JAMA Internal Medicine | Original Investigation

Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With Outcomes After Acute Kidney Injury

Sandeep Brar, MD; Feng Ye, MSc; Matthew T. James, MD, PhD; Brenda Hemmelgarn, MD, PhD; Scott Klarenbach, MD, MSc; Neesh Pannu, MD, SM; for the Interdisciplinary Chronic Disease Collaboration

IMPORTANCE Patients with acute kidney injury (AKI) are at an increased long-term risk of death. Effective strategies that improve long-term outcomes in patients with AKI are unknown.

OBJECTIVE To evaluate whether the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) after hospital discharge is associated with better outcomes in patients with AKI.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from the Alberta Kidney Disease Network population database to evaluate 46 253 adults 18 years or older with an episode of AKI during a hospitalization between July 1, 2008, and March 31, 2015, in Alberta, Canada. All patients who survived to hospital discharge were followed up for a minimum of 2 years.

EXPOSURES Use of an ACEI or ARB within 6 months after hospital discharge.

MAIN OUTCOMES AND MEASURES The primary outcome was mortality; secondary outcomes included hospitalization for a renal cause, end-stage renal disease (ESRD), and a composite outcome of ESRD or sustained doubling of serum creatinine concentration. An AKI was defined as a 50% increase between prehospital and peak in-hospital serum creatinine concentrations. Propensity scores were used to construct a matched-pairs cohort of patients who did and did not have a prescription for an ACEI or ARB within 6 months after hospital discharge.

RESULTS The study evaluated 46 253 adults (mean [SD] age, 68.6 [16.4] years; 24 436 [52.8%] male). Within 6 months of discharge, 22 193 (48.0%) of the participants were prescribed an ACEI or ARB. After adjustment for comorbidities, ACEI or ARB use before admission, demographics, baseline kidney function, other factors related to index hospitalization, and prior health care services, ACEI or ARB use was associated with lower mortality in patients with AKI after 2 years (adjusted hazard ratio, 0.85; 95% CI, 0.81-0.89). However, patients who received an ACEI or ARB had a higher risk of hospitalization for a renal cause (adjusted hazard ratio, 1.28; 95% CI, 1.12-1.46). No association was found between ACEI or ARB use and progression to ESRD.

CONCLUSIONS AND RELEVANCE Among patients with AKI, ACEI or ARB therapy appeared to be associated with lower mortality but a higher risk of hospitalization for a renal cause. These results suggest a potential benefit of ACEI or ARB use after AKI, but cautious monitoring for renal-specific complications may be warranted.

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Author Affiliations: Department of Nephrology, University of Toronto, Toronto, Ontario, Canada (Brar); Department of Medicine, University of Alberta, Edmonton, Alberta, Canada (Ye, Klarenbach, Pannu); Department of Medicine, Division of Nephrology, University of Calgary, Calgary, Alberta, Canada (James, Hemmelgarn); Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada (James, Hemmelgarn); Institute of Health Economics, Edmonton, Alberta, Canada (Klarenbach).

Group Information: The Interdisciplinary Chronic Disease Collaboration members are listed at the end of this article.

Corresponding Author: Neesh Pannu, MD, SM, Department of Medicine, University of Alberta, 11-107 CSB, 8440-112 St, Edmonton, Alberta T6G 2G3, Canada (npannu@ualberta.ca).

JAMA Intern Med. 2018;178(12):1681-1690. doi:10.1001/jamainternmed.2018.4749
Published online October 27, 2018.

Acute kidney injury (AKI) is a common complication in hospitalized patients and has been consistently associated with increased long-term risk of death, de novo or worsening chronic kidney disease (CKD), and end-stage renal disease (ESRD).[1-11] Patients discharged after an episode of AKI have a 40% increased risk of death in the 2 years after hospitalization[12] compared with patients who do not develop AKI. Increased risk of mortality in these patients may be driven by higher rates of hypertension[13] and cardiovascular events[14] after AKI. There are currently no known effective therapies for AKI. Although recent data suggest that nephrologist follow-up was associated with a 24% reduction in risk of death after hospitalization in patients with severe AKI requiring dialysis,[15] little is known about the specific processes of care that modify outcomes after episodes of AKI. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are effective for reducing cardiovascular events and mortality in patients with CKD.[16,17] We sought to evaluate whether the use of an ACEI or ARB was associated with better outcomes after hospitalization in patients with AKI.

Key Points

Question Is angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use associated with better outcomes after hospitalization in patients with acute kidney injury?

Findings In this cohort study of 46 253 adults with an episode of acute kidney injury during hospitalization, postdischarge angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use was associated with lower mortality. There was a higher risk of hospitalization for renal causes.

Meaning Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use may improve postdischarge outcomes in patients with acute kidney injury, but cautious monitoring for renal-specific complications may be warranted.

Methods

Study Population and Data Sources

We used the Alberta Kidney Disease Network population-based database, which has been described in detail elsewhere.[18] The study cohort, which has been previously described, comprised adults 18 years or older residing in Alberta who were admitted to the hospital between July 1, 2008, and March 31, 2013, and had an episode of AKI during hospitalization.[19] To be eligible for inclusion, patients had to have at least 1 outpatient serum creatinine measurement within 180 days before hospitalization to establish baseline kidney function and 1 or more measurements during the hospitalization to establish AKI. If participants had more than 1 hospitalization during this period, only the first was considered (index hospitalization). Participants who died or whose condition progressed to ESRD (estimated glomerular filtration rate [eGFR]<15 mL/min/1.73 m^2, long-term dialysis, prior kidney transplant) before or during the index hospitalization were excluded. All patients were followed up from the discharge date of their index hospitalization until March 31, 2015, with a minimum follow-up of 2 years. The study was reviewed and approved by the Health Research Ethics Board at the University of Alberta and the Conjoint Health Research Ethics Board at the University of Calgary, which determined that patient consent was not required. The details of the data (how they were linked and deidentified) are summarized in the article by Hemmelgarn et al.[18]

Assessment of Baseline Kidney Function

The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate the eGFR.[20] Baseline kidney function was defined as the mean outpatient serum creatinine concentration in the 180 days before the index hospitalization.

Identification of AKI

An AKI event was identified by changes between baseline (prehospital) and peak in-hospital serum creatinine concentration. An AKI was defined as an increase in serum creatinine concentration of 50% or greater during hospitalization or of 0.3 mg/dL (to convert to micromoles per liter, multiply by 88.4) within 48 hours and/or a need for dialysis during the index hospitalization. Severity of the AKI was determined using the consensus criteria for AKI staging from the Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines.[21] Need for short-term dialysis for AKI was determined using a validated approach based on diagnosis and procedural administrative codes.[22]

Assessment of Medication Use After Discharge

Prescription drug information was obtained from the Pharmaceutical Information Network database. Community pharmacies in Alberta, Canada, are mandated to contribute drug-dispensing data to the Pharmaceutical Information Network database, and approximately 96% of drugs dispensed from community pharmacies are available in this system.[23] For the primary analysis, ACEI or ARB users were defined as patients who received at least 1 prescription within 6 months after discharge. For the secondary analysis, we classified ACEI or ARB exposure into the following groups: no use (no prescription in the 6 months before or 6 months after the index hospitalization), new use (at least 1 prescription within 6 months after discharge from the index hospitalization, with no prescriptions in the 6 months before admission), prior use (at least 1 prescription in the 6 months before admission), and continued use. Patients were classified in the continuing use group if they had at least 1 prescription in the 6 months before admission and at least 1 prescription within 6 months after discharge.

Assessment of Comorbid Conditions

Relevant demographic characteristics, preexisting comorbid conditions (defined using validated algorithms),[19,24] hospitalizations and outpatient physician visits (general practitioner and specialist visits), details of the index hospitalization (including primary admission diagnosis), and intensive care unit stay were obtained using hospitalization data, claims files, and ambulatory care classification system files. We obtained primary *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes and used these to classify primary admission diagnoses using a previously published approach.[24] Resource intensity weight, similar to diagnostic related group weight, was used to categorize acuity and

severity of illness.[25,26] Cholesterol level was defined as the mean outpatient total cholesterol concentration in the 1 year before the index hospitalization. The cholesterol levels were classified into 5 risk categories according to the Framingham Coronary Heart Disease Risk Score.[27] Patients who did not have a cholesterol measurement during this period were classified as an unknown group.

Outcomes

The primary outcome was all-cause mortality; secondary outcomes included hospitalization for a renal cause, ESRD, and a composite outcome of ESRD or sustained doubling of serum creatinine concentration. All-cause mortality was identified using provincial vital statistics. Hospitalization for a renal cause was defined as any hospitalization after the index hospitalization discharge date until March 31, 2015, with a most responsible diagnosis code of acute renal failure, congestive heart failure, hypervolemia, hyperkalemia, or malignant hypertension (eTable 1 in the Supplement).[22,28] If multiple hospitalizations occurred, only the first one was included. Transfers among hospitals were excluded from the hospitalization for a renal cause outcome. End-stage renal disease was defined as a sustained eGFR less than 15 mL/min/1.73 m^2, which was at least 2 consecutive eGFR measurements of less than 15 mL/min/1.73 m^2 until the end of the study follow-up period. Sustained doubling of the serum creatinine concentration was defined as a 2-fold increase from the baseline outpatient serum creatinine concentration (determined within 180 days before the index hospitalization) until the end of the study follow-up period provided that all subsequent outpatient serum creatinine concentrations during the follow-up period remained at least twice as high compared with baseline.

Statistical Analysis

Continuous variables were described using mean (SD) or median (interquartile range [IQR]) as appropriate. Categorical variables were described as proportions. Baseline differences between ACEI or ARB users and nonusers were addressed using a propensity score approach. Differences between groups were also compared using χ^2 tests for categorical variables and *t* tests for all continuous variables. Statistical significance was defined as $P < .05$.

A multivariable logistic regression model that included age, sex, neighborhood income quintile, aboriginal race, location of residency, health care use preceding the index hospitalization, Canadian Institute for Health Information resource intensity weight, intensive care unit admission during the index hospitalization, primary diagnostic code for hospitalization, procedures associated with AKI (cardiac catheterization, cardiac and abdominal aortic surgery), comorbid conditions, baseline kidney function (based on eGFR), cholesterol concentration (**Table 1**), and statin, ACEI, ARB, and β-blocker use in the 6 months before admission and after discharge was used to estimate the probability of being treated with an ACEI or ARB. We used 1-to-1 matching on the logit of the propensity score without replacement and a caliper width of 0.2 of the SD of the logit of the propensity score.[29] We assessed the balance in baseline covariates before and after matching using the standardized mean difference, for which an absolute value of standardized mean difference of 10% or less indicated a high degree of similarity of the distribution of both groups.[30]

Multivariable Cox proportional hazards regression models were used to estimate the association between use of ACEI or ARB after index hospitalization and all-cause mortality, hospitalization for a renal cause, ESRD, and ESRD or sustained doubling of serum creatinine concentration. Use of an ACEI or ARB was treated as a time-varying covariate. In these time-varying models, a person who was prescribed an ACEI or ARB would contribute person-time to the no ACEI or ARB use exposure group before the first ACEI or ARB was prescribed and contribute person-time to the ACEI or ARB use group after the first ACEI or ARB was prescribed. The adjusted factors included all the covariates used to estimate propensity score to minimize confounding. For the outcomes with low event rates, the adjusted models only included age and sex. Patients were censored if they moved out of the province or reached the end of the study date (March 31, 2015) for all outcomes. For the secondary outcomes, cause-specific Cox proportional hazards regression models were used in which patients were censored on the day they died. The proportional hazards assumption was evaluated and satisfied by examining plots of the log-negative log, within-group survivorship functions vs log time.

Analyses were repeated after further categorizing ACEI or ARB users into the following groups: no previous use, new use after discharge, prior use (stopping use of a prehospital admission prescription), and continued use (continuing use of a previous prescription within 6 months after discharge). No use was the control group. Given that there are a number of potential indications for ACEI or ARB use, subgroup analyses were performed in patients stratified by those with and without proteinuria, baseline eGFR of 60 mL/min/1.73 m^2 or greater vs less than 60 mL/min/1.73 m^2, and the presence or absence of comorbidities, including diabetes, hypertension, chronic heart failure, or cardiovascular disease (myocardial infarction or stroke), to test statistical interactions and to determine whether similar associations were present for ACEI or ARB use across other stratifications.

We performed a sensitivity analysis that compared outcomes in those patients who started taking an ACEI or ARB within 90 days of discharge vs after 90 days (3-6 months after discharge) to determine whether patients had worse outcomes when use of these medications was started earlier after an episode of AKI. Patients who used an ACEI or ARB within 90 days of discharge were matched to patients who used an ACEI or ARB after 90 days after discharge. To achieve balanced distribution of the pretreatment covariates, 1-to-1 matching was used as described above.

Results

Patient Characteristics

Between July 1, 2008, and March 31, 2013, a total of 59 951 patients 18 years or older who resided in Alberta, Canada, were hospitalized with an episode of AKI (eFigure 1 in the Supplement). The study cohort included 46 253 patients (mean [SD] age, 68.6 [16.4] years; 24 436 [52.8%] male; 39 738 [85.9%]

Table 1. Baseline Characteristics of ACEI or ARB Users and Nonusers[a]

Characteristic	All Patients (N = 46 253)	ACEI or ARB users (n = 22 193)[b]	Nonusers (n = 24 060)	*P* Value	Standardized Mean Difference, %
Age, mean (SD), y	68.6 (16.4)	71.8 (13.1)	65.6 (18.4)	1.00×10^{-36}	38.9
Male	24 436 (52.8)	11 892 (53.6)	12 544 (52.1)	1.83×10^{-3}	2.9
Aboriginal race	1774 (3.8)	773 (3.5)	1001 (4.2)	.10	3.5
Income quintile					
Lowest (level 1)	11 002 (23.8)	5306 (23.9)	5696 (23.7)	.55	0.6
Middle (level 3)	9060 (19.6)	4412 (19.9)	4648 (19.3)	.13	1.4
Highest (level 5)	7371 (15.9)	3507 (15.8)	3864 (16.1)	.45	0.7
Urban location	39 738 (85.9)	18920 (85.3)	20818 (86.5)	8.94×10^{-5}	3.6
Health care access 3 y before hospital admission, mean (median) [IQR]					
No. of hospitalizations	1.4 (1) [0-2]	1.3 (1) [0-2]	1.4 (1) [0-2]	1.22×10^{-11}	6.3
No. of general practitioner visits	24.8 (20) [10-33]	26.9 (22) [12-36]	22.9 (18) [9-31]	1.58×10^{-78}	17.5
No. of nephrologist visits	0.6 (0) [0-0]	0.7 (0) [0-0]	0.6 (0) [0-0]	2.92×10^{-5}	3.9
No. of cardiologist visits	1.6 (0) [0-1]	2.1 (0) [0-2]	1.1 (0) [0-1]	2.96×10^{-138}	23.2
No. of internist visits	4.7 (2) [0-5]	4.8 (2) [0-6]	4.7 (1) [0-5]	.45	0.7
No. of emergency visits	5.1 (3) [1-6]	5 (3) [1-6]	5.1 (3) [1-6]	.14	1.4
CIHI resource intensity weight, mean (SD)	2.9 (5.4)	2.5 (4.3)	3.2 (6.3)	1.20×10^{-36}	11.9
Intensive care unit during hospitalization	8496 (18.4)	4619 (20.8)	3877 (16.1)	7.40×10^{-39}	12.1
Primary diagnostic code for hospitalization					
Cardiovascular	7848 (17.0)	5196 (23.4)	2652 (11.0)	1.54×10^{-275}	33.3
Respiratory	4241 (9.2)	2123 (9.6)	2118 (8.8)	4.50×10^{-03}	2.6
Gastrointestinal	4782 (10.3)	1966 (8.9)	2816 (11.7)	1.00×10^{-23}	9.4
Infectious disease	2211 (4.8)	966 (4.4)	1245 (5.2)	.01	3.9
Cancer	4066 (8.8)	1349 (6.1)	2717 (11.3)	4.02×10^{-87}	18.6
Orthopedics	2063 (4.5)	1247 (5.6)	816 (3.4)	4.46×10^{-31}	10.8
Hematologic	2477 (5.4)	1213 (5.5)	1264 (5.3)	.31	0.9
Genitourinary	5218 (11.3)	2304 (10.4)	2914 (12.1)	4.24×10^{-9}	5.5
Injury or poisoning	2406 (5.2)	1100 (5.0)	1306 (5.4)	.02	2.1
Other disease	10 941 (23.7)	4729 (21.3)	6212 (25.8)	4.02×10^{-30}	10.6
Procedure or condition during index hospitalization					
Sepsis	2338 (5.1)	874 (3.9)	1464 (6.1)	6.41×10^{-26}	9.9
Cardiac surgery	1173 (2.5)	739 (3.3)	434 (1.8)	1.82×10^{-25}	9.7
Cardiac catheterization	1484 (3.2)	1116 (5.0)	368 (1.5)	5.46×10^{-101}	19.7
Abdominal aortic aneurysm repair	210 (0.5)	127 (0.6)	83 (0.3)	2.81×10^{-4}	3.4
Pneumonia	4935 (10.7)	2293 (10.3)	2642 (11.0)	.02	2.1
Liver failure	360 (0.8)	71 (0.3)	289 (1.2)	4.54×10^{-27}	10.2
Acute myocardial infraction	4068 (8.8)	2746 (12.4)	1322 (5.5)	4.13×10^{-150}	24.3
Noncardiac surgery	8220 (17.8)	3384 (15.2)	4836 (20.1)	2.43×10^{-42}	12.7
Comorbid disease					
Diabetes	17 657 (38.2)	10 832 (48.8)	6825 (28.4)	1.00×10^{-36}	42.9
Hypertension	35 104 (75.9)	20 585 (92.8)	14 519 (60.3)	1.00×10^{-36}	82.8
Myocardial infarction	5275 (11.4)	3355 (15.1)	1920 (8.0)	1.35×10^{-128}	22.5
Chronic heart failure	13 499 (29.2)	9264 (41.7)	4235 (17.6)	4.70×10^{-261}	32.4
Stroke or TIA	9690 (20.9)	5355 (24.1)	4335 (18.0)	1.41×10^{-58}	15.0
Cancer	6613 (14.3)	2545 (11.5)	4068 (16.9)	1.35×10^{-62}	15.6
Liver disease	1169 (2.5)	244 (1.1)	925 (3.8)	8.82×10^{-79}	17.7
Peripheral vascular disease	3053 (6.6)	1796 (8.1)	1257 (5.2)	2.26×10^{-35}	11.5

(continued)

Table 1. Baseline Characteristics of ACEI or ARB Users and Nonusers[a] (continued)

Characteristic	All Patients (N = 46 253)	ACEI or ARB users (n = 22 193)[b]	Nonusers (n = 24 060)	*P* Value	Standardized Mean Difference, %
Kidney function					
Baseline eGFR in mL/min/1.73 m^2, mean (SD)	67.8 (27.3)	61.9 (23.7)	73.2 (29.3)	1.00×10^{-36}	42.5
Prior CKD	23 407 (50.6)	13 001 (58.6)	10 406 (43.3)	4.54×10^{-238}	31.0
Prior CKD defined by eGFR	14114 (30.5)	7813 (35.2)	6301 (26.2)	2.95×10^{-98}	19.6
Prior CKD defined by proteinuria	4074 (8.8)	2107 (9.5)	1967 (8.2)	5.77×10^{-7}	4.6
Prior CKD defined by eGFR and proteinuria	5219 (11.3)	3081 (13.9)	2138 (8.9)	1.41×10^{-64}	15.8
AKI stages					
Stage 1	35 221 (76.1)	17 541 (79.0)	17 680 (73.5)	1.43×10^{-44}	13.1
Stage 2	6781 (14.7)	3004 (13.5)	3777 (15.7)	5.08×10^{-11}	6.1
Stage 3 (no dialysis)	3268 (7.1)	1261 (5.7)	2007 (8.3)	7.00×10^{-29}	10.4
Dialysis	983 (2.1)	387 (1.7)	596 (2.5)	4.67×10^{-8}	5.1
Baseline total cholesterol, mg/dL					
≤159	13 114 (28.4)	7584 (34.2)	5530 (23.0)	9.73×10^{-157}	25.0
160-199	8434 (18.2)	4371 (19.7)	4063 (16.9)	5.50×10^{-15}	7.3
200-239	4588 (9.9)	2220 (10.0)	2368 (9.8)	.56	0.5
240-279	1415 (3.1)	727 (3.3)	688 (2.9)	9.40×10^{-3}	2.4
≥280	563 (1.2)	296 (1.3)	267 (1.1)	1.20×10^{-232}	2.0
Unknown	18 139 (39.2)	6995 (31.5)	11 144 (46.3)	.03	30.7

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CIHI, Canadian Institute for Health Information; CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate; IQR, interquartile range, SCr, serum creatinine; TIA, transient ischemic attack.

SI conversion factors: to convert total cholesterol to millimoles per liter, multiply by 0.0259.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] ACEI or ARB users had at least 1 prescription within 6 months after discharge from the index hospitalization.

living in an urban location) who survived to discharge without developing ESRD before or during the index hospitalization (Table 1). A total of 23 407 (50.6%) of the cohort had prior CKD. The mean number of hospitalizations during the 3 years preceding the index hospitalization was 1.4 (IQR, 0-2), and 7848 (17.0%) of the cohort had a cardiovascular diagnostic code as the diagnosis most responsible for the index hospitalization. Most of the participants had hypertension (35 104 [75.9%]), and a large number had diabetes (17 657 [38.2%]), chronic heart failure (13 499 [29.2%]), and history of stroke or transient ischemic attack (9 690 [20.9%]). Of these patients, 9456 (42.6%) were matched 1:1 to similar patients who had no dispensed ACEI or ARB prescription within 6 months after discharge, resulting in a final study cohort of 18 912 patients. Before propensity score matching, there was moderate imbalance in the distribution of some covariates by ACEI or ARB use. After propensity score matching, balance was achieved across all included covariates (eTable 2 in the Supplement).

Primary Outcomes

A total of 25 211 patients (54.5%) were using an ACEI or ARB within 6 months before their index hospitalization and 22 193 (48.0%), 6 months after discharge. A large portion (17 852 [38.6%]) of the cohort never used an ACEI or ARB, whereas 3190 (6.9%) received a new prescription within 6 months after discharge. A total of 19 003 (41.1%) continued using an ACEI or ARB within 6 months after hospital discharge, and 6208 (13.4%) of previous users did not restart use of an ACEI or ARB after hospital discharge.

In the matched analysis, the adjusted hazard ratio (HR) for mortality associated with ACEI or ARB use after hospital discharge, compared with no ACEI or ARB use, was 0.85 (95% CI, 0.81-0.89) (**Table 2**). Use of an ACEI or ARB after hospitalization, however, was associated with a higher risk of hospitalization for a renal cause (HR, 1.28; 95% CI, 1.12-1.46), mainly acute renal failure, congestive heart failure, and hyperkalemia. No association was found between ACEI or ARB use and progression to ESRD or between ACEI or ARB use and the composite of progression to ESRD or sustained doubling of serum creatinine concentration.

Both new ACEI or ARB use (HR, 0.85; 95% CI, 0.78-0.93) and continued use (HR, 0.77; 95% CI, 0.73-0.80) after hospital discharge were associated with lower mortality compared with no ACEI or ARB use (**Table 3**). However, stopping use of an ACEI or ARB prescribed before hospital admission was associated with increased mortality (HR, 1.23; 95% CI, 1.17-1.30). Higher rates of hospitalization for a renal cause were found in patients who were given a new ACEI or ARB prescription or continued use of a previous ACEI or ARB prescription after hospital discharge compared with no ACEI or ARB use.

Tests for interaction in matched patients showed that use of an ACEI or ARB in participants with an eGFR less than 60

Table 2. Survival, Hospitalization for a Renal Cause, ESRD, and Composite Outcome of ESRD and Sustained Doubling of SCr Concentration Associated With ACEI or ARB Use in Propensity Score–Matched Patients

Outcome and Exposure	No. of Events/ No. of Patients[a]	Hazard Ratio (95% CI)	
		Crude	Adjusted[b]
All-cause mortality			
ACEI or ARB users	3713/9456	0.89 (0.85-0.93)	0.85 (0.81-0.89)
Nonusers	4781/9456	1 [Reference]	1 [Reference]
Hospitalization for a renal cause			
ACEI or ARB users	549/9414	1.31 (1.15-1.49)	1.28 (1.12-1.46)
Nonusers	496/9498	1 [Reference]	1 [Reference]
Acute renal failure			
ACEI or ARB users	407/9427	1.26 (1.09-1.46)	1.25 (1.08-1.46)
Nonusers	383/9485	1 [Reference]	1 [Reference]
Congestive heart failure			
ACEI or ARB users	81/9446	1.65 (1.16-2.36)	1.69 (1.18-2.41)[c]
Nonusers	60/9466	1 [Reference]	1 [Reference]
Hypervolemia			
ACEI or ARB users	13/9455	0.79 (0.37-1.66)	0.79 (0.38-1.67)[c]
Nonusers	17/9457	1 [Reference]	1 [Reference]
Hyperkalemia			
ACEI or ARB users	73/9455	1.57 (1.08-2.29)	1.56 (1.07-2.27)[c]
Nonusers	48/9457	1 [Reference]	1 [Reference]
Hypertension			
ACEI or ARB users	8/9454	1.06 (0.38-2.95)	1.06 (0.38-2.95)[c]
Nonusers	7/9458	1 [Reference]	1 [Reference]
ESRD[d]			
ACEI or ARB users	760/9439	0.94 (0.85-1.04)	0.96 (0.86-1.06)
Nonusers	887/9473	1 [Reference]	1 [Reference]
ESRD and SCr doubling			
ACEI or ARB users	1272/9423	0.96 (0.89-1.04)	0.92 (0.85-1.00)
Nonusers	1460/9489	1 [Reference]	1 [Reference]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; SCr, serum creatinine.

[a] The number of patients in the ACEI or ARB user groups varies for each outcome because the outcomes could have occurred before or after the patients were dispensed an ACEI or ARB.

[b] Adjusted for ACEI or ARB, β-blocker, and statin use within 6 months before admission, statin and β-blocker use within 6 months after discharge, age, sex, income quintile, urban location, health care use 3 years preceding hospital admission, Canadian Institute for Health Information resource intensity weight, intensive care unit stay, primary diagnostic code for hospitalization, procedure or condition during index hospitalization, comorbid disease, baseline kidney function, and total cholesterol risk categories.

[c] Models adjusted for age and sex.

[d] ESRD was defined as a sustained estimated glomerular filtration rate less than 15 mL/min/1.73 m^2.

mL/min/1.73 m^2 (HR, 0.89; 95% CI, 0.84-0.9) compared with those with an eGFR of 60 mL/min/1.73 m^2 or greater (HR, 0.81; 95% CI, 0.75-0.87; P = .03) and patients without hypertension (HR, 1.10; 95% CI, 0.94-1.28) compared with those with hypertension (HR, 0.84; 95% CI, 0.80-0.88; P = .001) had less survival benefit (ACEI) (**Figure** and eFigure 2 in the Supplement). Participants with an eGFR less than 60 mL/min/1.73 m^2 (HR, 1.01; 95% CI, 0.90-1.12) compared with those with an eGFR of 60 mL/min/1.73 m^2 or greater (HR, 0.75; 95% CI, 0.58-0.96; P = .03) more likely had conditions that progressed to ESRD (eFigure 3 in the Supplement). Participants with myocardial infarction or stroke (HR, 1.03; 95% CI, 0.91-1.18) compared with those with no myocardial infarction or stroke (HR, 0.87; 95% CI, 0.79-0.96; P = .04) more likely had conditions that progressed to ESRD or doubling of serum creatinine concentrations (eFigure 4 in the Supplement).

Sensitivity Analysis

When survival was compared in patients who started taking an ACEI or ARB within 90 days after discharge from the index hospitalization vs after 90 days, there was an increased risk of mortality (HR, 1.15; 95% CI, 1.03-1.28) (**Table 4**). No significant differences in hospitalization for a renal cause (HR, 1.28; 95% CI, 0.99-1.65), ESRD (HR, 1.18; 95% CI, 0.96-1.47), and ESRD or sustained doubling of serum creatinine concentration (HR, 1.07; 95% CI, 0.91-1.27) were found.

Discussion

Using a large population-based cohort, we characterized ACEI or ARB use in patients with AKI. A large portion of the cohort (38.6%) was never prescribed an ACEI or ARB, and 13.4% of the cohort did not continue taking an ACEI or ARB after discharge. During a follow-up period of at least 2 years after discharge, patients with AKI dispensed an ACEI or ARB after the index hospitalization (new or continued use) had a lower risk of death compared with those with no ACEI or ARB use. However, ACEI or ARB use was also associated with an increased risk of hospitalization for a renal cause, mainly acute renal failure and hyperkalemia; no difference was found for ESRD.

Recent studies have found that AKI is an independent risk factor for subsequent development of hypertension,[18] stroke,[31] and long-term cardiovascular events.[14,32-35] To date, no studies have examined the consequences of long-term use of ACEI or ARB after an AKI episode. The association between ACEI or ARB use and survival in our study may be secondary to a reduction in cardiovascular events. Multiple previous random-

ized clinical trials have found that ACEI or ARB therapy is associated with a reduction in mortality in patients with cardiovascular disease, including myocardial infarctions and heart failure.[36-41] A large portion of our cohort had known cardiovascular risk factors, including hypertension, diabetes, previous myocardial infarction, and chronic heart failure. In addition, more than half of the cohort had prior CKD, which is another risk factor for cardiovascular disease.

Conservative population-based estimates of AKI incidence in hospitalized adults are in the range of 3000 per 100 000 person-years,[42] and most of these patients will survive to hospital discharge. Recent KDIGO guidelines recommended that patients be followed up 3 months after an AKI episode to assess for CKD[21]; however, information is lacking to guide the care that these patients should receive. On the basis of our results, patients with AKI may benefit from ACEI or ARB therapy after discharge, an intervention that does not require specialized care and could be readily implemented with appropriate monitoring. In our study, only 48.0% of the cohort was dispensed an ACEI or ARB within 6 months of the index hospitalization. We also observed better survival in the subgroup of patients who were given a new ACEI or ARB prescription compared with those who did not receive an ACEI or ARB prescription. These findings suggest that there is an opportunity to improve postdischarge care in patients with AKI.

Our findings also highlight that use of an ACEI or ARB to reduce mortality in patients with AKI may be accompanied by a tradeoff in higher rates of hospitalization for a renal cause. Use of an ACEI or ARB is known to lead to the development of AKI in hospitalized patients with hypotension, those undergoing surgery,[43] or those using a combination of nonsteroidal anti-inflammatory drugs and diuretics.[44] It is also unclear whether ACEI or ARB use should be continued in patients with low kidney function.[45] Patients with AKI using an ACEI or ARB may require close monitoring for potential complications, such as, stopping use of an ACEI or ARB in a patient with an acute illness to prevent additional AKI events or minimizing use of other medications that may cause hyperkalemia. It is possible that the advantage of nephrologist follow-up seen in another study[15] was attributable to increased surveillance of renal complications of ACEI or ARB medications.

A previous study[17] found that ACEI or ARB use slows progression of CKD and reduces risk of ESRD, particularly in those with proteinuria. Our results did not indicate any improvement in the risk of ESRD; however, the low event rate and short follow-up period may have been insufficient to detect an association with this outcome. There is a concern that prescribing an ACEI or ARB too soon after an episode of AKI can lead to deterioration in renal function. We did not see higher rates of ESRD or doubling of serum creatinine concentrations in patients who were given an ACEI or ARB in the first 90 days compared with those who received these medications after the first 90 days. It is possible that slowing the progression of CKD was offset by hemodynamic consequences of ACEI or ARB on eGFR and increased rates of acute renal failure, leading to hospitalizations. However, we found an increased risk of mortality when ACEI or ARB therapy was started within 90 days after

Table 3. Outcomes Associated With No Previous Use, New Use, Prior Use, and Continued Use of an ACEI or ARB

ACEI or ARB Use	No. of Events/ No. of Patients[a]	Adjusted Hazard Ratio (95% CI)[b]
Survival		
New use		
No	1209/2745	1 [Reference]
Yes	980/2745	0.85 (0.78-0.93)
Prior use		
No	3028/5492	1 [Reference]
Yes	3293/5492	1.23 (1.17-1.30)
Continued use		
No	4564/9375	1 [Reference]
Yes	3562/9375	0.77 (0.73-0.80)
Hospitalization for a Renal Cause		
New use		
No	145/2763	1 [Reference]
Yes	147/2727	1.32 (1.03-1.69)
Prior use		
No	253/5492	1 [Reference]
Yes	257/5492	1.13 (0.95-1.35)
Continued use		
No	343/9375	1 [Reference]
Yes	489/9342	1.34 (1.16-1.55)
ESRD[c]		
New use		
No	255/2752	1 [Reference]
Yes	203/2738	1.00 (0.83-1.22)
Prior use		
No	522/5492	1 [Reference]
Yes	537/5492	1.14 (1.00-1.28)
Continued use		
No	691/9375	1 [Reference]
Yes	657/9363	0.89 (0.79-0.99)
ESRD and Doubling SCr Concentration		
New use		
No	378/2756	1 [Reference]
Yes	367/2734	1.09 (0.94-1.27)
Prior use		
No	793/5492	1 [Reference]
Yes	880/5492	1.24 (1.12-1.36)
Continued uses		
No	1164/9375	1 [Reference]
Yes	1144/9352	0.92 (0.85-1.00)

Abbreviations: ACEI, angiotensin converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; SCr, serum creatinine.

[a] The number of patients in the ACEI or ARB users group varies for each outcome because the outcomes could have occurred before or after the patients were dispensed an ACEI or ARB.

[b] Patients were stratified into the following groups: no use, new use, prior use, and continued use. No use was the control group. We used 1-to-1 matching to match on the logit of propensity score without replacement using calipers of width equal to 0.2 of the SD of the logit of the propensity score. A total of 2745 new use, 5492 prior use, and 9375 continued use patients were matched to no use patients in each group. Balanced distribution of the pretreatment covariates was achieved for all matched patients.

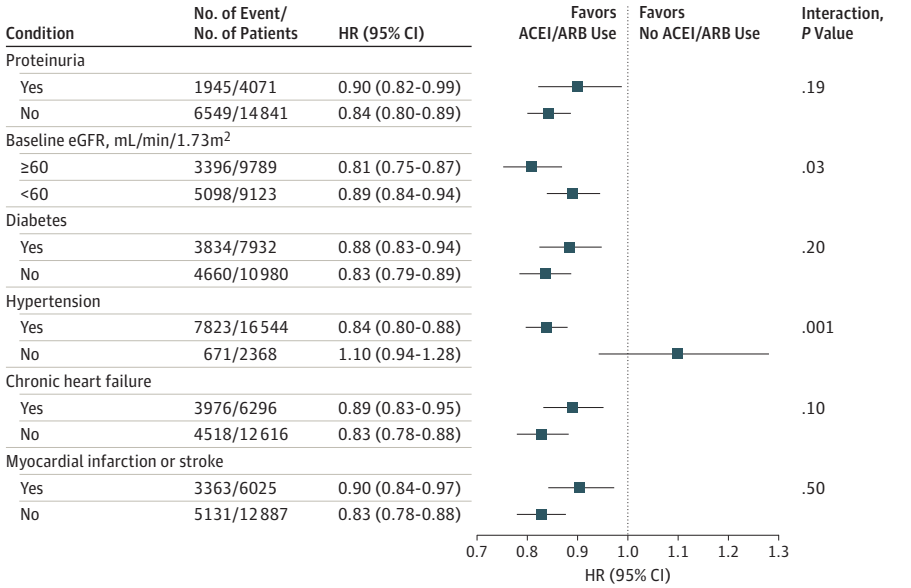
[c] ESRD was defined as a sustained estimated glomerular filtration rate less than 15 mL/min/1.73 m^2.

hospital discharge, suggesting that it may be better to start use of these medications after the first 90 days.

Strengths and Limitations

Our study has several strengths, including a population-based design, a large cohort size, comprehensive data on community prescribing, and the ability to adjust for many important confounders. Nonetheless, there are some limitations to our analysis, related primarily to the retrospective use of administrative and laboratory data and observational design. First, entry into the cohort was limited to patients who had 1 or more outpatient serum creatinine measurements within 180 days before hospitalization and more than 1 inpatient serum creatinine measurement performed as part of hospital care in Alberta, Canada. However, additional measurements of serum creatinine levels are common in patients hospitalized for short-term medical and surgical problems. Based on prior work,[46] patients who do not have serum creatinine levels measured after hospitalization have outcomes similar to those who do not have AKI; therefore, it is likely that we were able to identify all patients with AKI at high risk for

Figure. Forest Plots for Mortality Associated With Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB) Use in Patients Stratified by the Presence of Proteinuria, Baseline Renal Function, and the Presence of Comorbidities



Error bars indicates 95% CIs. eGFR indicates estimated glomerular filtration rate; HR, hazard ratio.

Table 4. Outcomes for ACEI or ARB Use in Patients Given a Prescription Within the First 90 Days After Discharge vs After 90 Days After Discharge

Outcome	No. of Events/No. of Patients[a]	Hazard Ratio (95% CI)	
		Adjusted	Unadjusted
Survival			
ACEI or ARB use after 90 d after discharge	803/1771	1 [Reference]	1 [Reference]
ACEI or ARB use within 90 d of discharge	675/1771	1.15 (1.03-1.28)	1.09 (0.98-1.22)
Hospitalization for a renal cause			
ACEI or ARB use after 90 d after discharge	146/1766	1 [Reference]	1 [Reference]
ACEI or ARB use within 90 d of discharge	111/1735	1.28 (0.99-1.65)	1.21 (0.93-1.57)
ESRD			
ACEI or ARB use after 90 d after discharge	185/1768	1 [Reference]	1 [Reference]
ACEI or ARB use within 90 d of discharge	161/1760	1.18 (0.96-1.47)	1.19 (0.94-1.49)
ESRD and doubling SCr concentration			
ACEI or ARB use after 90 d after discharge	291/1763	1 [Reference]	1 [Reference]
ACEI or ARB use within 90 d of discharge	278/1756	1.07 (0.91-1.27)	1.04 (0.88-1.24)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease, SCr, serum creatinine.

[a] The number of patients in the ACEI or ARB users group varies for each outcome because the outcomes could have occurred before or after the patients were dispensed an ACEI or ARB.

poor outcomes after discharge. Second, we were unable to obtain measures of some potentially important covariates, such as blood pressure, urine output, nutritional status, and deconditioning after hospitalization with AKI, which may influence outcomes. Third, because patients were not randomized to different processes of care, there is potential for treatment × indication bias, whereby certain patient characteristics prompt differences in prescription of an ACEI or ARB thereby introducing confounding. However, using propensity score matching, we were able to balance the distribution of pretreatment covariates, thereby minimizing this risk. It is also possible that ACEI or ARB use was a marker of better follow-up or access to care. Fourth, our exposure was defined as a dispensed prescription, and the rate of adherence among patients in the ACEI or ARB group was likely not 100%.

Conclusions

We found that the use of an ACEI or ARB in patients with AKI after hospital discharge was associated with lower mortality but a higher rate of hospitalization for a renal cause. This observation requires further evaluation in prospective studies evaluating postdischarge care strategies for patients with AKI. In particular, our results suggest a need for a trial to evaluate treatment with an ACEI or ARB in patients with AKI to determine whether this intervention improves long-term outcomes in high-risk patients.

ARTICLE INFORMATION

Accepted for Publication: July 24, 2018.

Published Online: October 27, 2018. doi:10.1001/jamainternmed.2018.4749

Author Contributions: Drs Ye and Pannu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Brar, Ye, James, Klarenbach, Pannu.
Acquisition, analysis, or interpretation of data: Brar, Ye, James, Hemmelgarn, Pannu.
Drafting of the manuscript: Brar, Ye.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Brar, Ye, James, Hemmelgarn.
Obtained funding: James, Pannu.
Administrative, technical, or material support: Pannu.
Supervision: Pannu.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded through an operating grant from the Canadian Institute of Health Research (Dr Pannu). Dr James was supported by a Canadian Institute for Health Research New Investigator Award. The Interdisciplinary Chronic Disease Collaboration is funded through a Collaborative Research and Innovation Opportunities Team Grant from Alberta Innovates–Health Solutions.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Group Members: The Interdisciplinary Chronic Disease Collaboration members are Brenda Hemmelgarn, MD, Braden Manns, MD, and Marcello Tonelli, MD.

Disclaimer: The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta nor Alberta Health Services express any opinion in relation to this study.

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Invited Commentary

Use of Renin Angiotensin System Blockers After Acute Kidney Injury
Balancing Tradeoffs

Robert J. Alpern, MD; Aldo J. Peixoto, MD

Acute kidney injury (AKI) is a common complication among acutely ill hospitalized patients. Depending on the definition used, AKI complicates 1% to 25% of intensive care unit admissions and is associated with mortality rates of 15% to 60%.[1] Through a variety of mechanisms that affect the kidneys and the vasculature, patients with AKI are at increased risk for the subsequent development of not only chronic kidney disease but also hypertension, stroke, and cardiovascular disease.[2] Because of the known nephroprotective and cardioprotective effects of renin angiotensin system (RAS) blockers (angiotensin converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]),[3,4] it has been postulated that these agents should be used after AKI to mitigate the risk of

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