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Relationship between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prescribing and delirium in the ICU-A secondary analysis

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Abstract

Background: Studies suggest Angiotensin-Converting Enzyme inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) may slow the decline of memory function in individuals with mild to moderate Alzheimer's disease by regulating migroglial activation and oxidative stress within the brain's reticular activating system. Therefore, we evaluated the relationship between delirium prevalence and being prescribed ACEI and ARB in participants admitted to the intensive care units (ICU).

Methods: A secondary analysis of data from two parallel pragmatic randomized controlled trials was performed. ACEI and ARB exposure was defined as being prescribed an ACEI or an ARB within six months prior to the ICU admission. The primary endpoint was the first positive delirium assessment based on Confusion Assessment Method for the ICU (CAM-ICU) for up to thirty days.

Results: A total of 4791 patients admitted to the medical, surgical, and progressive ICU and screened for eligibility for the parent studies between February 2009 and January 2015 from two level 1 trauma and one safety net hospital in a large urban academic health system were included. Delirium rates in the ICU were not significantly different among participants with no exposure to ACEI/ARB (12.6%), or exposure to ACEI (14.4%), ARB (11.8%), or ACEI and ARB in combination (15.4%) in six months prior to the ICU admission. Exposure to ACEI (OR = 0.97[0.77, 1.22]), ARB (OR = 0.70 [0.47, 1.05]), or both (OR = 0.97 [0.33, 2.89]) in six months prior to ICU admission was not significantly associated with odds of delirium during the ICU admission after adjusting for age, gender, race, co-morbidities, and insurance status.

Conclusions: While the impact of ACEI and ARB exposure prior to the ICU admission was not associated with the prevalence of delirium in this study,

further research is needed to fully understand the impact of antihypertensive medications on delirium.

KEYWORDS

ACE inhibitor, angiotensin receptor blocker, critical care, delirium, intensive care

BACKGROUND

Delirium affects approximately seven million hospitalized patients in the United States each year.[1] Delirium is a complex syndrome characterized by an acute change in cognition and disturbance of consciousness best explained using multi-factorial models.[2] Presence of delirium is associated with prolonged hospital and intensive care unit (ICU) length of stay, higher likelihood of mechanical ventilation, long-term cognitive impairment, new nursing home placement, and higher mortality.[2,3] As delirium severity and duration increase, post-discharge cognitive and functional outcomes worsen.[3,4] Delirium pathophysiological models propose a dynamic relationship between pre-existing conditions (e.g., prior cognitive impairment and co-morbidities) and an increased vulnerability for cerebral insults during hospitalization.[2,5] Reductions in cerebral perfusion and disruption of the blood-brain barrier (BBB) that occur with hypo-and hypertension often result in a decline in cognitive function.[2,5–8]

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have been postulated to slow the decline of memory function in individuals with mild to moderate Alzheimer's disease.[9] Both ACEI and ARB exert their effect within the brain by regulating the activity of the reticular activating system (RAS).[10] ACEI block the production of angiotensin II supply by inhibiting inflammatory responses within the RAS.[6] ARB stabilize the BBB and exert neuronal effects within the RAS by downregulating the angiotensin type 1 receptor response in the cerebral endothelial cells. This may be particularly important in preventing delirium, as the RAS modulates microglial activation and oxidative stress which may impact learning and memory.[7] Regulation of modifiable risk factors such as hypertension caused by angiotensin receptor activation may also assist with the prevention and management of delirium. Whether these beneficial effects of ACEI and ARB extend to inpatient settings, especially critical care is not clear at present and has not been explored in detail. While both classes have favorable findings in the setting of hypertension and heart failure, evidence suggests that the cardio-cerebrovascular protective effects of the two types of medicines might be not identical.[11,12]

Key points

- Reductions in cerebral perfusion and disruption of the BBB associated with hypo-and hypertension often result in a decline in cognitive function.
- ACEIs and ARBs stabilize the BBB by inhibiting inflammatory responses that may be important in preventing delirium.
- We found no reduction in delirium prevalence for participants prescribed both an ACEI and ARB 6 months prior to ICU admission, consistent with the previous literature.

Why does this paper matter?

ACEI and ARBs slow the progression of cognitive decline in dementia. Understanding whether these medications assist with reducing the prevalence of delirium may assist with identifying underlying pathophysiological processes and improving therapy.

We only identified one study that evaluated the potential neuroprotective effects of ACEI and ARB in critically ill patients.[13] In this study, researchers examined the effects of ACEI and ARB administration for up to one month prior to hospitalization on the presence or absence of delirium in post-surgical ICU participants administered general anesthesia. They found administration of these medications was associated with a 50% reduction in delirium.[13] However, investigators did not differentiate between the two classes of drugs and did not identify which of these medications participants were prescribed (ACEI only, ARB only, or both ACEI + ARB).

Therefore, our objective was to evaluate the relationship between delirium prevalence and prescriptions for ACEI or ARB in participants admitted to the ICU. We conducted a secondary data analysis to examine the relationships between ACEI, ARB, and ACEI and ARB in combination during the six-month period prior to hospitalization and the development of delirium during

hospitalization in ICU patients. The central hypothesis was that ICU participants who received either an ACEI, ARB, or both medications within the 6 months prior to hospitalization would have a lower prevalence of ICU delirium compared to participants who were not prescribed these medications.

METHODS

Study design

Data for this analysis were obtained from patients screened for eligibility for two parallel, pragmatic randomized controlled trials conducted by the Delirium Working Group at the Indiana University Center for Aging Research within the School of Medicine. The two studies included the "Pharmacological Management of Delirium (PMD)" and the "Deprescribing in the Pharmacologic Management of Delirium (dePMD) trials."[14,15] Indiana University-Purdue University institutional review board approved both the studies. Details of the trials have been published elsewhere.[15,16] As part of the enrollment process for the trial, patients admitted to the ICUs were screened daily for delirium. The presence of a large screening cohort allowed us to examine the relationship between ACEI, ARB, or ACEI plus ARBs and ICU delirium.

Setting

Screened participants were admitted to either the medical, surgical, or progressive stepdown ICU at one of three hospitals in Indianapolis between February 2009 and January 2015. These three hospitals are part of a large 16-hospital urban comprehensive academic health system serving as major referral hospitals for the state of Indiana and affiliated with the Indiana University School of Medicine. Two of these hospitals are quaternary care centers and the third is a safety net hospital. The three hospitals combined have 1516 beds, including 123 medical and surgical ICU beds and 29 progressive/step-down ICU beds averaging more than 300 ICU admissions per month. The health system is uniquely positioned to serve a diverse population including 63% White, 28% African American and 10% Hispanic.

Sample

Inclusion criteria included: (1) admission to the ICU for 24 h or more; (2) age 18 years or older; (3) English speaking. Exclusion criteria were: (1) history of severe mental illness; (2) delirium due to alcohol intoxication; (3) aphasic stroke; (4) pregnant or nursing; (5) or prisoners. In cases where the same participant was admitted more than once, only the first admission was included.

Measures

ACEI and ARB Exposure: We defined exposure to ACEI and ARB as having a prescription/order for an ACEI or ARB in the patient's electronic health record at the following time points: (1) 1-month prior to admission; (2) 3-months prior to admission; and (3) 6 months prior to admission. This method of identifying medication exposure was utilized because medication dosing frequency and quantity of prescriptions (30-day vs. 90-day) were not available for this secondary analysis. Participants with discontinuation orders prior to admission were not counted as being on medication at admission. The primary endpoint was the prevalence of delirium defined as the first positive delirium assessment during hospitalization using the Confusion Assessment Method for the ICU (CAM-ICU).

Screening and outcome measures

The Richmond Agitation Sedation Scale (RASS)[17] is a behavioral assessment designed to evaluate patients for an altered level of consciousness based on a 10-point scale with scores ranging from unarousable to combative.[18] Patients were identified as comatose if their RASS scores were −4 (responsive to physical but not to verbal stimulus) or −5 (unresponsive to verbal and physical stimulus).[17] Consistent with CAM-ICU validation studies, the RASS[17] was used to assess the patients' sedation status and therefore able to complete the CAM-ICU. A cutoff of RASS ≥−3 (i.e., any response to verbal stimulation) was used to identify CAM-ICU-eligible patients.

The CAM-ICU is a validated (k > 0.79) behavioral assessment designed to assess nonverbal and restrained patients for delirium (+/−).[19] This interactive assessment has four components based on the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV).[18] These components include (a) acute onset or fluctuation in mental status within the previous 24 h, (b) inattention, (c) altered level of consciousness (RASS ≠ 0), and (d) disorganized thinking.[19–21] Inattention is determined based on the number of errors that occur when having the patient squeeze the examiner's hand each time the examiner says the letter "A." Disorganized thinking is assessed by asking the patient to answer four yes/no

questions and to complete a 2-step command. A positive delirium assessment includes acute onset or fluctuating mental status (Feature 1) and inattention (Feature 2) plus either an altered level of consciousness (Feature 3) or disorganized thinking (Feature 4).

Trained research assistants performed twice daily RASS assessments and, if >-3 they proceeded to perform the CAM-ICU assessments after patients' ICU admission until the patients became delirious, died, or were discharged from the ICU. Patients were considered delirious if they had a positive CAM-ICU result, achieved by showing signs of acute change in mental status or fluctuating course, displaying features of inattention, and either disorganized thinking or altered level of consciousness.[19]

Regenstrief Medical Record System (RMRS): The computerized Regenstrief Medical Record System (RMRS) is the primary instrument for processing data and monitoring patient and physician activity for the hospital.[22] The RMRS is a modular system, composed of Registration and Scheduling, Laboratory, Pharmacy, and Database modules. It maintains other databases including vital signs, laboratory and diagnostic tests, discharge summaries, and patient charges. Data in the RMRS are extracted from the participating hospitals electronic medical records.

Other data collection: Baseline demographic factors including age, race, sex, tobacco use, co-morbid conditions (hyperlipidemia, hypertension, heart failure (HF), coronary vascular disease, coronary artery disease, peripheral vascular disease, diabetes, myocardial infarction, obesity, depression, and atrial fibrillation) insurance type (Medicare, Medicaid, Advantage) and medication prescribing data for ACEI, ARBs, and other antihypertensives, such as beta blockers or calcium channel blockers, were extracted from the patient's EMR as part of the parent studies. A list of ACEI, ARBs, and other anti-hypertensives prescribed to these patients can be found in Supplemental Table 1.

METHODS

Statistical analysis

Chi-square tests were used to assess differences in the prevalence of in-hospital delirium based on clinical and demographic factors including age, race, sex, clinical condition, insurance type, being prescribed an ACEI alone, ARB alone, both drugs, neither drug, nor prescribed other antihypertensive medications. We did not exclude patients with delirium on admission. Logistic regression was used to assess the relationship between delirium and ACEI and ARB prescriptions while controlling for

differences in clinical and demographic data. A sensitivity analysis was performed including participants with hypertension and heart failure. Results were similar across pre-ICU time periods (1 month, 3 months and, 6 months), therefore, we decided to provide 6 months results in the main manuscript and 1 and 3 months are included in the Supplemental Tables. All analyses were performed using SAS v9.4.

RESULTS

Study population

We included 4791 participants in the study after application of inclusion/exclusion criteria from February 2009 to January 2015. The mean age of the participants was 60.7 years (SD16.1) with 39% African Americans and 47% females. 70% of participants had no exposure to ACEI or ARB in the prior 6 months, 23% received ACEI alone, 6% ARB alone, and 0.5% had exposure to both ACEI and ARB. Most prevalent diagnoses in the cohort included hypertension (69%), hyperlipidemia (50%), depression (43%), and diabetes mellitus (41%). Table 1 provides the overall characteristics of the study cohort and as a function of exposure to ACEI, ARB, or both.

Utilization of ACEI, ARB, or both increased with increasing age. African Americans tended to have a higher exposure to ARB (55.2%) or both ACEI and ARB (46.2%). Prescriptions for the medications were also associated with higher diagnoses of hypertension, hyperlipidemia, and diabetes mellitus. Patients on ACEI, ARB, or both also had higher exposure to other anti-hypertensive medications (Table 1).

### Rates of delirium, length of stay, and mortality outcomes

Participant delirium prevalence was 13%. Supplemental Table 2 provides the univariate relationship between patient characteristics and development of ICU delirium. Age, diagnoses of heart failure, diabetes mellitus, and depression, and Medicaid insurance status were significantly associated with ICU delirium. The rates of delirium were not significantly different among participants with no exposure to ACEI/ARB (423/12.6%), or exposure to ACEI (160/14.4%), ARB (34/11.8%), or ACEI and ARB in combination (4/15.4%). Median (IQR) hospital length of stay (no ACEI/ARB (8 [5, 14]), ACEI (7 [4, 12]), ARB(7 [5, 12]), ACEI plus ARB (7 [4, 11])) was significantly higher in the no ACEI/ARB group but in-hospital mortality (no ACEI/ARB (3.1%), ACEI (3.3%), ARB (2.8%),

TABLE 1 Comparison of demographic and clinical conditions with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) prescription during prior 6 months.

	Overall (*n* = 4791)	No ACEI, ARB (*n* = 3364)	ACEI Only (*n* = 1113)	ARB Only (*n* = 288)	ACEI & ARB (*n* = 26)	*p*-value
Age, *n* (%)						<0.001
18–49	1368 (28.6)	1188 (35.3)	156 (14.0)	20 (6.9)	4 (15.4)	
50–59	1055 (22.0)	774 (23.0)	230 (20.7)	45 (15.6)	6 (23.1)	
60–69	1320 (27.6)	820 (24.4)	392 (35.2)	98 (34.0)	10 (38.5)	
70+	1048 (21.9)	582 (17.3)	335 (30.1)	125 (43.4)	6 (23.1)	
Race, *n* (%)						<0.001
African-American	1852 (38.7)	1199 (35.6)	482 (43.3)	159 (55.2)	12 (46.2)	
Other	236 (4.9)	183 (5.4)	47 (4.2)	6 (2.1)	0 (0.0)	
White	2703 (56.4)	1982 (58.9)	584 (52.5)	123 (42.7)	14 (53.8)	
Gender						
Female, *n* (%)	2250 (47.0)	1467 (43.6)	578 (51.9)	192 (66.7)	13 (50.0)	<0.001
Clinical conditions, *n* (%)						
Hypertension	3308 (69.0)	1881 (55.9)	1113 (100.0)	288 (100.0)	26 (100.0)	<0.001
Hyperlipidemia	2408 (50.3)	1245 (37.0)	904 (81.2)	237 (82.3)	22 (84.6)	<0.001
HF	884 (18.4)	422 (12.5)	355 (31.9)	100 (34.7)	7 (26.9)	<0.001
CVD	161 (3.4)	85 (2.5)	64 (5.8)	11 (3.8)	1 (3.8)	<0.001
CAD	1008 (21.0)	492 (14.6)	409 (36.8)	102 (35.4)	5 (19.2)	<0.001
PVD	284 (5.9)	158 (4.7)	103 (9.3)	22 (7.6)	1 (3.8)	<0.001
Diabetes mellitus	1968 (41.1)	1031 (306)	716 (64.3)	204 (70.8)	17 (65.4)	<0.001
MI	500 (10.4)	248 (7.4)	208 (18.7)	41 (14.3)	3 (11.5)	<0.001
Obesity	526 (11.0)	306 (9.1)	161 (14.5)	56 (19.4)	3 (11.5)	<0.001
Tobacco use	1399 (29.2)	964 (28.7)	361 (32.4)	70 (24.3)	4 (15.4)	0.008
Depression	2083 (43.5)	1244 (37.0)	642 (57.7)	178 (61.8)	19 (73.1)	<0.001
Atrial fibrillation	398 (8.3)	205 (6.1)	146 (13.1)	45 (15.6)	2 (7.7)	<0.001
Insurance, *n* (%)						
Medicaid	1927 (40.2)	1227 (36.5)	547 (49.2)	139 (48.3)	14 (53.8)	<0.001
Advantage	1499 (31.3)	890 (26.5)	471 (42.3)	125 (43.4)	13 (50.0)	<0.001
Medicare	2106 (44.0)	1208 (35.9)	680 (61.1)	203 (70.5)	15 (57.7)	<0.001
Other antihypertensive prior 6 months, *n* (%)						
Alpha blockers	84 (1.8)	43 (1.3)	27 (2.4)	11 (3.8)	3 (11.5)	<0.001
Alpha-adrenergic agonists	133 (2.8)	51 (1.5)	59 (5.3)	17 (5.0)	6 (23.1)	<0.001
Beta blockers	1283 (26.8)	469 (13.9)	623 (56.0)	174 (60.4)	17 (65.4)	<0.001
Calcium channel blockers	923 (19.3)	385 (11.4)	402 (36.1)	120 (41.7)	16 (61.5)	<0.001
Diuretics	467 (9.8)	195 (5.8)	179 (16.1)	87 (30.2)	6 (23.1)	<0.001
Vasodilators	255 (5.3)	98 (2.9)	105 (9.4)	49 (17.0)	3 (11.5)	<0.001
Nitrates	148 (3.1)	42 (1.2)	81 (7.3)	23 (8.0)	2 (7.7)	<0.001

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; PVD, peripheral vascular disease.
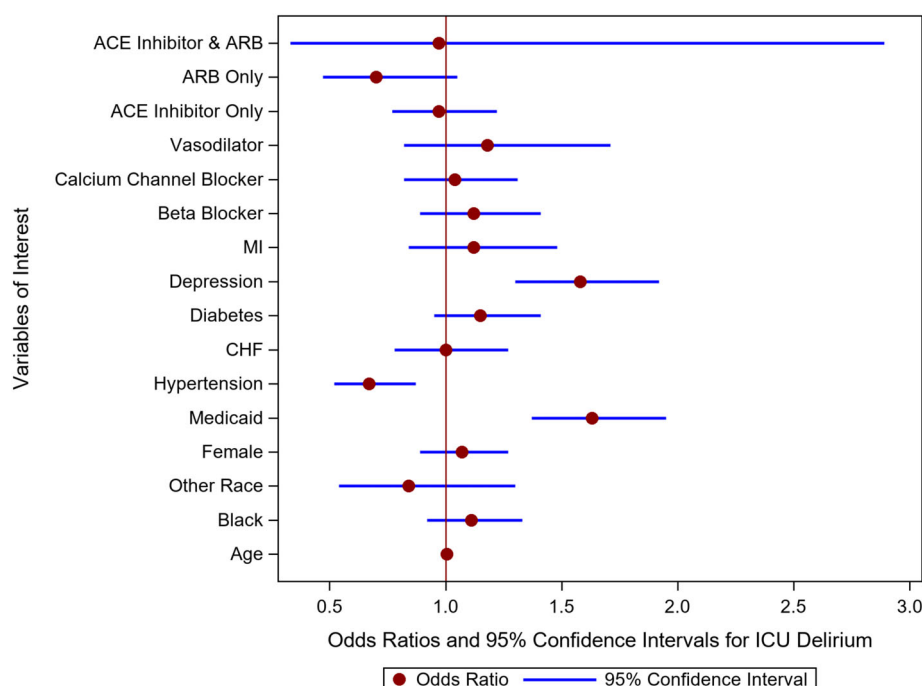
FIGURE 1 Logistic regression analysis with adjusted odds for developing delirium among ICU patients prescribed an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) 6 months prior to hospital admission.

ACEI plus ARB (0.0%)) was not significantly different among groups.

insurance status and diagnosis of hypertension and depression were associated with ICU delirium.

Relationship between ACEI & ARB prior to admission & delirium prevalence

Supplemental Table 3 shows the distribution of exposure to ACEI or ARB at 1, 3, and 6 prior to ICU admission. At six months, ACEI were prescribed in 23.2%, ARB in 6.0%, and both in 0.5%. In a logistic regression analysis (Figure 1, Supplemental Table 4), exposure to ACEI (OR = 0.97[0.77, 1.22]), ARB (OR = 0.70 [0.47, 1.05]), or both (OR = 0.97 [0.33, 2.89]) six months prior to ICU admission was not significantly associated with odds of ICU delirium after adjusting for age, and co-morbidities (hypertension and depression), and insurance status. A diagnosis of depression (OR = [1.58 (1.30, 1.92)]) and Medicaid insurance status (OR = [1.63 (1.37, 1.95)]) were found to be significantly associated with increased odds of ICU delirium. A diagnosis of hypertension was associated with decreased odds of delirium (OR = [0.67 (0.52, 0.87)]) (Figure 1, Supplemental Table 4). A sensitivity analysis restricted to participants with hypertension or heart failure showed similar results with no association with ACEI or ARB exposure on development of ICU delirium (Supplemental Table 5).

Supplemental Table 6 provides logistic regression results based on exposure to ACEI or ARB 1 and 3 months prior to ICU admission. At both time points, similar to the six months results, only Medicaid

DISCUSSION

We found no reduction in prevalence of ICU delirium for participants prescribed an ACEI, ARB, or both ACEI and ARB 6 months prior to ICU admission. Even with chronic exposure to ACEI or ARB, the postulated neuroprotective mechanisms of this class of medications are not getting translated into prevention of ICU delirium. Another factor could be likely due to most formulations of ACEI and ARB being relatively short acting and because it is often routine practice to hold anti-hypertensive medications at the time of ICU admission, the likelihood of ACEI, and ARB being biologically active over days of critical illness is limited. While delirium assessments conducted by a member of the research team rather than clinicians have shown higher sensitivity and specificity our results did not differ from the prior study conducted by Farag, et al.[23-26] Although ACEI and ARB can improve cognitive function and reduce depression and anxiety, we found that participants prescribed an ACEI or ARB who developed delirium were more likely to have a diagnosis of depression. Other medications participants were prescribed or de-prescribed prior to or at the time of ICU admission such as other antihypertensive medications may have moderated the protective effects of ACEI and/or ARB.[27]

A lack of difference in the prevalence of delirium for participants prescribed an ACEI or ARB 6 months prior to admission compared to those who were not may be the

result of severity of illness preventing administration of anti-hypertensive medications. It may also be the result of greater BBB permeability due to critical illness, resulting in higher exposure to multidimensional molecular cascades including excitotoxicity, immune response imbalances, oxidative stress, and apoptotic-like processes with resultant excessive micro-glial activation overwhelming the protective effects of ACEI or ARB. Lack of an identified benefit in reducing the preva-lence of delirium from ACEI or ARB prior to hospitalization may also be the result of poor adherence to treatment regi-mens or that these drugs were biologically inactive after the first 24 h of participant's ICU stay. For those prescribed ACEI alone prior to hospitalization, discontinuation in the outpa-tient setting may have been secondary to side effects, particu-larly cough.[12] When administered together, ACEI frequently render non-steroidal anti-inflammatory medications ineffec-tive, potentially being another cause for either lack of identi-fied benefit or discontinuation.[12]

Strengths/Limitations

Strengths of our work include the inclusion of a diverse population and twice-daily delirium assessments conducted by trained research staff. Limitations include generalizabil-ity to all patients admitted to an ICU due to recruitment of participants from three academic medical centers in a sin-gle city. Use of data extracted from electronic medical record systems is limited to the accuracy and completeness of the documentation. Evaluations of prior to hospitaliza-tion medication exposure are limited to what was pre-scribed. It is not known what doses were ordered, whether prescriptions were filled or whether participants took these medications as prescribed. Similarly, we were not able to evaluate the exact timing of medication dispensing during hospitalization in relationship to delirium assessment.

CONCLUSIONS

There is a paucity of research evaluating the neuroprotec-tive effects of ACEI and ARB in reducing delirium preva-lance and severity. While the impact of ACEI and ARB exposure prior to the ICU admission was not associated with the prevalence of delirium in this study, further research is needed to fully understand the impact of anti-hypertensive medications on ICU delirium.

AUTHOR CONTRIBUTIONS
Malissa Mulkey drafted the manuscript; Anthony Perkins and Sujuan Gao conducted the statistical analyses. All authors reviewed, revised, and edited the manuscript prior to submission.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplementary Table 1. List of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and other antihypertensive medications.

Supplemental Table 2. Comparison of ICU delirium status by demographic and clinical conditions ($n = 4791$).

Supplemental Table 3. Distribution of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) use by time frame.

Supplemental Table 4. Odds ratios for developing delirium among participants exposed to angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or ACEI/ARB in six months prior to ICU admission.

Supplemental Table 5. Logistic regression results showing odds of delirium development restricting analysis to those with hypertension or congestive heart failure.

Supplemental Table 6. Logistic regression results using prior 1 and 3 months as the exposure time.