ANESTHESIOLOGY

Association between Use of Angiotensin-converting Enzyme Inhibitors or Angiotensin Receptor Blockers and Postoperative Delirium

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium is common in surgical intensive care patients
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers improve cognitive function

What This Article Tells Us That Is New

- In a single-center cohort study of adults admitted to a surgical intensive care unit, preoperative use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was not associated with reduced postoperative delirium
- However, rapidly starting angiotensin-converting enzyme inhibitors or angiotensin receptor blockers postoperatively was associated with reduced delirium

ABSTRACT

Background: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers improve cognitive function. The authors therefore tested the primary hypothesis that preoperative use of angiotensin inhibitors is associated with less delirium in critical care patients. *Post hoc*, the association between postoperative use of angiotensin system inhibitors and delirium was assessed.

Methods: The authors conducted a single-site cohort study of adults admitted to Cleveland Clinic critical care units after noncardiac procedures between 2013 and 2018 who had at least one Confusion Assessment Method delirium assessment. Patients with preexisting dementia, Alzheimer's disease or other cognitive decline, and patients who had neurosurgical procedures were excluded. For the primary analysis, the confounder-adjusted association between preoperative angiotensin inhibitor use and the incidence of postoperative delirium was assessed. *Post hoc*, the confounder-adjusted association between postoperative angiotensin system inhibitor use and the incidence of delirium was assessed.

Results: The incidence of delirium was 39% (551 of 1,396) among patients who were treated preoperatively with angiotensin system inhibitors and 39% (1,344 of 3,468) in patients who were not. The adjusted odds ratio of experiencing delirium during critical care was 0.98 (95% CI, 0.86 to 1.10; $P = 0.700$) for preoperative use of angiotensin system inhibitors *versus* control. Delirium was observed in 23% (100 of 440) of patients who used angiotensin system inhibitors postoperatively before intensive care discharge, and in 41% (1,795 of 4,424) of patients who did not (unadjusted $P < 0.001$). The confounder-adjusted odds ratio for experiencing delirium in patients who used angiotensin system inhibitors postoperatively was 0.55 (95% CI, 0.43 to 0.72; $P < 0.001$).

Conclusions: Preoperative use of angiotensin system inhibitors is not associated with reduced postoperative delirium. In contrast, treatment during intensive care was associated with lower odds of delirium. Randomized trials of postoperative angiotensin-converting enzymes inhibitors and angiotensin receptor blockers seem justified.

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Delirium is a major perioperative complication, especially in the elderly.[1] It is characterized by an acute and fluctuating disturbance in cognition and attention. The pathophysiology of delirium remains poorly understood, but inflammation, neurotransmitter imbalance, and metabolic derangement are possible mechanisms. Delirium is associated with cognitive impairment and is associated with increased postoperative morbidity and mortality.[2–4]

Two studies that included a total of 241 patients demonstrated that delirium is associated with dementia (odds ratio, 12.5; 95% CI, 1.9 to 84).[5] Furthermore, delirium is associated with a severe punctuated decline in cognitive function that can persist several months after cardiac surgery before cognitive function recovers over a period of 6 to 12 months.[6] Delirium is especially common in patients who have preoperative biomarkers for Alzheimer's disease including amyloid β and tau, and in those who develop cognitive impairment later in life.[7,8] Collectively, these findings suggest that postoperative delirium may be an initial sign of dementia.[1]

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Angiotensin-converting enzyme inhibitors such as captopril or perindopril that are capable of crossing the blood–brain barrier enhance memory function in patients with mild to moderate Alzheimer's disease.[9] Data from the Systolic Hypertension in Europe trial with enalapril, and the Perindopril Protection Against Stroke Study trial, both showed that use of angiotensin enzyme inhibitors reduces dementia and cognitive decline.[9–12] Similarly, candesartan, an angiotensin II receptor 1 antagonist, diminishes the incidence of nonfatal stroke.[13,14] These trials suggest that use of angiotensin receptor blockers improves cognitive function independent of their effects on blood pressure.[9,11,12,15,16] However, there is no existing study that evaluates the relationship between the use of angiotensin enzyme inhibitor or angiotensin receptor blocker and postoperative delirium. We therefore tested the primary hypothesis that preoperative use of angiotensin enzyme inhibitor and/or angiotensin receptor blocker is associated with a lower incidence of delirium in postsurgical intensive care unit (ICU) patients. In a *post hoc* analysis, we evaluated the association between postoperative use of angiotensin enzyme inhibitor and/or angiotensin receptor blocker and delirium.

Materials and Methods

Patient Selection

In this single-site retrospective cohort analysis, we considered patients who had at least one Confusion Assessment Method—ICU assessment while in the surgical ICU of the Cleveland Clinic main campus after noncardiac procedures between January 2013 and June 2018. Patients with preexisting dementia, Alzheimer's disease, or other cognitive decline, and patients undergoing neurosurgical procedures were excluded from the study. With Institutional Review Board approval from the Cleveland Clinic (Cleveland, Ohio) and waived consent, data were extracted from our electronic health record system and the Perioperative Health Documentation System registry of the Anesthesia Institute (Cleveland, Ohio). The analysis plan was developed *a priori* and approved by the Institutional Review Board.

Patients who were treated with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers preoperatively were compared to patients who used neither. Angiotensin-converting enzyme inhibitors included benazepril, captopril, fosinopril, quinapril, ramipril, enalapril, and lisinopril. Angiotensin receptor blockers included irbesartan, losartan, telmisartan, olmesartan, and valsartan. We considered patients to be angiotensin-converting inhibitor and angiotensin receptor blocker users when the medications were taken within 1 month before the date of surgery. Normally, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are held the morning of surgery. Postoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blockers use was determined as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers use before the first positive Confusion Assessment Method—ICU test for those with postoperative delirium and as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers use before the last surgical ICU discharge and within 7 days postsurgery for the group without postoperative delirium. Postoperative benzodiazepines use was similarly defined as any of midazolam, lorazepam, or diazepam.

Delirium was assessed using the Confusion Assessment Method. Normally, critical care patients at the Cleveland Clinic are evaluated at 12-h intervals by trained nurses. We considered patients to have experienced postoperative delirium when their Confusion Assessment Method—ICU tests were positive at any assessment during their surgical ICU stay within 12 h to 7 days after surgery. The Confusion Assessment Method—ICU evaluates four features: (1) acute onset and fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered consciousness. A positive Confusion Assessment Method test was defined by the presence of features 1 and 2, and either 3 or 4.[17–20]

Statistical Methods

For the primary analysis, the association between preoperative use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and the incidence of postoperative delirium was assessed through a conditional logistic regression model, with baseline variables in table 1 adjusted for through propensity score matching. Specifically, the probability (*i.e.*, the propensity score) of being treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers preoperatively (*vs.* neither) was estimated in a logistic regression model using demographic and baseline variables, emergency surgery, surgery type, and surgery length (as a proxy of surgery complexity) as predictors. American Society of Anesthesiologists status was treated as a continuous variable in the model. Patients treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were then matched with controls at a 1:2 treatment–control ratio with a matching calliper of within 0.2 SDs of the logit of the propensity score. Treatment and control patients were required to have the same surgery type, and surgery within a year of each other. A conditional logistic regression model was then used for comparing the matched pairs on the outcome, adjusting for imbalanced confounding variables (absolute standardized difference greater than 0.10) after matching.

The association between postoperative use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and delirium was similarly assessed. All of the variables in table 1 (details in tables A1 and A2), as well as preoperative use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and intraoperative use of midazolam, were considered as confounding factors and used in the propensity score model. To reduce potential bias arising from the fact that early delirium patients are less likely to have had the postoperative exposure, each exposed patient was matched to controls who had not yet had

Table 1. Patient Characteristics after Propensity Score Matching on Preoperative and Postoperative Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use

	Preoperative Use			Postoperative Use†		
Variable	Angiotensin- converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 1,151)	Control (N = 1,627)	Absolute Standardized Difference*	Angiotensin- converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 321)	Control (N = 577)	Absolute Standardized Difference*
Demographic and baseline variables						
Age, yr	66 ± 12	65 ± 12	0.057	67 ± 12	67 ± 12	0.038
Sex, No. (%)			0.028			0.031
Female	476 (45)	651 (46)		137 (43)	255 (44)	
Male	697 (55)	976 (54)		184 (57)	322 (56)	
Race, No. (%)			0.019			0.020
Caucasian	952 (83)	1334 (82)		272 (85)	493 (85)	
Non-Caucasian	199 (17)	293 (18)		49 (15)	84 (15)	
Body mass index, kg/m^2	32 ± 9	31± 9	**0.115**	32 ± 9	32 ± 9	0.058
Comorbidity, No. (%)						
History of stroke or transient ischemic attack	189 (16)	261 (16)	0.010	59 (18)	104 (18)	0.009
History of coronary artery disease	272 (24)	338 (21)	0.069	81 (25)	148 (26)	0.010
History of congestive heart failure	0.2 (0.4)	0.2 (0.4)	0.046	0.2 (0.4)	0.2 (0.4)	0.030
Vascular disease	138 (12)	228 (14)	0.060	30 (9)	58 (10)	0.024
Diabetes	488 (42)	593 (36)	**0.122**	131 (41)	242 (42)	0.023
Hypertension	1096 (95)	1519 (93)	0.080	314 (98)	567 (98)	0.032
Psychiatric disease	65 (6)	86 (5)	0.025	21 (7)	29 (5)	0.065
Preoperative angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use	—	—	—	267 (83)	454 (79)	**0.115**
Preoperative creatinine level, mg/dl	1.5 ± 1.8	1.6 ± 1.6	0.040	1.2 ± 1.3	1.2 ± 0.9	0.047
ASA Physical Status, No. (%)			0.091			0.021
I	0 (0)	1 (0.06)		0 (0)	0 (0)	
II	23 (2)	50 (3)		5 (2)	16 (3)	
III	632 (55)	881 (54)		210 (65)	355 (62)	
IV	481 (42)	682 (42)		106 (33)	210 (36)	
V	15 (1)	13 (1)		5 (2)	1 (0.2)	
Intraoperative variables						
Emergent surgery, No. (%)	209 (18)	296 (18)	0.001	32 (10)	55 (10)	0.015
Type of procedure,‡ No. (%)			—			—
Exploratory laparotomy	105 (9)	192 (12)		9 (3)	18 (3)	
Colorectal resection	99 (9)	128 (8)		26 (8)	51 (9)	
Other organ transplantation	61 (5)	109 (7)		2 (1)	4 (1)	
Other operating room gastrointestinal therapeutic procedures	54 (5)	65 (4)		20 (6)	39 (7)	
Hip replacement, total and partial	52 (5)	68 (4)		18 (6)	31 (5)	
Duration of surgery, h	5.7 [3.7, 8.6]	5.6 [3.6, 8.5]	0.024	5.3 [3.6, 8.2]	6.1 [3.6, 9.5]	0.055
General anesthesia, No. (%)	988 (86)	1,433 (88)	0.066	276 (86)	507 (88)	0.056
Estimated blood loss, l	0.3 [0.1, 0.9]	0.3 [0.1, 0.9]	0.095	0.3 [0.1, 0.6]	0.3 [0.1, 1.1]	0.011
Blood transfusion, No. (%)	492 (43)	712 (44)	0.021	105 (33)	199 (34)	0.038
Hypotension, No. (%)	829 (72)	1,110 (68)	0.083	209 (65)	388 (67)	0.045
Total opioid dose (IV morphine equivalent), mg	25 [15, 44]	25 [15, 40]	0.029	28 [18, 49]	28 [15, 48]	0.074

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was matched with controls using propensity score at a 1:2 treatment–control ratio, with exact match on surgery type and ± 1 yr on year of surgery. Variables were summarized as mean ± SD, No. (%), or median [interquartile range].

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD (values greater than 0.10 are bolded in the table to indicate imbalance). †Postoperative angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use defined as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use before first positive Confusion Assessment Method—Intensive Care Unit assessment for patients who had delirium and before final intensive care unit discharge for those who did not have delirium. ‡Type of surgery was characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. The most frequent five categories are listed due to limited space.

ASA, American Society of Anesthesiologists; IV, intravenous.

delirium at the time when the exposed patient started or resumed angiotensin-converting enzyme inhibitor or used angiotensin receptor blocker.

Two sensitivity analyses were performed for the association between preoperative use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and delirium. In a

preplanned sensitivity analysis, we compared the two groups on in-hospital mortality (instead of delirium) using a conditional logistic regression model in the matched patients. In the other sensitivity analysis, we assessed the association between preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use and the detection of delirium using a logistic regression model, adjusting for all of the potentially confounding factors directly in the model instead of using propensity score matching.

Three sensitivity analysis were performed for the association between postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use and delirium. First, because postoperative use of benzodiazepines (midazolam, lorazepam, or diazepam) is strongly associated with delirium, we included postoperative use of benzodiazepines in the propensity score model when assessing the association between postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use and outcome. Because angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and benzodiazepines could be used concurrently postoperatively, the interaction between angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and benzodiazepines was also tested, at a significance level of 0.10. Second, to correct for potential bias arising from the timing of postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, we constructed a time-to-delirium survival model using all patients and considering the use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker as a time-varying covariate, such that patients were designated as "exposed" for the remaining follow-up period once they started/resumed angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients without delirium were censored at 7 days postoperatively, and baseline variables were adjusted for directly in the model. Finally, to reduce bias induced by early delirium detection, in a third sensitivity analysis we compared the angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and control groups on the incidence of delirium after 24 h, adjusting for baseline variables through propensity score matching.

In secondary analyses, we assessed the association between detection of postoperative delirium and preoperative use of angiotensin-converting enzyme inhibitor only, angiotensin receptor blocker only, or neither, in a logistic regression model while adjusting for the same confounding factors as in the main analysis. An analogous model was constructed for postoperative use of angiotensin-converting enzyme inhibitor only, angiotensin receptor blocker only, or neither.

Two-sided tests were used for all analyses. Based on a *post hoc* power calculation, we had more than 90% power at the 0.05 significance level to detect an odds ratio of 0.80 or smaller for preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use *versus* delirium detection, and an odds ratio of 0.70 or smaller for postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, with 4,989 patients who met the enrolment criteria and a delirium incidence of 38% in the control group. Power calculations were conducted *post hoc* using SAS software version 9.4 (SAS Institute, USA), and R and SAS software version 9.4 (SAS Institute, USA) was used for all statistical analysis.

Results

We identified 4,864 patients who met our inclusion and exclusion criteria, including 1,396 who were given angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the preoperative period and 440 who were given angiotensin-converting enzyme inhibitors or angiotensin receptor blockers postoperatively before delirium or intensive care unit discharge. Confusion Assessment Method—ICU score was assessed a mean ± SD of 3 ± 1 times per day for the first 7 postoperative days in both preoperative angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and control groups, and in both postoperative angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and control groups (fig. 1), and timing of the assessments was similar in each group. Complete baseline data were available for 5,421 patients. Patient characteristics are detailed in table A1; opioid, propofol, and other perioperative medications are summarized in table 2 and detailed in tables A3 and A4. In addition, Blood pressure and heart rate were summarized by 4-h intervals postoperatively, and based on a visual check, hemodynamic data were similar between patients who used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers postoperatively *versus* not (fig. 2).

Delirium was detected in 39% (551 of 1,396) of patients who were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the preoperative period and in 39% (1,344 of 3,468) of patients who were not (unadjusted P value = 0.643). We matched 1,151 patients treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker preoperatively to 1,627 patients who were not. All of the baseline variables were adequately balanced between the treatment and the control groups after matching (absolute standardized difference less than 0.10) except for body mass index and diabetes, which were adjusted for directly in the model.

In the propensity-matched patients, preoperative treatment with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was not associated with postoperative delirium (P = 0.700), with an estimated odds ratio (95% CI) of 0.98 (0.86 to 1.10) for angiotensin-converting enzyme inhibitor or angiotensin receptor blocker compared to control (fig. 3). Consistent results were obtained from the sensitivity analysis where confounders were included directly in the model with outcome, with an estimated odds ratio of 0.91 (95% CI, 0.79 to 1.05; P = 0.202). Mortality was 4% (43 of 1,151) in the matched angiotensin-converting enzyme inhibitor or angiotensin receptor blocker group, and 5% (84 of 1,627) in the matched controls. In-hospital

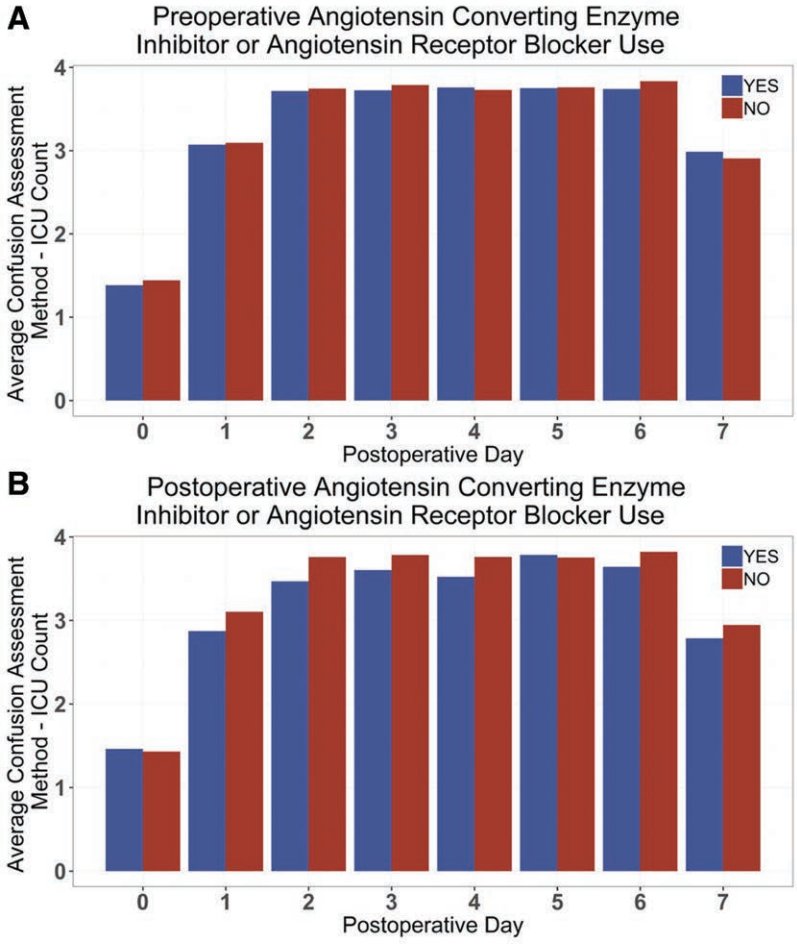

Fig. 1. Number of Confusion Assessment Method assessments during surgical intensive care unit stay by day.

mortality did not differ in patients who did and did not use angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, with an estimated odds ratio of 0.76 (95% CI, 0.51 to 1.12; $P = 0.169$).

Delirium was detected in 23% (100 of 440) of patients who received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers postoperatively before the first incidence of delirium or final ICU discharge (as described in Materials and Methods), compared to 41% (1,795 of 4,424) of patients who did not receive angiotensin-converting enzyme inhibitor or angiotensin receptor blocker before delirium or ICU discharge. After matching 321 patients with postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use to 577 control patients, we observed a confounder-adjusted odds ratio for delirium of 0.55 (95% CI, 0.43 to 0.72; $P < 0.001$) comparing postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker users to control patients. Baseline and intraoperative confounders were balanced after matching, except for preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, which was adjusted for directly in the model. No interaction was detected between preoperative and postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use ($P = 0.55$) and delirium.

In the sensitivity analysis in which postoperative benzodiazepines was included in the propensity score model, we also observed a significant association between postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use and delirium, with an estimated odds ratio of 0.54 (95% CI, 0.40 to 0.71; $P < 0.001$). The groups were well balanced with respect to postoperative benzodiazepines use, making confounding due to this factor very unlikely even though it is associated with delirium. The interaction between postoperative use of benzodiazepines and postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was not significant ($P = 0.359$).

Among patients with delirium, the time to onset of delirium (median [first quartile, third quartile]) was 57 [30, 110] h in those treated with angiotensin-converting enzyme

Table 2. Length of Stay and Perioperative Medication Usage after Propensity Score Matching on Preoperative and Postoperative Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use

	Preoperative Use		Postoperative Use‡	
Variable	**Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 1,151)**	**Control (N = 1,627)**	**Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 326)**	**Control (N = 582)**
Initial ICU length of stay (h)	57 [41, 94]	54 [40, 94]	50 [38, 74]	55 [42, 94]
Hospital length of stay (days)	10 [7, 16]	11 [8, 17]	9 [7, 14]	9 [7, 15]
Intraoperative medication usage				
Midazolam used (%)	717 (62)	959 (59)	203 (62)	361 (62)
Midazolam dose (mg)*	2.0 [1.5, 2.0]	2.0 [1.0, 2.0]	2.0 [1.0, 2.0]	2.0 [1.0, 2.0]
Postoperative benzodiazepines usage before delirium§				
Midazolam/lorazepam/diazepam (%)	123 (11)	198 (12)	42 (13)	83 (14)
Postoperative medication usage				
Midazolam used (%)	75 (7)	116 (7)	15 (5)	40 (7)
Midazolam dose (mg)*	3.0 [2.0, 4.0]	2.0 [1.8, 5.0]	2.0 [1.0, 4.0]	2.0 [2.0, 6.2]
Average daily midazolam dose (mg)*	0.1 [0.1, 0.3]	0.1 [0.1, 0.2]	0.1 [0.0, 0.3]	0.1 [0.1, 0.3]
Lorazepam used (%)	162 (14)	239 (15)	46 (14)	84 (14)
Lorazepam dose (mg)*	2.0 [1.0, 5.0]	2.0 [1.0, 5.5]	1.4 [1.0, 5.2]	2.0 [1.0, 4.0]
Average daily lorazepam dose (mg)*	0.1 [0.1, 0.3]	0.1 [0.1, 0.4]	0.1 [0.1, 0.6]	0.1 [0.1, 0.2]
Diazepam used (%)	94 (8)	159 (10)	32 (10)	66 (11)
Diazepam dose (mg)*	12.5 [5.0, 29.8]	10.0 [5.0, 30.0]	13.8 [5.0, 26.2]	10.0 [5.0, 25.0]
Average daily diazepam dose (mg)+	1.1 [0.4, 2.3]	0.8 [0.3, 2.5]	1.2 [0.4, 2.1]	0.9 [0.4, 2.7]
Morphine equivalents used in initial ICU stay (%)	994 (86)	1434 (88)	272 (83)	501 (86)
Morphine equivalents dose in initial ICU stay (mg)*	74 [28, 169]	75 [30, 180]	61 [23, 140]	68 [24, 175]
Perioperative morphine equivalent dose (mg)†	102 [44, 213]	105 [46, 227]	89 [38, 197]	101 [45, 234]
Postoperative day 1 medications used (%)				
Benzodiazepines	84 (7)	140 (9)	30 (9)	58 (10)
Dexmedetomidine	70 (6)	104 (6)	17 (5)	52 (9)
Propofol	745 (65)	996 (61)	147 (45)	362 (62)
Opioid	1,007 (87)	1,399 (86)	274 (84)	521 (90)
Postoperative day 2 medications used (%)				
Benzodiazepines	81 (7)	115 (7)	22 (7)	42 (7)
Dexmedetomidine	85 (7)	106 (7)	15 (5)	51 (9)
Propofol	194 (17)	269 (17)	18 (6)	92 (16)
Opioid	961 (83)	1,334 (82)	264 (81)	492 (85)
Postoperative day 3 medications used (%)				
Benzodiazepines	67 (6)	111 (7)	22 (7)	41 (7)
Dexmedetomidine	81 (7)	103 (6)	15 (5)	48 (8)
Propofol	139 (12)	207 (13)	29 (9)	69 (12)
Opioid	893 (78)	1,284 (79)	248 (76)	458 (79)

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was matched with controls using propensity score at a 1:2 treatment–control ratio, with exact match on surgery type and ± 1 yr on year of surgery. Summary statistics presented as median [first quartile, third quartile] or N (%) as appropriate.

*Dose among patients who received some amount of medication. †Intraoperative + initial ICU stay dose. ‡Postoperative angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use defined as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use before first positive Confusion Assessment Method—ICU assessment for patients who had delirium and before final ICU discharge for those who did not have delirium. §Postoperative midazolam/lorazepam/diazepam use defined as midazolam/lorazepam/diazepam use before first positive Confusion Assessment Method—ICU assessment for patients who had delirium and before final ICU discharge for those who did not have delirium.

ICU, intensive care unit.

inhibitor or angiotensin receptor blocker postoperatively, and 19 [14, 46] h in those who were not. The hazard ratio of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker *versus* control was an estimated 0.73 (95% CI, 0.60 to 0.89; $P = 0.002$) when we took into account the time at which angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were started/resumed postoperatively in a time-varying covariate analysis.

Considering all patients, the incidence of delirium after 24 h was 14% (93 of 653) in patients using angiotensin-converting enzyme inhibitor or angiotensin receptor blocker postoperatively and 33% (1,408 of 4,211) in control patients. After matching to control for confounding, the odds ratio comparing 423 postoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker users matched with 745 controls was an estimated 0.46 (95% CI, 0.35 to 0.59; $P < 0.001$), a result consistent with the main analysis.

In the secondary analysis, we compared patients who preoperatively used angiotensin-converting enzyme inhibitor

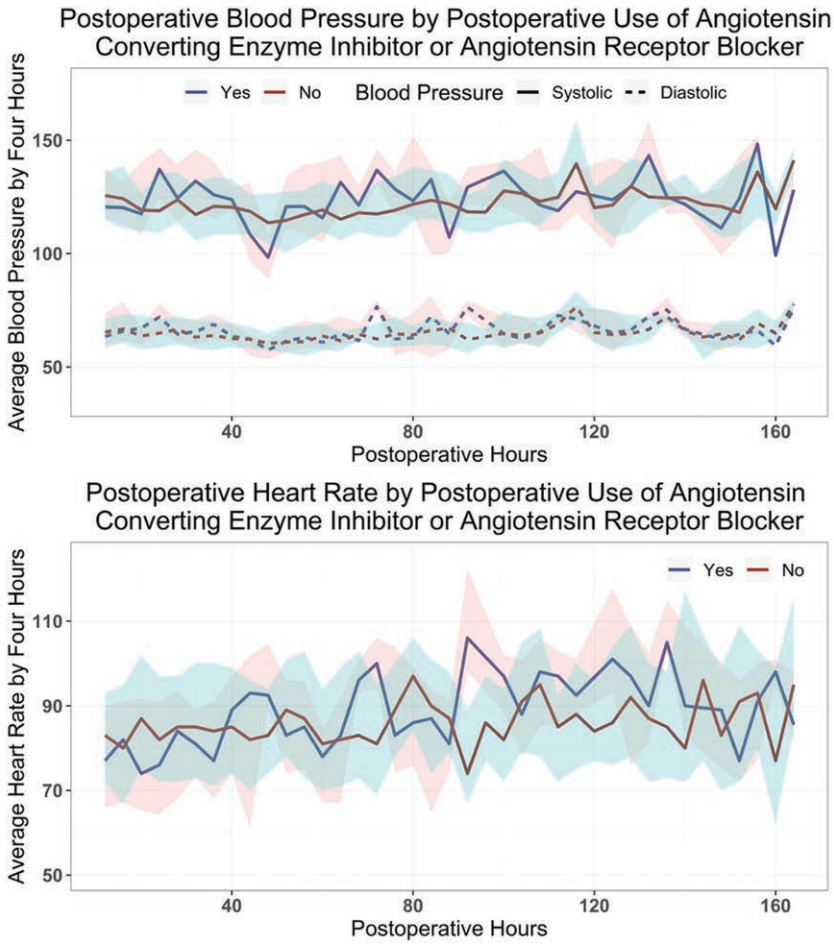

Fig. 2. Postoperative hemodynamics. Blood pressure (BP) and heart rate were summarized for patients who were postoperatively treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers *versus* who were not, matched on baseline variables through propensity score. Blood pressure and heart rate were averaged by 4-h intervals staring 12 h postsurgery until discharge from the intensive care unit or incidence of delirium, whichever came first. *Lines* in the graph represent median average hemodynamics, and *shaded areas* represent interquartile range average hemodynamics.

only, angiotensin receptor blocker only, and neither. We did not observe significant differences in the detection of delirium between the three groups after adjusting for the same variables as in the primary analysis above (overall $P = 0.774$). When comparing postoperative use of angiotensin-converting enzyme inhibitor only, angiotensin receptor blocker only, and neither, we found that patients who used angiotensin-converting enzyme inhibitor only or angiotensin receptor blocker only had a significantly lower odds of having delirium compared to patients who used neither ($P < 0.001$). No significant difference was observed between angiotensin-converting enzyme inhibitor only and angiotensin receptor blocker only patients (fig. 2).

Discussion

Preoperative use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers was not independently associated with detection of postoperative delirium in surgical ICU patients. The most likely reason is simply that most formulations are relatively short-acting. Since our routine is to hold angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the morning of surgery, it is unlikely that these drugs were biologically active even by the evening of surgery, much less over days of critical care.

In contrast to the lack of preoperative association between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and delirium, patients who used angiotensin-converting enzyme inhibitors and angiotensin receptor blockers postoperatively had about half the odds of developing delirium, after adjusting for baseline and intraoperative confounding factors. Furthermore, patients in the postoperative control group not only had more delirium, but had a much earlier delirium onset at 19 [14, 48] h *versus* to 64 [35, 112] h. Our results therefore suggest that

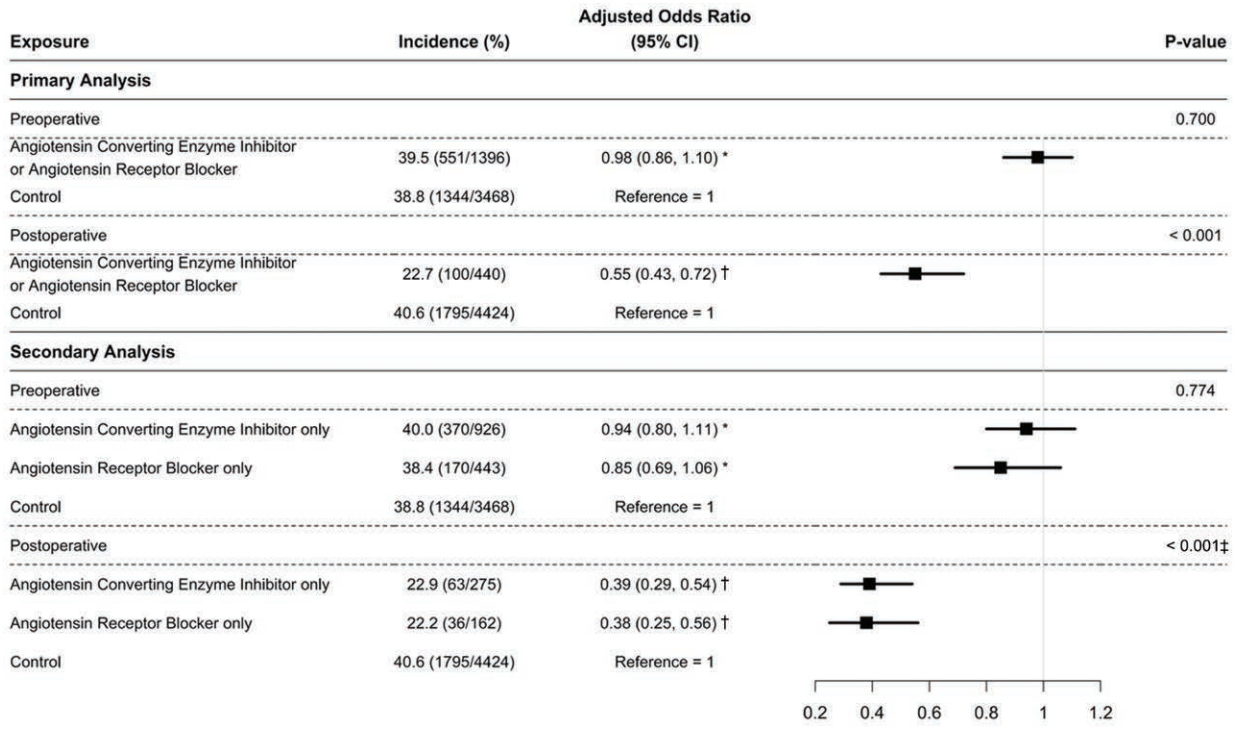

Fig. 3. Association between exposure group and delirium. *Adjusted for demographic and baseline variables, emergency surgery, surgery type, surgery length, and year of surgery. †Adjusted for demographic and baseline variables, intraoperative variables, intraoperative use of benzodiazepines, emergency surgery, surgery type, surgery length, and year of surgery. ‡*P* value < 0.001 for each of the two comparisons *versus* control.

angiotensin-converting enzyme inhibitors and angiotensin receptor blockers must be present in biologically relevant concentrations to prevent delirium.

The observed suggestion of a protective effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers against delirium may be explained by new discoveries in the classic renin angiotensin system. In particular, angiotensin II has neurotoxic effects mediated by its actions on angiotensin type 1 receptor. In contrast, there are neuroprotective effects of alternate renin angiotensin system that are mediated by angiotensin (1-7), angiotensin III, and angiotensin IV.[21] Angiotensin-converting enzyme inhibitors increase brain substance *P*, which is normally degraded by angiotensin-converting enzyme, which in turn enhances the activity of neprilysin,[22] a recognized amyloid β degrading enzyme.[23] Additionally, angiotensin-converting enzyme inhibitors enhance production of angiotensin (1-7), which has neuroprotective, antiinflammatory, and cerebral vasodilation effects.[21] The injurious effects of angiotensin II on the brain are mainly mediated by its action on angiotensin receptor 1A subtype and include hypertension, inflammation, increased oxidative stress, blood–brain barrier disruption, and neurotoxicity.

Angiotensin II also induces nitric oxide production, neurite outgrowth, and brain development through angiotensin receptor 2 activation.[21,24] Use of angiotensin receptor 1 blockers enhances the stimulation of neuroprotective angiotensin receptor 2 by angiotensin II. In addition to their blocking actions on angiotensin receptor 1, angiotensin receptor blockers also stimulate the peroxisome proliferator–activated receptor-γ, which is a nuclear receptor. Peroxisome proliferator–activated receptor-γ induces the polarization of the microglia into type M2. Type M2 microglia has antiinflammatory and neuroprotective effects.[25–27]

The beneficial effect of stimulating peroxisome proliferator–activated receptor-γ by candesartan was shown in a subgroup analysis of the Study on Cognition and Prognosis in the Elderly. Use of candesartan was associated with less decline in the Mini Mental State Examination, especially in patients with slightly low cognitive function at baseline (Mini Mental State Examination score 24 to 28).[28,29] Losartan treatment compared with atenolol in elderly hypertensive patients significantly improves cognitive function, in particular immediate and delayed memory cognition domains.[30] Additionally, use of losartan in hypertensive patients improves cognitive function including memory, attention/concentration, comprehension, anxiety/depression, and interpersonal relationships.[31] Available evidence thus suggests that inhibition of classic renin angiotensin system pathway and simultaneous stimulation of alternate

renin angiotensin system pathways by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has neuroprotective and antiinflammatory effects that might explain reduced postoperative delirium.

The standard delirium diagnostic criteria for delirium are specified in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders.[17] However, the most widely used instrument is the Confusion Assessment Method.[19] We used the intensive care version, Confusion Assessment Method—ICU, which was developed to accurately diagnose delirium in intensive care unit patients, who are often nonverbal due to mechanical ventilation.[18] The Confusion Assessment Method—ICU test has a sensitivity of 95% and specificity of 89%.[20] It therefore seems unlikely that our negative preoperative results are consequent to an insensitive measurement tool. Furthermore, the median number of Confusion Assessment Method—ICU assessments was about 10, which should have been quite sufficient to detect clinically important delirium.

We performed a comprehensive confounder-adjusted analysis to assess independent associations between the intraoperative use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and postoperative delirium, with year of surgery and type of surgery well-adjusted through propensity score matching. However, the association between postoperative angiotensin-converting enzyme inhibitors or angiotensin receptor blockers use (exposure) and delirium was subject to immortal time bias[32] because the definition of exposure required that patients had not already developed the outcome (delirium) until after resumption of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. In other words, it would be difficult for patients with early delirium detection to have an exposure in our study design, and patients who never restarted (the controls) had a longer period to develop delirium. To reduce such survival bias we performed the following steps: (1) matched exposed patients to controls who had not yet developed delirium in the main postoperative exposure analysis; (2) conducted a sensitivity analysis using time-varying covariate survival analysis to account for the timing of the exposures; and (3) added another analysis limiting delirium outcomes to after 24 h. While these sensitivity analyses provided results consistent with the main analysis, none completely eliminates the risk of immortal time bias.

The postoperative exposure analyses surely suffer from some unmeasured confounding bias. While the confounder adjustment was comprehensive for preoperative variables, we did not thoroughly adjust for postoperative confounding variables co-occurring with the exposure and outcome. For example, the appendix table 4 showed that some postoperative medications (*e.g.*, propofol) remained imbalanced after matching. Additionally, variations in the duration of action of the drugs added heterogeneity to the inference. For example, captopril has no active metabolite and a half-life of only 1.7 h, whereas ramipril has an active metabolite and a half-life up to 50 h. Among angiotensin receptor blockers, there was similar variation: losartan has the shortest half-life of only 2 h, whereas telmisartan has a half-life of 24 h. Angiotensin receptor blockers also have varying degrees of lipid solubility and therefore a different ability to cross the blood–brain barrier.[27,33]

In summary, preoperative use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was not associated with lower incidence of postoperative delirium in critical care patients—presumably because most drugs were no longer active during the relevant period. In contrast, postoperative use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with about half the incidence of delirium. Given the limitations inherent to our study design, especially overlapping exposure and outcome, our results should be considered exploratory rather than a basis for practice change. However, our results provide strong support for randomized trials to assess whether resumption of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can prevent delirium in critical care patients.

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Competing Interests

The authors declare no competing interests.

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Appendix

Table A1. Patient Characteristics before and after Propensity Score Matching on Preoperative Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use

	Preoperative before Matching			Preoperative after Matching		
Variable	**Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 1,396)**	**Control (N = 3,468)**	**Absolute Standardized Difference***	**Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 1,151)**	**Control (N = 1,627)**	**Absolute Standardized Difference***
Demographic and baseline variables						
Age, yr	66 ± 12`	59 ± 15	**0.514**	66 ± 12	65 ± 12	0.057
Sex, No. (%)			**0.106**			0.028
Female	608 (44)	1,693 (49)		476 (45)	651 (46)	
Male	788 (56)	1,775 (51)		697 (55)	976 (54)	
Race, No. (%)			0.047			0.019
Caucasian	1,151 (82)	2,920 (84)		952 (83)	1334 (82)	
Non-Caucasian	245 (18)	548 (16)		199 (17)	293 (18)	
Body mass index, kg/m^2	32 ± 9	32± 9	**0.333**	32 ± 9	31± 9	**0.115**
Comorbidity, No. (%)						
History of stroke or transient ischemic attack	221 (16)	426 (12)	**0.102**	189 (16)	261 (16)	0.010
History of coronary artery disease	347 (25)	444 (13)	**0.312**	272 (24)	338 (21)	0.069
History of congestive heart failure	0.2 (0.4)	0.1 (0.3)	**0.303**	0.2 (0.4)	0.2 (0.4)	0.046
Vascular disease	167 (12)	363 (10)	0.047	138 (12)	228 (14)	0.060
Diabetes	657 (47)	887 (26)	**0.458**	488 (42)	593 (36)	**0.122**
Hypertension	1,332 (95)	1,859 (54)	**1.093**	1,096 (95)	1,519 (93)	0.080
Psychiatric disease	80 (6)	179 (5)	0.025	65 (6)	86 (5)	0.025
Preoperative creatinine level, mg/dl	1.5 ± 1.7	1.4 ± 1.5	0.042	1.5 ± 1.8	1.6 ± 1.6	0.040
ASA Physical Status, No. (%)			0.087			0.091
I	0 (0)	6 (0.2)		0 (0)	1 (0.06)	
II	26 (2)	212 (6)		23 (2)	50 (3)	
III	779 (56)	1,798 (52)		632 (55)	881 (54)	
IV	574 (41)	1,411 (41)		481 (42)	682 (42)	
V	17 (1)	41 (1)		15 (1)	13 (1)	
Intraoperative variables						
Emergent surgery, No. (%)	231 (17)	738 (21)	**0.121**	209 (18)	296 (18)	0.001
Type of procedure,† No. (%)			—			—
Exploratory laparotomy	108 (8)	424 (12)		105 (9)	192 (12)	
Colorectal resection	108 (8)	231 (7)		99 (9)	128 (8)	
Other organ transplantation	62 (4)	560 (16)		61 (5)	109 (7)	
Other operating room gastrointestinal therapeutic procedures	73 (5)	130 (4)		54 (5)	65 (4)	
Hip replacement, total and partial	53 (4)	109 (3)		52 (5)	68 (4)	
Duration of surgery, h	5.6 [3.7, 8.6]	6.5 [3.9, 9.8]	**0.215**	5.7 [3.7, 8.6]	5.6 [3.6, 8.5]	0.024
General anesthesia, No. (%)	1,207 (86)	3,089 (89)	0.080	988 (86)	1433 (88)	0.066
Estimated blood loss, l	0.3 [0.1, 0.8]	0.4 [0.1, 1.4]	**0.249**	0.3 [0.1, 0.9]	0.3 [0.1, 0.9]	0.095
Blood transfusion, No. (%)	566 (41)	1,691 (49)	**0.166**	492 (43)	712 (44)	0.021
Hypotension, No. (%)	983 (70)	2,541 (73)	0.063	829 (72)	1110 (68)	0.083
Total opioid dose (IV morphine equivalent), mg	25 [15, 43]	30 [18, 50]	0.037	25 [15, 44]	25 [15, 40]	0.029

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was matched with controls using propensity score at a 1:2 treatment–control ratio, with exact match on surgery type and ± 1 yr on year of surgery. Variables were summarized as mean ± SD, N (%), or median [interquartile range].

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD (values greater than 0.10 are bolded in the table to indicate imbalance).
†Type of surgery was characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. The most frequent five categories are listed due to limited space.

ASA, American Society of Anesthesiologists; IV, intravenous.

Table A2. Patient Characteristics before and after Propensity Score Matching on Postoperative Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use

Variable	Postoperative before Matching			Postoperative after Matching		
	Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 440)†	Control (N = 4,424)	Absolute Standardized Difference*	Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 321)†	Control (N = 577)	Absolute Standardized Difference*
Demographic and baseline variables						
Age, yr	67 ± 12	60 ± 15	**0.475**	67 ± 12	67 ± 12	0.038
Sex, No. (%)			**0.152**			0.031
Female	178 (40)	2,123 (48)		137 (43)	255 (44)	
Male	262 (60)	2,301 (52)		184 (57)	322 (56)	
Race, No. (%)			**0.019**			0.020
Caucasian	371 (84)	3,700 (84)		272 (85)	493 (85)	
Non-Caucasian	69 (16)	724 (16)		49 (15)	84 (15)	
Body mass index, kg/m^2	32 ± 9	30 ± 9	**0.174**	32 ± 9	32 ± 9	0.058
Comorbidity, No. (%)						
History of stroke or transient ischemic attack	88 (20)	559 (13)	**0.200**	59 (18)	104 (18)	0.009
History of coronary artery disease	119 (27)	672 (15)	**0.294**	81 (25)	148 (26)	0.010
History of congestive heart failure	0.2 (0.4)	0.1 (0.3)	**0.190**	0.2 (0.4)	0.2 (0.4)	0.030
Vascular disease	40 (9)	490 (11)	0.066	30 (9)	58 (10)	0.024
Diabetes	178 (40)	1,366 (31)	**0.201**	131 (41)	242 (42)	0.023
Hypertension	433 (98)	2,758 (62)	**1.019**	314 (98)	567 (98)	0.032
Psychiatric disease	25 (6)	234 (5)	0.017	21 (7)	29 (5)	0.065
Preoperative angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use	382 (87)	1,014 (23)	**1.675**	267 (83)	454 (79)	**0.115**
Preoperative creatinine level, mg/dl	1.2 ± 1.2	1.5 ± 1.6	**0.192**	1.2 ± 1.3	1.2 ± 0.9	0.047
ASA Physical Status, No. (%)			0.098			0.021
I	0 (0)	6 (0.01)		0 (0)	0 (0)	
II	8 (2)	230 (5)		5 (2)	16 (3)	
III	284 (65)	2,293 (52)		210 (65)	355 (62)	
IV	143 (33)	1,824 (42)		106 (33)	210 (36)	
V	5 (1)	53 (1)		5 (2)	1 (0.2)	
Intraoperative variables						
Emergent surgery, No. (%)	36 (8)	933 (21)	**0.371**	32 (10)	55 (10)	0.015
Type of procedure,‡ No. (%)			—			—
Exploratory laparotomy	9 (2)	523 (12)		9 (3)	18 (3)	
Colorectal resection	26 (6)	313 (7)		26 (8)	51 (9)	
Other organ transplantation	2 (0.5)	620 (14)		2 (1)	4 (1)	
Other operating room gastrointestinal therapeutic procedures	22 (5)	181 (4)		20 (6)	39 (7)	
Hip replacement, total and partial	23 (5)	139 (3)		18 (6)	31 (5)	
Duration of surgery, h	5.4 [3.8, 8.2]	5.8 [3.9, 8.6]	**0.242**	5.3 [3.6, 8.2]	6.1 [3.6, 9.5]	0.055
General anesthesia, No. (%)	363 (82)	3,933 (89)	**0.184**	276 (86)	507 (88)	0.056
Estimated blood loss, l	0.3 [0.1, 0.7]	0.3 [0.1, 0.7]	**0.330**	0.3 [0.1, 0.6]	0.3 [0.1, 1.1]	0.011
Blood transfusion, No. (%)	128 (29)	2,129 (48)	**0.399**	105 (33)	199 (34)	0.038
Hypotension, No. (%)	270 (61)	3,254 (74)	**0.262**	209 (65)	388 (67)	0.045
Total opioid dose (IV morphine equivalent), mg	28 [18, 48]	27 [18, 48]	0.078	28 [18, 49]	28 [15, 48]	0.074

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was matched with controls using propensity score at a 1:2 treatment–control ratio, with exact match on surgery type and ± 1 yr on year of surgery. Variables were summarized as mean ± SD, No. (%), or median [interquartile range].

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD (values greater than 0.10 are bolded in the table to indicate imbalance). †Postoperative angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use defined as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use before first positive Confusion Assessment Method—ICU assessment for patients who had delirium and before final intensive care unit discharge for those who did not have delirium. ‡Type of surgery was characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. The most frequent five categories are listed due to limited space.

ASA, American Society of Anesthesiologists; IV, intravenous.

Table A3. Length of Stay and Perioperative Medication Usage in All Patients and in Matched Preoperative Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Treatment–Controls

	Preoperative All Patients		Preoperative after Matching	
Variable	Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 1,396)	Control (N = 3,468)	Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 1,151)	Control (N = 1,627)
Initial ICU length of stay (h)	58 [41, 94]	54 [40, 92]	57 [41, 94]	54 [40, 94]
Hospital length of stay (days)	10 [7, 16]	11 [8, 17]	10 [7, 16]	11 [8, 17]
Intraoperative medication usage				
Midazolam used (%)	867 (62)	2341 (68)	717 (62)	959 (59)
Midazolam dose (mg)*	2.0 [1.0, 2.0]	2.0 [2.0, 2.0]	2.0 [1.5, 2.0]	2.0 [1.0, 2.0]
Postoperative benzodiazepines usage before delirium‡				
Midazolam/lorazepam/diazepam (%)	155 (11)	451 (13)	123 (11)	198 (12)
Postoperative medication usage				
Midazolam used (%)	92 (7)	248 (7)	75 (7)	116 (7)
Midazolam dose (mg)*	2.5 [2.0, 4.2]	2.0 [2.0, 5.0]	3.0 [2.0, 4.0]	2.0 [1.8, 5.0]
Average daily midazolam dose (mg)*	0.1 [0.1, 0.3]	0.1 [0.1, 0.2]	0.1 [0.1, 0.3]	0.1 [0.1, 0.2]
Lorazepam used (%)	192 (14)	593 (17)	162 (14)	239 (15)
Lorazepam dose (mg)*	2.0 [1.0, 5.0]	2.0 [1.0, 6.0]	2.0 [1.0, 5.0]	2.0 [1.0, 5.5]
Average daily lorazepam dose (mg)*	0.1 [0.0, 0.3]	0.1 [0.1, 0.4]	0.1 [0.1, 0.3]	0.1 [0.1, 0.4]
Diazepam used (%)	109 (8)	358 (10)	94 (8)	159 (10)
Diazepam dose (mg)*	10.0 [5.0, 30.0]	12.2 [5.0, 35.0]	12.5 [5.0, 29.8]	10.0 [5.0, 30.0]
Average daily diazepam dose (mg)*	1.1 [0.4, 2.5]	1.0 [0.3, 3.0]	1.1 [0.4, 2.3]	0.8 [0.3, 2.5]
Morphine equivalents used in initial ICU stay (%)	1195 (86)	3121 (90)	994 (86)	1,434 (88)
Morphine equivalents dose in initial ICU stay (mg)*	70 [26, 170]	90 [35, 213]	74 [28, 169]	75 [30, 180]
Perioperative morphine equivalent dose (mg)†	97 [43, 213]	127 [58, 268]	102 [44, 213]	105 [46, 227]
Postoperative day 1 medications used (%)				
Benzodiazepines	102 (7)	319 (9)	84 (7)	140 (9)
Dexmedetomidine	92 (7)	229 (7)	70 (6)	104 (6)
Propofol	871 (62)	2308 (67)	745 (65)	996 (61)
Opioid	1,223 (88)	3,096 (89)	1,007 (87)	1,399 (86)
Postoperative day 2 medications used (%)				
Benzodiazepines	91 (7)	271 (8)	81 (7)	115 (7)
Dexmedetomidine	104 (7)	243 (7)	85 (7)	106 (7)
Propofol	232 (17)	630 (18)	194 (17)	269 (17)
Opioid	1,148 (82)	2,969 (86)	961 (83)	1,334 (82)
Postoperative day 3 medications used (%)				
Benzodiazepines	83 (6)	271 (8)	67 (6)	111 (7)
Dexmedetomidine	100 (7)	222 (6)	81 (7)	103 (6)
Propofol	174 (12)	437 (13)	139 (12)	207 (13)
Opioid	1,067 (76)	2,817 (81)	893 (78)	1,284 (79)

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was matched with controls using propensity score at a 1:2 treatment–control ratio, with exact match on surgery type and ± 1 year on year of surgery. Summary statistics presented as median [first quartile, third quartile] or No. (%) as appropriate.

*Dose among patients who received medication. †Intraoperative + initial ICU stay dose. ‡Postoperative midazolam/lorazepam/diazepam use defined as midazolam/lorazepam/diazepam use before first positive Confusion Assessment Method—ICU assessment for patients who had delirium and before final ICU discharge for those who did not have delirium.

ICU, intensive care unit.

Table A4. Length of Stay and Perioperative Medication Usage in All Patients and in Matched Postoperative Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Treatment–Controls

	Postoperative All Patients		Postoperative after Matching	
Variable	**Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 440)**	**Control (N = 4,424)**	**Angiotensin-converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (N = 326)**	**Control (N = 582)**
Initial ICU length of stay (h)	52 [39, 83]	56 [40, 93]	50 [38, 74]	55 [42, 94]
Hospital length of stay (days)	9 [7, 14]	11 [8, 17]	9 [7, 14]	9 [7, 15]
Intraoperative medication usage				
Midazolam used (%)	283 (64)	2,925 (66)	203 (62)	361 (62)
Midazolam dose (mg)*	2.0 [1.0, 2.0]	2.0 [2.0, 2.0]	2.0 [1.0, 2.0]	2.0 [1.0, 2.0]
Postoperative benzodiazepines usage before delirium‡				
Midazolam/lorazepam/diazepam (%)	68 (15)	538 (12)	42 (13)	83 (14)
Postoperative medication usage				
Midazolam used (%)	23 (5)	317 (7)	15 (5)	40 (7)
Midazolam dose (mg)*	3.0 [1.5, 4.5]	2.0 [2.0, 5.0]	2.0 [1.0, 4.0]	2.0 [2.0, 6.2]
Average daily midazolam dose (mg)*	0.1 [0.1, 0.3]	0.1 [0.1, 0.2]	0.1 [0.0, 0.3]	0.1 [0.1, 0.3]
Lorazepam used (%)	71 (16)	714 (16)	46 (14)	84 (14)
Lorazepam dose (mg)*	2.0 [1.0, 5.8]	2.0 [1.0, 6.0]	1.4 [1.0, 5.2]	2.0 [1.0, 4.0]
Average daily lorazepam dose (mg)*	0.1 [0.1, 0.6]	0.1 [0.1, 0.4]	0.1 [0.1, 0.6]	0.1 [0.1, 0.2]
Diazepam used (%)	45 (10)	422 (10)	32 (10)	66 (11)
Diazepam dose (mg)*	15.0 [7.5, 35.0]	10.0 [5.0, 35.0]	13.8 [5.0, 26.2]	10.0 [5.0, 25.0]
Average daily diazepam dose (mg)*	1.5 [0.4, 2.5]	0.9 [0.4, 2.8]	1.2 [0.4, 2.1]	0.9 [0.4, 2.7]
Morphine equivalents used in initial ICU stay (%)	357 (81)	3,959 (89)	272 (83)	501 (86)
Morphine equivalents dose in initial ICU stay (mg)*	58 [20, 140]	87 [35, 207]	61 [23, 140]	68 [24, 175]
Perioperative morphine equivalent dose (mg)†	83 [35, 192]	120 [55, 257]	89 [38, 197]	101 [45, 234]
Postoperative day 1 medications used (%)				
Benzodiazepines	47 (11)	374 (8)	30 (9)	58 (10)
Dexmedetomidine	22 (5)	299 (7)	17 (5)	52 (9)
Propofol	181 (41)	2,998 (68)	147 (45)	362 (62)
Opioid	343 (78)	3,976 (90)	274 (84)	521 (90)
Postoperative day 2 medications used (%)				
Benzodiazepines	36 (8)	326 (7)	22 (7)	42 (7)
Dexmedetomidine	24 (5)	323 (7)	15 (5)	51 (9)
Propofol	26 (6)	836 (19)	18 (6)	92 (16)
Opioid	333 (76)	3,784 (86)	264 (81)	492 (85)
Postoperative day 3 medications used (%)				
Benzodiazepines	34 (8)	320 (7)	22 (7)	41 (7)
Dexmedetomidine	21 (5)	301 (7)	15 (5)	48 (8)
Propofol	34 (8)	577 (13)	29 (9)	69 (12)
Opioid	315 (72)	3,569 (81)	248 (76)	458 (79)

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was matched with controls using propensity score at a 1:2 treatment–control ratio, with exact match on surgery type and ± 1 yr on year of surgery. Postoperative angiotensin-converting enzyme inhibitor /angiotensin receptor blocker use defined as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use before first positive Confusion Assessment Method—ICU assessment for patients who had delirium and before final ICU discharge for those who did not have delirium. Summary statistics presented as median [first quartile, third quartile] or No. (%) as appropriate.

*Dose among patients who received medication. †Intraoperative + initial ICU stay dose. ‡Postoperative midazolam/lorazepam/diazepam use defined as midazolam/lorazepam/diazepam use before first positive Confusion Assessment Method—Intensive Care Unit assessment for patients who had delirium and before final ICU discharge for those who did not have delirium.

ICU, intensive care unit.