reduces thrombosis.[9] Renin-angiotensin-aldosterone

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inhibition also reduces the proliferation of vascular smooth muscle, improves vascular compliance and reduces the cerebral vasoconstriction consequent to angiotensin II, thus potentially reducing stroke risk via 2 mechanisms.[10] For example, inhibition of renin-angiotensin-aldosterone for at least 6 to 9 months measurably decreases carotid intimal medial thickness,[11–15] thereby potentially reducing stroke risk.[16,17] The most commonly used renin-angiotensin-aldosterone inhibitors are angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Previous work performed in nonsurgical settings suggests a benefit of chronic effects of renin-angiotensin-aldosterone pathway inhibition on stroke reduction, and that the benefit may be independent of blood pressure reduction.[7,18–22] However, meta-analyses also suggest that chronic use of ACEIs or ARBs may have different effects on strokes.[22–24] It thus remains uncertain whether the chronic use of ACEIs/ARBs has a plausible role in postoperative stroke reduction. We therefore tested the hypothesis that patients who take ACEIs or ARBs during the 6 months before non-neurological, noncarotid, noncardiac surgeries have fewer postoperative strokes than those who do not.

METHODS

With approval from the Cleveland Clinic Institutional Review Board (IRB 17-035, March 1, 2017) and waived patient consent, we extracted patient information from electronic medical records and perioperative health documentation systems. In this retrospective, single-center, cohort study, we considered adults with American Society of Anesthesiologists (ASA) Physical Status I to IV who had non-neurological, noncardiac, and noncarotid surgeries at the Cleveland Clinic Main Campus between January 2005 and December 2017. For patients who had multiple surgeries during this period, we included only the index surgery for each patient's last surgical hospitalization. Patients were excluded if key demographic or baseline characteristics or perioperative variables were missing.

The exposure was chronic use of ACEIs/ARBs for at least 6 months before the index surgery, irrespective of whether the drug was withheld on the day of surgery. A 6-month window was chosen for ACEI/ARB exposure because that is the minimum time required to ameliorate carotid intimal thickening.[15,25] Chronic use of ACEIs or ARBs was retrieved from the electronic medical records system by searching Cleveland Clinic pharmacy records. Reference patients were those who did not have active ACEI/ARB pharmacy orders for at least 6 months before surgery. For subgroups of ACEI/ARB-treated patients, the "ACEI only group" consisted of patients who did not have an active pharmacy order for ARBs for at least 6 months, and the "ARB only group" consisted of patients who did not have an active pharmacy order for ACEIs for at least 6 months. We excluded patients in whom drug prescriptions were interrupted >90 days in the preoperative 6 months.[26,27]

Postoperative stroke was our primary outcome. We defined postoperative stroke as ischemic, embolic, hemorrhagic, or thrombotic cerebrovascular events that occurred during or within 30 days after surgery and were documented radiologically. We first identified potential postoperative stroke cases using the International Classification of Diseases, Ninth Revision, codes. Potential strokes were independently assessed by 2 investigators (A.M. and A.P.), and discrepancies were adjudicated by 2 other investigators (S.R. and S.A.).

Types of surgery were characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. Both the exposure and the outcome were defined *a priori*. This manuscript adheres to the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology.

Statistical Analysis

Confounder Adjustment

Patient demographic and baseline comorbidities were considered as potential confounding variables in this study. As proxy for surgery risk and complexity, surgery type and surgery duration were controlled through inverse probability of treatment weighting. On the basis of inverse of probability of receiving treatment, weights were assigned to the included patients to form a pseudo-population where the treatment and control groups were balanced on the confounding variables. For example, smaller weights were assigned to patients with a higher probability of receiving treatment whereas larger weights were assigned to patients with a lower probability of receiving treatment. Weighting was estimated as the inverse of the propensity score for patients who received the treatment, and as the inverse (1−propensity score) for the control patients. To avoid extremes, weights smaller than the first percentile were rounded up to the value of first percentile and weights greater than the 99th percentile were rounded down to the value of the 99th percentile. The propensity score was then calculated as the probability of receiving the treatment, estimated from a multivariable logistic regression model that incorporated all the variables shown in Supplemental Digital Content 1 (Supplementary Table 1: Summary patient profile before and after inverse probability of treatment weighting by ACEI/ARB use, http://links.lww.com/JNA/A377) as predictors, independent of the treatment assignment. Because we included patients over a wide timeframe, we also included year of surgery as a categorical variable in the propensity score model to control for the time effect from changing techniques more thoroughly.

For each treatment, we assessed the balance on patients' demographics and baseline comorbidities after weighting, using absolute standardized difference. Variables with absolute standardized difference >0.20 were considered as imbalanced between treatment and control groups, and such variables, except for type of surgery, were adjusted for directly in the analysis model after weighing the patients.

Analysis

For the primary analysis, we assessed the confounder-adjusted association between preoperative use of ACEIs/ARBs and postoperative stroke using logistic regression models, adjusting for confounding variables as described earlier. Odds ratios with 95% confidence intervals (CI) are reported. For the secondary analysis, we assessed the association between preoperative use of ACEIs and postoperative stroke and between preoperative use of ARBs and postoperative stroke separately, each using a logistic regression model with adjustment for potential confounders as described earlier. The 2 exposures were compared in separate models to allow for better adjustment of potential confounding variables. Significance criteria of $0.05/2 = 0.025$ were applied under the Bonferroni correction, adjusting for testing 2 exposures simultaneously.

Post Hoc Power Estimation

Because of the overall low incidence of postoperative strokes (< 0.1%), we included all available patients who had surgery between January 2005 and December 2017. With 10,449 ACEI/ARB users and 62,771 controls, we had 17% power to test an odds ratio of 0.8 and 80% power for an odds ratio of 0.45 or smaller, under the incidence of 0.19% for postoperative stroke.

RESULTS

We identified 173,351 surgeries in 164,204 patients who met our inclusion/exclusion criteria and considered 164,204 index surgeries from the patients' last surgical hospitalization in the analysis (Fig. 1). A total of 4569 (2.8%) patients were excluded under a complete case analysis, assuming that all missingness was at random after inspection of the missing patterns. 23,170 patients who used ACEIs or ARBs within 1 year but did not satisfy chronic ACEI/ARB use were excluded from the control group. An additional 63,245 surgeries were excluded while matching patients according to surgery types with no postoperative stroke. Postoperative stroke was identified in 46 surgery types, involving 139 strokes cases from 73,220 patients, with an incidence rate of 0.19%. Stroke types included 8 (6%) cases of occlusion and stenosis of precerebral arteries, 23 (16%) cases of hemorrhagic stroke and 108 (78%) cases of occlusion of cerebral arteries (Supplemental Digital Content 2, Supplementary Table 2: Type of postoperative strokes, http://links.lww.com/JNA/A378).

For the primary analysis, 10,449 (14.3%) patients used ACEIs/ARBs for at least 6 months before the index surgery, of whom 500 (0.7%) used both ACEIs and ARBs, 6848 (9.4%) used ACEIs only and 3101 (4.2%) used ARBs only. The incidence of postoperative stroke was 0.26% (27/10,449) in ACEI/ARB users and 0.18% (112/62,771) in the control group (Table 1).

Demographics and baseline comorbidities summarized by ACEI/ARB use are shown in Supplemental Digital Content 1 (left panel of Supplementary Table 1, http://links.lww.com/JNA/A377). Patients who used ACEIs/ARBs were older, had higher body mass index, worse ASA physical status, and were more likely to have congestive heart failure, peripheral vascular disease, hypertension, diabetes, renal failure, and coronary artery disease compared with controls. The 2 groups were also unbalanced on race or surgery type. After inverse probability of treatment weighting, control and treatment groups were still not balanced for age, ASA physical status, hypotension, diabetes, renal failure, coronary artery disease or surgery type (Supplementary Digital Content 1: Right panel of Supplementary Table 1, http://links.lww.com/JNA/A377). After confounder adjustment, there was no significant difference between ACEI/ARB users and the control group, with an odds ratio of 1.15 (95% CI: 0.91-1.44; $P = 0.24$), comparing ACEI/ARB users to controls (Table 1).

For subgroups in the treatment group, the incidence of postoperative stroke was 0.24% (17/6848) for patients who used ACEIs only and 0.23% (7/3101) for patients who used ARBs only. Compared with the control group, patients who used ACEIs only or who used ARBs only did not have lower incidence of stroke after confounder adjustment, with odds ratios of 0.88 (97.5% CI: 0.65-1.19; $P = 0.33$) and 1.05 (97.5% CI: 0.75-1.48; $P = 0.75$), respectively (Table 1). Patient profiles for "ACEI only users" and for "ARB only users" are summarized in Supplemental Digital Contents 3 and 4, respectively (Supplementary Table 3: Patient profiles before and after inverse probability of treatment weighting by ACEI use, http://links.lww.com/JNA/A379, Supplementary Table 4: Summary of patient profile before and after inverse probability of treatment weighting by ARB use, http://links.lww.com/JNA/A380).

DISCUSSION

In contrast to our expectations, we did not find a statistically significant or clinically meaningful association between chronic ACEI or ARB exposure and postoperative stroke. With a total of 139 strokes, we had 17% power to detect a 20% reduction in an event. Thus, while our power was low, there was also no evidence that ACEI/ARB treatment reduces stroke risk. Even if benefit is identified at some point, the number needed-to-treat would certainly be prohibitive. We specifically evaluated the effects of chronic inhibition (at least 6 mo) of renin-angiotensin-aldosterone on postoperative stroke, irrespective of whether a preoperative dose was withheld on the day of surgery. Importantly, the neuroprotective effects of ACEIs and ARBs on carotid intimal medial thickness appear to depend on duration of exposure.[14,18–21,28,29] Our results are consistent with a systematic review that reported no meaningful associations between preoperative ACEI/ARB use and perioperative complications such as stroke, myocardial infarction and unplanned intensive care unit admission.[30] However, a meta-analysis reported fewer cerebrovascular events among 459 cardiac surgery patients who continued ACEIs/ARBs (relative risk 0.48, 95% CI: 0.18-1.28;

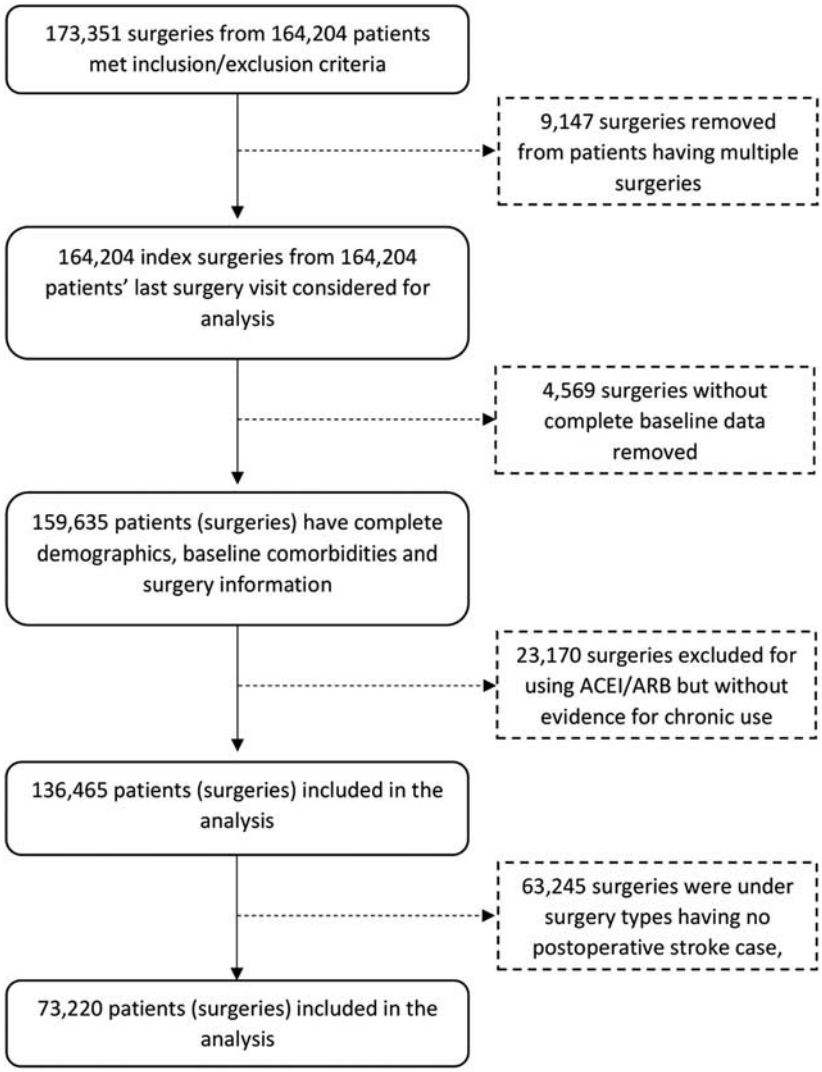

FIGURE 1. Study flow chart. ACEIs indicates angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

TABLE 1. Incidence of Postoperative Stroke in ACEI/ARB Users and Controls

	Incidence of Postoperative Stroke			
Treatment	**Treatment**	**Control**	**Odds Ratio (CI)**	***P***
Primary				
ACEI/ARB	0.26% (27/10,449)	0.18% (112/62,771)	1.15 (95% CI: 0.91-1.44)	0.24
Secondary				
ACEI	0.24% (17/6848)	0.18% (112/62,771)	0.88 (97.5% CI: 0.65-1.19)	0.33
ARB	0.23% (7/3101)	0.18% (112/62,771)	1.05 (97.5% CI: 0.75-1.48)	0.75

ACEI indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval.

$P = 0.14$).[31] Importantly, this outcome was a secondary analysis and there were only 17 strokes, making the results fragile. The clinical benefit and reproducibility of neuroprotective effects of ACEIs/ARBs were also found to differ when compared with other antihypertensives in nonsurgical settings. In a recent Cochrane review of 4 trials, for example, the authors report an increased incidence of stroke in patients who took renin-angiotensin-aldosterone inhibitors (relative risk 1.19, 95% CI: 1.08-1.32; absolute risk increase 0.7%) when compared with thiazides and calcium channel blockers, but a decreased incidence of stroke when compared with beta blocker use (relative risk 0.75, 95% CI: 0.63-0.88; absolute risk reduction 1.7%).[32] An important limitation in this review was the unbalanced proportion of other antihypertensive drugs and the uncertainty that the study drugs were balanced between treatment groups.

There are 2 major mechanisms by which ACEIs and ARBs might reduce stroke risk. The first is the vascular-protective effect on proliferation of endothelial smooth muscle. Inhibition of the renin-angiotensin-aldosterone system reduces vascular smooth muscle proliferation and prevents plaque destabilization. This property of ACEIs/ARBs has been evaluated in clinical trials and a meta-analysis in nonsurgical settings.[33] Four major trials showed a benefit of renin-angiotensin-aldosterone pathways inhibition on stroke, and that the benefit appears to be distinct from blood pressure reduction, possibly involving neurohormonal effects such as remodeling.[18–21,28,29] Additional data demonstrate that renin-angiotensin-aldosterone blockade and statin therapy improve endothelial cell function and suppress oxidative stress.[34] The second mechanism is reduction of angiotensin II related vasoconstrictor effects on cerebral vessels via down-regulation of angiotensin receptors (angiotensin type 1 receptors) within brain parenchyma.[7,35] Circulating angiotensin II has contractile effects on cerebral arteries, which may worsen cerebral perfusion and lead to ischemia.[8] Furthermore, animal data suggest that angiotensin II increases oxidative stress.[35] Notably, the effects of these mechanisms are independent of blood pressure control.

Many anesthesia practitioners withhold ACEIs and ARBs on the day of surgery in an effort to avoid intraoperative hypotension. A recent meta-analysis confirmed that withholding ACEIs/ARBs is associated with less frequent intraoperative hypotension.[36] In addition, in that analysis the incidence of cerebrovascular events did not differ significantly in those who continued or withheld ACEIs/ARBs on the day of surgery (odds ratio 0.95, 95% CI: 0.44-2.06), however, the CI was wide indicating inconclusive evidence of any benefit or harm.[36] A few studies directly investigated the association of intraoperative hypotension and postoperative strokes. No association was found between mild intraoperative hypotension and stroke in general surgical patients.[37] In a systemic review of 4 studies, nonsignificant, small associations were noted between intraoperative hypotension and ischemic strokes.[38] In contrast, an increased risk of ischemic strokes were found with increased severity and duration of intraoperative hypotension.[39,40] Notably, the strength of associations and effect estimates were significantly different among these studies with respect to the chosen intraoperative hypotension model, perhaps due to limited statistical power. Nevertheless, the neuroprotective effects of ACEIs and ARBs observed in nonsurgical settings are presumably due to neurohormonal involvement, such as remodeling.[19–21,29]

A limitation of our analysis is that ACEIs and ARBs were presumably prescribed primarily to treat hypertension. It therefore remains possible that doses and exposure duration were insufficient for vascular-protective effects. We relied on electronic medical pharmacy records to identify chronic ACEI/ARB exposure and excluded 23,170 patients who had preoperative drug interruptions. We were also unable to account for various types of ACEIs and ARBs in our analysis. We selected a pre-exposure cutoff of 6 months based on sonographic finding of carotid intimal medial thickness reduction,[15,25] but it is possible that intimal thinning correlates poorly with clinical outcomes. The imbalances in our treatment and control groups on variables (such as age, ASA status and surgery types) persisted even after propensity score weighting. Although we adjusted for most of the possible confounding variables, unmeasured confounding cannot be excluded. We intentionally restricted our analysis to clinically apparent strokes, which is clinically meaningful. Less severe complications, such as transient ischemic attacks, covert strokes, postoperative cognitive dysfunction, seizures, and transient paralysis, were not included in our analysis. Lastly, registry studies evaluating rare events, such as perioperative strokes, are challenging due to their extremely low incidence and sometimes poor coding in electronic health records.

In summary, our analysis does not support the hypothesis that chronic use of ACEIs and ARBs reduces postoperative stroke in patients having non-neurological, noncardiac, and noncarotid surgery. There is considerable evidence that ACEIs and ARBs are effective antihypertensive agents and independently reduce serious cardiovascular complications and overall mortality. But, within the limits of low power, preventing perioperative strokes does not appear to be among their benefits.

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