Kidney Medicine

Effect of Post-Acute Kidney Injury Use of Renin-Angiotensin Inhibitors on Long-term Mortality and Major Adverse Kidney Events: A 5-year Retrospective Observational Cohort Study

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Rationale & Objective: Acute kidney injury (AKI) is common in hospitalized adults and a risk factor for chronic kidney disease and mortality. The effect of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) post-AKI on mortality and long-term kidney function remains unclear.

Study Design: Propensity-weighted retrospective observational cohort study.

Setting & Participants: A total of 3,289 patients with AKI admitted to a tertiary care hospital from November 2015-October 2016, with follow-up until September 2020.

Exposures: ACEi/ARB use within 180 days post-AKI.

Outcomes: All-cause mortality, and major adverse kidney events (MAKE) as defined by composite of renal replacement therapy post-AKI, sustained estimated glomerular filtration rate (eGFR) decline >30% from baseline, or eGFR ≤15 mL/min/1.73 m^2.

Analytical Approach: We generated propensity weights for ACEi/ARB use post-AKI, using age, sex, comorbid conditions, prior medication, intensive care unit admission, severe sepsis, and index AKI Kidney Disease: Improving Global Outcomes severity. Cox proportional hazard models were used to test associations of post-AKI ACEi/ARB with mortality, MAKE, and joint models for eGFR slopes.

Results: A total of 2,309 (70.2%) participants died or experienced MAKE by end of follow-up. 161 (4.9%) and 406 (12.3%) patients initiated or resumed prior ACEi/ARB use within 180 days post-AKI, respectively. Although the overall cohort had no significant mortality association with post-AKI ACEi/ARB use, a significant association with lower mortality was observed in patients with KDIGO 3 AKI (HR, 0.40; 95% CI, 0.21-0.75; $P_{interaction}$ = 0.003). However, post-AKI ACEi/ARB use was associated with increased MAKE in patients without cardiovascular indications for ACEi/ARB use (HR, 1.52; 95% CI, 1.17-1.98; $P_{interaction}$ = 0.03). Although post-AKI use of ACEi/ARB was associated with acute eGFR decline (initial eGFR change −2.3 mL/min/1.73 m^2/year; 95% CI, −3.1 to −1.5; P < 0.001), no association with longer-term eGFR decline was observed.

Limitations: Retrospective observational study on heterogeneous AKI cohort without data on ACEi/ARB cumulative exposure.

Conclusions: Early ACEi/ARB post-AKI was not associated with better long-term survival or kidney function but was associated with lower mortality in patients with KDIGO 3 AKI.

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Key Points

- More than half of patients with acute kidney injury (AKI) experienced sustained deterioration in kidney function, kidney failure, or mortality within 5 years; overall, early angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use post-AKI was not associated with better long-term survival or kidney function.
- Among subgroups, post-AKI use of ACEi/ARB was associated with lower long-term mortality in patients with KDIGO 3 AKI but more major adverse kidney events in patients with AKI without cardiovascular indications for ACEi/ARB initiation.
- Although post-AKI use of ACEi/ARB was associated with a higher risk of acute kidney disease, it was otherwise not related to longer-term eGFR decline.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in hospitalized adults and is associated with increased risks of chronic kidney disease (CKD),[1] cardiovascular events,[2-4] and mortality.[4-7] The high rates of cardiac and renal complications underscore the need to develop therapeutic strategies to improve long-term post-AKI mortality and kidney function outcomes.

A proposed strategy is renin-angiotensin-aldosterone system blockade using angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). ACEis/ARBs derive their nephroprotective effects by reducing glomerular hyperfiltration, proteinuria, nephrosclerosis, and interstitial fibrosis.[8,9] Although AKI is

PLAIN LANGUAGE SUMMARY

Acute kidney injury (AKI) is common in hospitalized adults and increases the risk of death and kidney failure. Although angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) have been widely used in proteinuric kidney disease to slow kidney function decline, the effect of ACEi/ARB use post-AKI on long-term kidney function remains unclear. In this 5-year study of 3,289 patients with AKI, we found that although patients experienced a transient decrease in kidney function following early ACEi/ARB initiation after their kidney injury, long-term kidney function trajectory and survival in these patients were similar to patients without early ACEi/ARB use. However, ACEi/ARB use after an AKI may reduce the long-term risk of death in patients with severe AKI. Additionally, we noted sustained kidney function deterioration in a subgroup of patients on ACEi/ARB early post-AKI in the absence of cardiovascular indications. These observations suggest that clinicians should adopt more individualized approaches to early ACEi/ARB administration post-AKI.

a well-established risk factor for progression to acute kidney disease (AKD)[10,11] and CKD,[11] the role of ACEi/ARB in nephroprotection in the context of post-AKI recovery remains controversial. First, the association of ACEi/ARB use post-AKI with mortality is inconsistent.[12–15] Second, longitudinal data on long-term kidney outcomes post-AKI is lacking, whereas definitions of post-AKI kidney outcomes vary across studies.[12–14,16] Finally, long-term studies examining the effect of ACEi/ARB on the progression of AKI to CKD and kidney failure, both clinically relevant outcomes, are lacking.

We reasoned that major adverse kidney events (MAKE), defined by a composite of sustained decline in estimated glomerular filtration rate (eGFR) of >30% from baseline, to ≤15 mL/min/1.73 m^2,[17,18] or until the initiation of renal replacement therapy (RRT) would be highly relevant as a long-term outcome post-AKI. We hypothesized that ACEi/ARB use post-AKI would confer nephroprotection and reduce mortality and MAKE in affected patients over 5 years.

METHODS

Study Design and Patient Cohort

We performed a retrospective observational study of 3,841 patients aged 18 years or more and hospitalized from November 2015 to October 2016 with AKI in a tertiary care institution with 1,200 acute beds that offers cardiothoracic surgery, hematologic and solid organ transplantation, and anticancer therapy. We extracted patient demographics, diagnosis codes, laboratory values, prescribed medications, and death dates from our electronic health records from January 2015 to September 2020 (Computerized Patient Support System 2, CPSS2; Integrated Health Information System Pte Ltd). We excluded patients with missing inpatient records from November 1, 2015 to October 31, 2016, patients who had procedure or diagnoses codes for hemodialysis or peritoneal dialysis (Table S1) before the index admission with AKI, a baseline eGFR <15 mL/min/1.73 m^2, who had only 1 serum creatinine (sCr) value before the AKI peak, or who did not fulfill the sCr-based (Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition. Figure 1 presents the flowchart of the exclusion criteria of patients, with 3,289 patients ultimately included in our analyses.

Definitions

AKI was defined as an increase of sCr of 0.3 mg/dL within 48 hours or ≥50% of baseline sCr, with baseline sCr defined as the lowest creatinine value within 365 days before AKI onset[19] or 365 days post-AKI. Severity was graded based on KDIGO AKI guidelines.[20,21] CKD was defined by the KDIGO definition[22] of eGFR ≤60 mL/min/1.73m^2. eGFRs were calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation.[23]

MAKE was defined as a composite of the following: (1) RRT initiation after the index admission for AKI, obtained from diagnosis codes for hemodialysis, continuous RRT and peritoneal dialysis, and (2) sustained eGFR decline by >30% from baseline or to ≤15 mL/min/1.73 m^2 for 2 consecutive readings. AKI recovery was defined as the earliest time after peak sCr (during index AKI) in which sCr decreased to ≤125% of baseline sCr.[1]

Medical comorbid conditions were defined using the *International Classification of Diseases and Related Health Problems Ninth* or *Tenth Revision* diagnosis codes (Table S1). A list of medications used in the study is provided in Table S2.

ACEi/ARB users post-AKI were defined as patients receiving at least 1 prescription within 180 days after peak sCr of the index AKI event. A cutoff of 180 days was chosen for the following reasons: (1) mortality benefit associated with early ACEi/ARB use post-AKI was noted within 1 year,[24] and (2) the benefits to mortality and hospitalization of ACEi/ARB use in conditions that are common inciting factors for AKI, such as myocardial infarction and heart failure, were seen within months.[25–27]

A modified electronic health record-based definition of sepsis was used to identify patients with severe sepsis[28,29]: the presence of ≥1 diagnosis codes for infection (Table S1) and any of the following: (1) diagnosis codes for end-organ dysfunction, (2) procedure codes for mechanical ventilation or RRT, (3) diagnosis codes for RRT encounters or complications related to RRT (Table S1), or (4) severe thrombocytopenia (<20 × 10^9/L).

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes included the following: (1) MAKE, (2) composite of MAKE and mortality, and (3) rate of eGFR decline (in mL/min/1.73 m^2 per year) from peak sCr of the index AKI episode.

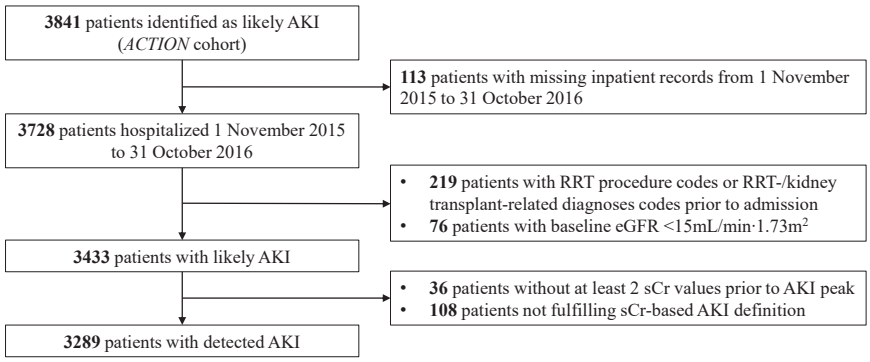

Figure 1. Flowchart of inclusion and exclusion criteria for the patient cohort used in the current study. Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; sCr, serum creatinine.

Statistical Analysis

Baseline patient characteristics are summarized as count and percentage (categorical variables) or mean with standard deviation (continuous variables). Fisher exact test was used to compare categorical variables between groups, and 1-way analysis of variance was used for continuous variables. Median follow-up time with interquartile range was obtained using the reverse Kaplan–Meier method[22] and compared with log-rank tests.

To adjust for clinically relevant risk factors, we chose a priori to include KDIGO severity stage of index AKI, baseline eGFR, intensive care unit (ICU) admission on index AKI, severe sepsis at index admission, time to AKI recovery, ACEi/ARB use before index admission, diuretic and nephrotoxic antimicrobial use within 14 days before AKI onset, cardiovascular risk factors (hypertension, diabetes mellitus, ischemic heart disease, and hyperlipidemia), heart failure, liver cirrhosis, and malignancies in all analyses.

Inverse propensity of treatment weighting with covariate balancing was performed with the *CBPS* R package. Propensity scores for the likelihood of ACEi/ARB use in the first 180 days post-AKI were estimated using logistic regression models in which treatment (ACEi/ARB use in the first 180 days post-AKI) was regressed on the covariates described above. Standardized mean differences were computed to assess the balance of covariates between treated and untreated groups in both weighted and unweighted cohorts (Table S3).

Kaplan–Meier curves and multivariable Cox proportional hazard models were used for survival analyses and were censored on September 1, 2020. Cumulative incidence curves and cause-specific Cox models were used for time-to-event analyses of MAKEs, with death as a competing event and censoring on September 1, 2020. ACEi/ARB use post-AKI was modeled as a time-varying covariate: a person prescribed an ACEi/ARB would contribute person-time to the exposure group without former use before the first ACEi/ARB prescription, and would contribute person-time to the ACEi/ARB use group after the first ACEi/ARB prescription only if the prescription was made within 180 days post-AKI. If the first ACEi/ARB prescription was made >180 days post-AKI, the person would contribute person-time only to the exposure group without ACEi/ARB use throughout the study time-frame instead. The Pepe and Fleming test was performed on cumulative incidence curves and survival curves.

To evaluate the time-dependency of hazard ratios (HRs) for ACEi/ARB use on MAKE and composite events (MAKE and mortality), parametric proportional hazard models with cubic M-splines for baseline hazard functions and a cubic B-spline for time-varying log HR for ACEi/ARB use were constructed with Bayesian modeling using the R package *rstanarm*, and HR curves were plotted.

To examine the effects of ACEi/ARB use post-AKI on MAKEs and eGFR decline, joint models[30] were constructed consisting of (1) a linear mixed model (LMM) for eGFR with time and comorbid conditions as predictors and (2) a Cox proportional hazard model for MAKE with the same comorbid conditions and eGFR slope as predictors. The effects of independent variables on the eGFR slope were investigated using 2-way interactions over time. The mathematical formula of the LMM model was as follows:

$$\mathrm{eGFR}_{i,j} = (b_0 + u_0) + \sum_k b_k x_{i,k} + (\beta_0 + \mu_0) t_{i,j} + \sum_k \beta_k x_{i,k} \times t_{i,j} + \varepsilon \quad (1)$$

in which $t_{i,j}$ represents time for patient i at time j, b_0 represents the intercept, b_k the coefficient for independent variable $x_{i,k}$ (ie, age, comorbid condition, or sCr change), β_0 the average eGFR slope, β_k the slope of the interaction between predictor $x_{i,k}$ and time $t_{i,j}$, u_0 the random intercept (variation in intercept of the whole population), μ_0 the random slope with time (variation in slope of the whole population), and ε the error term. Slopes with respect to $t_{i,j}$ were taken as eGFR slopes. LMMs were modeled with linear splines for time with

knots at 90 days and 180 days. Coefficients and confidence intervals (CIs) were derived from Bayesian estimates with 18,000 Monte Carlo Markov chain iterations. For patients who received RRT, eGFR values were removed from the day at which RRT was sustained, defined as the first occurrence of ≥2 RRT procedures in a 7-day interval. ACEi/ARB use post-AKI was modeled as a time-varying covariate in the same manner as time-to-event models.

To account for indications for ACEi/ARB, analyses included interaction terms between ACEi/ARB use and baseline eGFR strata, index AKI KDIGO stage, diabetes mellitus, hypertension, and ischemic heart disease. Sensitivity analysis was performed: (1) omission of AKI recovery time covariable, and (2) using only preadmission sCr values to define baseline sCr. The baseline characteristics of the cohort used for sensitivity analyses are presented in Tables S4-S6.

Data processing and statistical analysis were performed using R 4.1.3 and R packages *survival*, *CBPS*, *JMbayes2*, *nlme*, and *rstanarm*. A P value < 0.05 was considered statistically significant for analyses involving $P_{interaction}$ calculations within subgroups and analyses involving the overall cohort. To account for multiple comparisons in subgroup analyses, a Bonferroni correction was applied, and a threshold of $P < 0.05/8 \sim 0.00625$ was considered statistically significant.

Ethics

This study was determined to be exempt as secondary research by the National Healthcare Group institutional review board (NHG-DSRB2014/00485). Given the observational nature of the study, and deidentification of electronic health record data for analysis, the need for informed consent was waived.

RESULTS

Patient Characteristics

Table 1 presents the baseline characteristics of the cohort and the subgroups of patients who had no prior ACEi/ARB use, and patients who had prior use of ACEi/ARB. Briefly, 161 (7.5%) of 2,144 patients who had no prior ACEi/ARB use were initiated on ACEi/ARB, whereas 739 (64.5%) of 1,145 patients who were on ACEi/ARB before the index AKI admission had their ACEi/ARB discontinued after AKI. Patients who had no prior ACEi/ARB had higher baseline eGFR (86.4 ± 33.1 vs 77.6 ± 27.6 mL/min/1.73 m^2), were more likely to have hematologic (97 [4.5%] vs 15 [1.3%]) or solid organ malignancy (308 [14.4%] vs 129 [11.3%]), and were less likely to have diabetes mellitus (156 [7.3%] vs 349 [30.5%]), hyperlipidemia (197 [9.2%] vs 447 [39.0%]), hypertension (320 [14.9%] vs 585 [51.1%]), and ischemic heart disease (86 [4.0%] vs 252 [22.0%]). Concerning admission outcomes, patients who had no prior ACEi/ARB use had a higher incidence of ICU admission in the index AKI episode (590 [27.5%] vs 238 [20.8%]) and sepsis (679 [31.7%] vs 243 [21.2%]) and had a higher probability of being initiated on RRT (222 [10.4%] vs 108 [9.4%]) than patients who were prescribed ACEi/ARBs before admission. Patients who had not used ACEi/ARBs before admission were more likely to be exposed to nephrotoxic antimicrobials (435 [20.3%] vs 181 [15.8%]) and less likely to be exposed to diuretics (393 [18.3%] vs 387 [33.8%]) than patients who were prescribed ACEi/ARBs before admission.

Effect of ACEi/ARBs on Mortality and MAKE

Figure 2A presents cumulative incidence curves of MAKE, with mortality as a competing event, in patients who were prescribed ACEi/ARB post-AKI. The cumulative incidence curves of MAKE between patients prescribed ACEi/ARB post-AKI and patients without ACEi/ARB post-AKI were significantly different ($P = 0.02$). At 1,080 days, the MAKE incidence of patients prescribed ACEi/ARB post-AKI was 50.1% (95% CI, 46.1-54.4%) compared with 47.8% (95% CI, 44.8%-50.9%) in patients without ACEi/ARB use post-AKI. Figure 2B presents survival curves for the composite mortality outcome and MAKE in patients prescribed ACEi/ARB post-AKI. The median time to the composite outcome was 441 days (95% CI, 324-545 days) in patients without ACEi/ARB use post-AKI, compared with 662 days (95% CI, 491-786 days) in patients prescribed ACEi/ARB post-AKI ($P = 0.35$, Fig 2B).

Next, we examined the associations of post-AKI use of ACEi/ARB on mortality and MAKE (Table 2). We observed no significant mortality association with post-AKI use of ACEi/ARB in the overall cohort (HR, 0.95; 95% CI, 0.82-1.11; $P = 0.53$). In patients with KDIGO 3 AKI, post-AKI use of ACEi/ARB was associated with lower mortality risk (HR, 0.40; 95% CI, 0.21-0.75; $P_{interaction} = 0.003$). Unexpectedly, post-AKI use of ACEi/ARB was associated with a higher risk of MAKE in the overall cohort (HR, 1.19; 95% CI, 1.02-1.38; $P = 0.03$), especially in patients without hypertension (HR, 1.41; 95% CI, 1.15-1.73; $P_{interaction} = 0.03$) or patients without any cardiovascular indication for ACEi/ARB initiation (HR, 1.52; 95% CI, 1.17-1.98; $P_{interaction} = 0.03$). In contrast, no statistically significant association of MAKE with post-AKI ACEi/ARBuse was observed in subgroups based on the index AKI severity (KDIGO 2: HR, 1.04; 95% CI, 0.68-1.59; $P_{interaction} = 0.43$; KDIGO 3: HR, 0.84; 95% CI, 0.47-1.49; $P_{interaction} = 0.19$).

Figure S1A and S1B present the cumulative incidence curves of MAKE with mortality as a competing event for (1) patients with no pre-AKI ACEi/ARB exposure who were either newly initiated or never started on ACEi/ARB and (2) patients prescribed ACEi/ARB before the AKI event who were either restarted or never restarted on ACEi/ARB. Although there was a significant difference in the cumulative incidence curves in these analyses, there was no significant association of pre-AKI ACEi/ARB exposure with mortality or MAKE in Cox proportional hazard models

Table 1. Baseline Characteristics of the Cohort

		No Prior ACEi/ARB Use			Prior ACEi/ARB Use			
	Overall	Never Started	Newly Started	Subtotal	Prior Use Without Continued Use	Continued Use	Subtotal	*P*
N (%)	3,289 (100.0%)	1,983 (60.3%)	161 (4.9%)	2,144 (65.2%)	739 (22.5%)	406 (12.3%)	1,145 (34.8%)	
Sex, n (%)								
Male	1,834 (55.8%)	1,103 (55.6%)	89 (55.3%)	1,192 (55.6%)	418 (56.6%)	224 (55.2%)	642 (56.1%)	0.96
Female	1,455 (44.2%)	880 (44.4%)	72 (44.7%)	952 (44.4%)	321 (43.4%)	182 (44.8%)	503 (43.9%)	
Age, y, mean (SD)	69.5 (15.9)	67.8 (17.1)	71.5 (13.6)	68.0 (16.9)	72.9 (13.3)	71.0 (14.1)	72.2 (13.6)	<0.001
Age group, y (n, %)								
18-25	30 (0.9%)	25 (1.3%)	1 (0.6%)	26 (1.2%)	0 (0.0%)	4 (1.0%)	4 (0.3%)	<0.001
26-49	333 (10.1%)	264 (13.3%)	6 (3.7%)	270 (12.6%)	41 (5.5%)	22 (5.4%)	63 (5.5%)	
50-69	1,147 (34.9%)	722 (36.4%)	63 (39.1%)	785 (36.6%)	220 (29.8%)	142 (35.0%)	362 (31.6%)	
70-79	819 (24.9%)	436 (22.0%)	43 (26.7%)	479 (22.3%)	222 (30.0%)	118 (29.1%)	340 (29.7%)	
≥80	960 (29.2%)	536 (27.0%)	48 (29.8%)	584 (27.2%)	256 (34.6%)	120 (29.6%)	376 (32.8%)	
Ethnicity, n (%)								
Chinese	2,053 (62.4%)	1,284 (64.8%)	97 (60.2%)	1,381 (64.4%)	440 (59.5%)	232 (57.1%)	672 (58.7%)	<0.001
Malay	561 (17.1%)	302 (15.2%)	32 (19.9%)	334 (15.6%)	144 (19.5%)	83 (20.4%)	227 (19.8%)	
Indian	280 (8.5%)	142 (7.2%)	11 (6.8%)	153 (7.1%)	75 (10.1%)	52 (12.8%)	127 (11.1%)	
Eurasian	17 (0.5%)	9 (0.5%)	1 (0.6%)	10 (0.5%)	5 (0.7%)	2 (0.5%)	7 (0.6%)	
White	12 (0.4%)	8 (0.4%)	0	8 (0.4%)	4 (0.5%)	0	4 (0.3%)	
Sikh	21 (0.6%)	14 (0.7%)	3 (1.9%)	17 (0.8%)	3 (0.4%)	1 (0.2%)	4 (0.3%)	
Others	345 (10.5%)	224 (11.3%)	17 (10.6%)	241 (11.2%)	68 (9.2%)	36 (8.9%)	104 (9.1%)	
Baseline eGFR, mL/min/ 1.73 m^2, n (%)								
≥60	2,463 (74.9%)	1541 (77.7%)	104 (64.6%)	1,645 (76.7%)	518 (70.1%)	300 (73.9%)	818 (71.4%)	<0.001
45 to <60	324 (9.9%)	151 (7.6%)	19 (11.8%)	170 (7.9%)	93 (12.6%)	61 (15.0)	154 (13.4%)	
30 to <45	262 (8.0%)	133 (6.7%)	19 (11.8%)	152 (7.1%)	74 (10.0%)	36 (8.9%)	110 (9.6%)	
15 to <30	240 (7.3%)	158 (8.0%)	19 (11.8%)	177 (8.3%)	54 (7.3%)	9 (2.2%)	63 (5.5%)	
Baseline eGFR, mL/min/ 1.73 m^2, mean (SD)	83.3 (31.6)	87.5 (33.0)	71.65 (29.91)	86.4 (33.1)	76.5 (28.7)	79.7 (25.5)	77.6 (27.6)	<0.001
Index AKI KDIGO Stage, n (%)								
Stage 1	2,206 (67.1%)	1,261 (63.6%)	118 (73.3%)	1,379 (64.3%)	490 (66.3%)	337 (83.0%)	827 (72.2%)	<0.001
Stage 2	568 (17.3%)	359 (18.1%)	21 (13.0%)	380 (17.7%)	139 (18.8%)	49 (12.1%)	188 (16.4%)	
Stage 3	515 (15.7%)	363 (18.3%)	22 (13.7%)	385 (18.0%)	110 (14.9%)	20 (4.9%)	130 (11.4%)	
RRT initiation, n (%)								
During index AKI	155 (4.7%)	115 (5.8%)	6 (3.7%)	121 (5.6%)	29 (3.9%)	5 (1.2%)	34 (3.0%)	<0.001
After index AKI	175 (5.3%)	81 (4.1%)	20 (12.4%)	101 (4.7%)	45 (6.1%)	29 (7.1%)	74 (6.5%)	
Cumulative	330 (10.0%)	196 (9.9%)	26 (16.1%)	222 (10.4%)	74 (10.0%)	34 (8.4%)	108 (9.4%)	

(Continued)

Kidney Medicine

Table 1 (Cont'd). Baseline Characteristics of the Cohort

		No Prior ACEi/ARB Use			Prior ACEi/ARB Use			
	Overall	Never Started	Newly Started	Subtotal	Prior Use Without Continued Use	Continued Use	Subtotal	*P*
Comorbid conditions, n (%)								
Diabetes mellitus	505 (15.4%)	143 (7.2%)	13 (8.1%)	156 (7.3%)	212 (28.7%)	137 (33.7%)	349 (30.5%)	<0.001
Hyperlipidemia	644 (19.6%)	179 (9.0%)	18 (11.2%)	197 (9.2%)	268 (36.3%)	179 (44.1%)	447 (39.0%)	<0.001
Hypertension	905 (27.5%)	282 (14.2%)	38 (23.6%)	320 (14.9%)	370 (50.1%)	215 (53.0%)	585 (51.1%)	<0.001
Ischemic heart disease	338 (10.3%)	77 (3.9%)	9 (5.6%)	86 (4.0%)	160 (21.7%)	92 (22.7%)	252 (22.0%)	<0.001
Heart failure	270 (8.2%)	72 (3.6%)	8 (5.0%)	80 (3.7%)	108 (14.6%)	82 (20.2%)	190 (16.6%)	<0.001
Liver cirrhosis	132 (4.0%)	85 (4.3%)	7 (4.3%)	92 (4.3%)	26 (3.5%)	14 (3.4%)	40 (3.5%)	0.76
Hematological malignancy	112 (3.4%)	95 (4.8%)	2 (1.2%)	97 (4.5%)	8 (1.1%)	7 (1.7%)	15 (1.3%)	<0.001
Solid organ malignancy	437 (13.3%)	300 (15.1%)	8 (5.0%)	308 (14.4%)	92 (12.4%)	37 (9.1%)	129 (11.3%)	<0.001
Nephrotoxic medications ≤14 d before index AKI peak, n (%)								
Nephrotoxic antimicrobial use	616 (18.7%)	411 (20.7%)	24 (14.9%)	435 (20.3%)	122 (16.5%)	59 (14.5%)	181 (15.8%)	0.003
Diuretics	780 (23.7%)	331 (16.7%)	62 (38.5%)	393 (18.3%)	230 (31.1%)	157 (38.7%)	387 (33.8%)	<0.001
ICU admission during index AKI, n (%)	828 (25.2%)	552 (27.8%)	38 (23.6%)	590 (27.5%)	180 (24.4%)	58 (14.3%)	238 (20.8%)	<0.001
Severe sepsis, (n, %)	922 (28.0%)	640 (32.3%)	39 (24.2%)	679 (31.7%)	185 (25.0%)	58 (14.3%)	243 (21.2%)	<0.001
Time between creatinine values before MAKE, d, median (IQR)	4.0 (1.0-55.0)	3.0 (1.0-40.0)	10.0 (1.0-71.0)	3.5 (1.0-42.0)	4.0 (1.0-71.0)	9.5 (2.0-83.5)	5.0 (1.0-78.0)	<0.001
MAKE incidence, n (%)	1,635 (49.7%)	878 (44.3%)	105 (65.2%)	983 (45.8%)	424 (57.4%)	228 (56.2%)	652 (56.9%)	<0.001
Composite event (MAKE + mortality) incidence, n (%)	2,309 (70.2%)	1,345 (67.8%)	124 (77.0%)	1469 (68.5%)	552 (74.7%)	288 (70.9%)	840 (73.4%)	0.001
Follow-up, y, median (IQR)	4.4 (4.2-4.7)	4.5 (4.2-4.7)	4.36 (4.2-4.6)	4.4 (4.2-4.7)	4.4 (4.1-4.7)	4.5 (4.2-4.6)	4.4 (4.2-4.7)	0.23
Deceased, n (%)	1,576 (47.9%)	995 (50.2%)	66 (41.0%)	1,061 (49.5%)	349 (47.2%)	166 (40.9%)	515 (45.0%)	0.002

Note: The first row presents the sample size of each subgroup and expresses a percentage of the total population size (N). Percentages of categorical demographic, clinical, medical and outcome variables are calculated with the sample size of the respective subgroups (n).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; MAKE, major adverse kidney event; RRT, renal replacement therapy; SD, standard deviation.

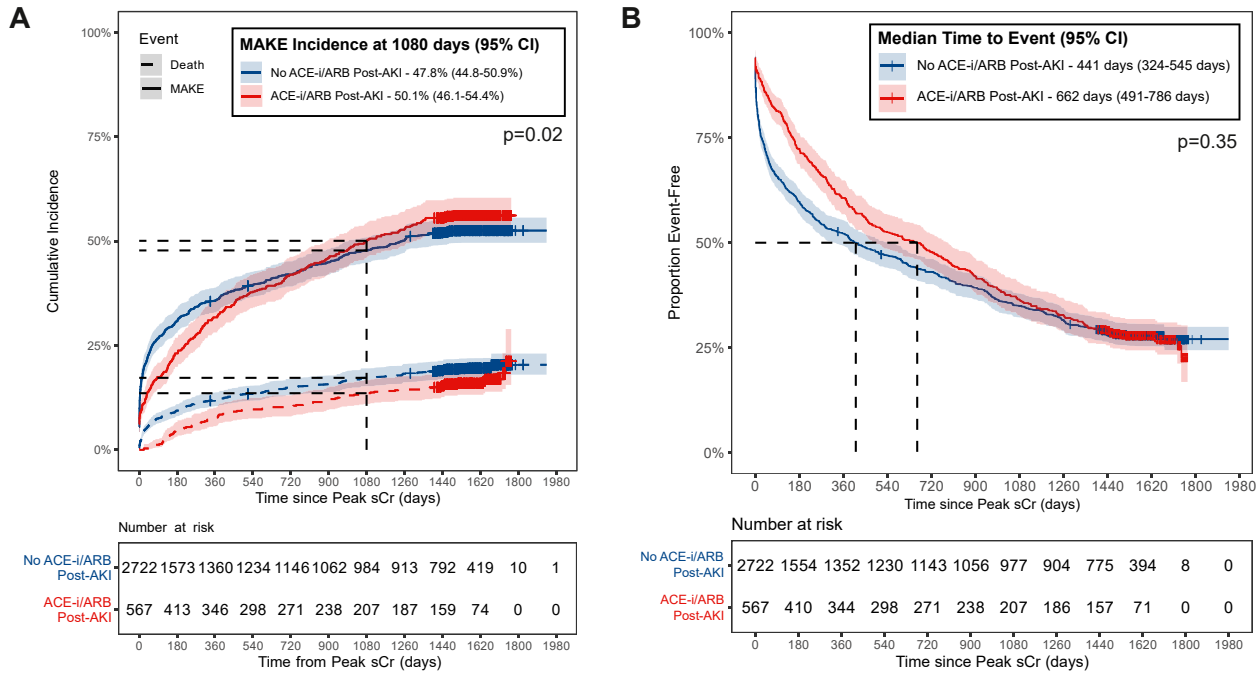

Figure 2. MAKE and mortality in patients with and without post-AKI use of ACEi/ARB. (A) Cumulative incidence curve of MAKE, with mortality as a competing event, in the overall cohort, stratified by the presence or absence of post-AKI use of ACEi/ARB. Curves were weighted with inverse propensity of treatment weighting and covariate balancing. *P* values were determined using Pepe and Fleming's test. Shaded areas represent 95% CIs. Tick marks represent time of censoring. Dashed lines in survival curves represent median or 75th percentiles as specified, colored dashed lines in cumulative incidence curves for MAKE represent death as a competing event, and black dashed lines in cumulative incidence curves represent MAKE cumulative incidence at 1,080 days. (B) Survival curve representing the composite event of MAKE and mortality, stratified by the presence or absence of post-AKI use of ACEi/ARB. Curves were weighted with inverse propensity of treatment weighting and covariate balancing. *P* values were determined using Pepe and Fleming's test. Shaded areas represent 95% CIs. Tick marks represent time of censoring. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AKI, acute kidney injury; CI, confidence interval; MAKE, major adverse kidney event; sCr, serum creatinine.

after multivariable adjustments (Table 2). Figure S2A and S2B presents the survival curves of the composite outcome of MAKE and mortality in (1) patients with no pre-AKI ACEi/ARB exposure who were either newly initiated or never started on ACEi/ARB and (2) patients with pre-AKI ACEi/ARB exposure who were either restarted or never restarted on ACEi/ARB post-AKI. Similarly, although there was a significant difference in survival curves in patients with pre-AKI ACEi/ARB exposure (Fig S2B), there was no significant association of pre-AKI ACEi/ARB exposure with composite outcome after multivariable adjustments (Table 2). Figures S3-S11 and Tables S7-S10 present the sensitivity analyses of MAKE and mortality outcomes in our cohort.

Post-AKI Use of ACEi/ARB on eGFR Decline

Although MAKE comprises an aggregate of clinical outcomes, we sought to quantitatively examine the effect of post-AKI use of ACEi/ARB on eGFR decline in 3 major periods after index AKI: AKD (0-90 days), the onset of CKD (91-180 days), and long-term CKD (>180 days). Table 3 presents the effect estimates of post-AKI use of ACEi/ARB on eGFR changes in these periods.

Concerning AKD outcomes (Table 3), post-AKI use of ACEi/ARB was associated with a greater initial decline of eGFR (−2.3 mL/min/1.73 m^2/month; 95% CI, −3.1 to −1.5; $P < 0.001$). In patients with more severe AKI, post-AKI use of ACEi/ARB was associated with greater eGFR decline (KDIGO 1: −1.4 mL/min/1.73 m^2/month; 95% CI, −2.6 to −0.3; KDIGO 2: −4.5 mL/min/1.73 m^2/month; 95% CI, −6.7 to −2.4; $P_{interaction} = 0.03$; KDIGO 3: −8.8 mL/min/1.73 m^2/month; 95% CI, −12.2 to −5.5; $P_{interaction} < 0.001$). Interestingly, we found greater eGFR decline in patients with prior ACEi/ARB use (prior ACEi/ARB use: −3.0 mL/min/1.73 m^2/month; 95% CI, −4.1 to −1.9; no prior ACEi/ARB use: −1.4 mL/min/1.73 m^2/month; 95% CI, −2.3 to −0.5; $P_{interaction} = 0.04$).

In the 91-180 day interval (Table 3), post-AKI use of ACEi/ARB was associated with better post-AKI eGFR outcomes (1.0 mL/min/1.73 m^2/month; 95% CI, 0.3-1.7; $P = 0.005$), for which the protective effects were seen mainly in patients who were previously on ACEi/ARB (1.8 mL/min/1.73 m^2/month; 95% CI, 0.8-2.8; $P_{interaction} = 0.02$). Concomitantly, we observed nephroprotective effects of post-AKI use of ACEi/ARB in severe AKI (KDIGO 2: 3.0 mL/min/1.73 m^2/month; 95% CI,

Table 2. Effect of Post-AKI Use of ACEi/ARB on Mortality and MAKE

	Mortality			MAKE			Composite (MAKE and Mortality)		
	HR (95% CI)	$P_{interaction}$	*P*	HR (95% CI)	$P_{interaction}$	*P*	HR (95% CI)	$P_{interaction}$	*P*
Overall[a]	0.95 (0.82-1.11)	—	0.53	1.19 (1.02-1.38)	—	0.03[d]	1.12 (0.98-1.28)	—	0.09
Subgroups[b]									
Pre-AKI ACEi/ARB use									
No	0.83 (0.65-1.08)	—	0.16	1.40 (1.07-1.82)	—	0.01	1.20 (0.95-1.51)	—	0.12
Yes	1.00 (0.83-1.22)	0.27	0.97	1.11 (0.92-1.34)	0.16	0.27	1.09 (0.93-1.28)	0.52	0.28
Baseline eGFR (mL/min/1.73 m^2)									
≥60	0.94 (0.77-1.14)	—	0.53	1.29 (1.07-1.55)	—	0.008	1.20 (1.02-1.41)	—	0.03
45 to <60	0.93 (0.63-1.37)	0.96	0.71	1.06 (0.70-1.59)	0.39	0.80	0.97 (0.70-1.36)	0.27	0.88
30 to <45	1.15 (0.73-1.80)	0.43	0.56	0.88 (0.58-1.33)	0.10	0.53	0.94 (0.63-1.40)	0.26	0.76
15 to <30	0.80 (0.45-1.43)	0.61	0.45	1.27 (0.65-2.48)	0.98	0.48	1.08 (0.59-2.00)	0.75	0.79
AKI KDIGO Stage									
KDIGO 1	1.08 (0.91-1.28)	—	0.40	1.25 (1.06-1.48)	—	0.009	1.21 (1.05-1.39)	—	0.01
KDIGO 2	0.62 (0.38-1.00)	0.04[d]	0.05	1.04 (0.68-1.59)	0.43	0.86	1.01 (0.70-1.46)	0.38	0.96
KDIGO 3	0.40 (0.21-0.75)	0.003[d]	0.005[e]	0.84 (0.47-1.49)	0.19	0.55	0.60 (0.34-1.06)	0.02[d]	0.08
Diabetes mellitus									
No	0.94 (0.79-1.13)	—	0.52	1.29 (1.08-1.54)	—	0.005[e]	1.18 (1.01-1.37)	—	0.04
Yes	0.97 (0.72-1.31)	0.85	0.86	0.98 (0.75-1.31)	0.11	0.94	1.01 (0.79-1.29)	0.29	0.96
Hypertension									
No	0.97 (0.79-1.20)	—	0.79	1.41 (1.15-1.73)	—	<0.001[e]	1.27 (1.07-1.52)	—	0.008
Yes	0.93 (0.74-1.17)	0.81	0.56	1.00 (0.80-1.25)	0.03[d]	0.98	0.99 (0.81-1.20)	0.06	0.89
Ischemic heart disease									
No	0.97 (0.82-1.15)	—	0.74	1.26 (1.07-1.49)	—	0.006[e]	1.17 (1.01-1.35)	—	0.03
Yes	0.87 (0.59-1.28)	0.62	0.49	0.91 (0.64-1.30)	0.10	0.61	0.94 (0.70-1.28)	0.21	0.71
Heart failure									
No	0.98 (0.83-1.17)	—	0.84	1.23 (1.05-1.45)	—	0.01	1.16 (1.00-1.34)	—	0.04
Yes	0.84 (0.58-1.23)	0.47	0.37	1.01 (0.70-1.46)	0.32	0.97	0.98 (0.71-1.34)	0.33	0.88
Composite cardiovascular indications[c]									
No	0.95 (0.72-1.25)	—	0.72	1.52 (1.17-1.98)	—	0.002[e]	1.34 (1.07-1.68)	—	0.01
Yes	0.95 (0.79-1.14)	0.99	0.58	1.06 (0.88-1.27)	0.03[d]	0.55	1.02 (0.87-1.20)	0.06	0.76

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; MAKE, major adverse kidney event.

[a]Models were adjusted for age, sex, intensive care unit admission on index AKI, severe sepsis, baseline eGFR, index AKI KDIGO stage, diabetes mellitus, hyperlipidemia, hypertension, liver cirrhosis, hematological malignancy, solid organ malignancy, ACEi/ARB use before index admission, diuretic use, and nephrotoxic antibiotic use.

[b]Models were adjusted for all except the defined variable of interest.

[c]Diabetes mellitus, hypertension, ischemic heart disease, heart failure, or baseline eGFR <60 mL/min/1.73 m^2.

[d]Significant at a priori threshold of $P_{interaction} < 0.05$ for subgroup analyses, and $P < 0.05$ for overall cohort.

[e]Significant at Bonferroni-corrected threshold of $P < 0.00625$ for subgroup analyses.

Table 3. Effect of Post-AKI Use of ACEi/ARB on eGFR Decline

	eGFR Slope Associated With ACEi/ARB Use								
	0-90 d			91-180 d			≥181 d		
	β (mL/min/1.73 m^2/mo) (95%CI)	$P_{interaction}$	P	β (mL/min/1.73 m^2/mo) (95% CI)	$P_{interaction}$	P	β (mL/min/1.73 m^2/y) (95%CI)	$P_{interaction}$	P
Overall[a]	−2.3 (−3.1 to −1.5)	—	<0.001[d]	1.0 (0.3-1.7)	—	0.005[d]	−0.8 (−2.0 to 0.3)	—	0.17
Subgroups[b]									
Prior ACEi/ARB use									
No	−1.4 (−2.3 to −0.5)	—	0.002[e]	−0.1 (−1.0 to 0.8)	—	0.88	−1.7 (−3.3 to 0.0)	—	0.05
Yes	−3.0 (−4.1 to −1.9)	0.04[d]	<0.001[e]	1.8 (0.8-2.8)	0.02[d]	<0.001[e]	−0.4 (−1.7 to 0.8)	0.25	0.49
Baseline eGFR (mL/min/1.72m^2)									
≥60	−2.9 (−4.1 to −1.7)	—	<0.001[e]	1.5 (0.6-2.4)	—	0.001[e]	−1.3 (−2.9 to 0.3)	—	0.10
45-<60	−1.6 (−3.3 to 0.2)	0.19	0.08	0.0 (−1.4 to 1.4)	0.05[d]	1.00	1.6 (−0.8 to 4.0)	0.05[d]	0.20
30-<45	2.0 (−0.2 to 4.2)	<0.001[d]	0.07	−1.8 (−3.5 to −0.1)	<0.001[d]	0.04	1.4 (−2.2 to 4.9)	0.14	0.46
15-<30	−1.6 (−4.8 to 1.5)	0.41	0.31	1.0 (−1.7 to 3.8)	0.75	0.46	−2.2 (−8.1 to 3.7)	0.78	0.47
AKI KDIGO Stage									
KDIGO 1	−1.4 (−2.6 to −0.3)	—	0.01	0.5 (−0.3 to 1.3)	—	0.20	−1.0 (−2.4 to 0.4)	—	0.17
KDIGO 2	−4.5 (−6.7 to −2.4)	0.03[d]	<0.001[e]	3.0 (1.5-4.6)	0.006[d]	<0.001[e]	3.2 (−0.1 to 6.4)	0.02[d]	0.05
KDIGO 3	−8.8 (−12.2 to −5.5)	<0.001[d]	<0.001[e]	2.9 (0.4-5.4)	0.06	0.02	1.1 (−3.2 to 5.4)	0.33	0.61
Diabetes Mellitus									
No	−2.4 (−3.4 to −1.4)	—	<0.001[e]	1.1 (0.4-1.9)	—	0.002[e]	−1.0 (−2.2 to 0.1)	—	0.08
Yes	−2.9 (−4.7 to −1.1)	0.63	0.002[e]	1.1 (−0.4 to 2.6)	0.94	0.16	0.1 (−2.0 to 2.2)	0.37	0.93
Hypertension									
No	−2.5 (−3.9 to −1.2)	—	<0.001[e]	1.3 (0.5-2.1)	—	0.002[e]	−2.0 (−3.7 to −0.4)	—	0.02
Yes	−2.2 (−3.4 to −0.9)	0.60	<0.001[e]	0.8 (−0.4 to 2.0)	0.43	0.20	0.8 (−0.9 to 2.5)	0.03[d]	0.38
Ischemic heart disease									
No	−2.3 (−3.5 to −1.1)	—	<0.001[e]	0.8 (−0.1 to 1.7)	—	0.08	−0.9 (−2.1 to 0.3)	—	0.13
Yes	−3.7 (−6.3 to −1.1)	0.26	0.005[e]	2.9 (0.8-5.0)	0.05[d]	0.008	0.5 (−2.1 to 3.1)	0.33	0.71
Heart failure									
No	−2.4 (−3.4 to −1.4)	—	<0.001[e]	1.0 (0.3-1.7)	—	0.005[e]	−0.9 (−2.0 to 0.1)	—	0.09
Yes	−2.5 (−4.8 to −0.3)	0.88	0.03	1.5 (−0.3 to 3.2)	0.58	0.11	1.0 (−1.5 to 3.5)	0.13	0.45
Composite cardiovascular indications[c]									
No	−3.2 (−4.7 to −1.7)	—	<0.001[e]	2.1 (1.0-3.2)	—	<0.001[e]	−2.2 (−3.9 to −0.4)	—	0.02
Yes	−1.9 (−3.0 to −0.7)	0.13	0.002[e]	0.4 (−0.5 to 1.2)	0.001[d]	0.38	0.9 (−0.7 to 2.5)	0.002[d]	0.27

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; MAKE, major adverse kidney event.

[a]Models were adjusted for age, sex, intensive care unit admission on index AKI, severe sepsis, baseline eGFR, index AKI KDIGO stage, diabetes mellitus, hyperlipidemia, hypertension, liver cirrhosis, hematological malignancy, solid organ malignancy, ACEi/ARB use before index admission, diuretic use, and nephrotoxic antibiotic use.

[b]Models were adjusted for all except the defined variable of interest.

[c]Diabetes mellitus, hypertension, ischemic heart disease, heart failure, or baseline eGFR <60 mL/min/1.73 m^2.

[d]Significant at a priori threshold of $P_{interaction} < 0.05$ for subgroup analyses and $P < 0.05$ for overall cohort.

[e]Significant at Bonferroni-corrected threshold of $P < 0.00625$ for subgroup analyses.

1.5-4.6; $P_{interaction} = 0.006$; KDIGO 3: 2.9 mL/min/1.73 m^2/month; 95% CI, 0.4-5.4: $P_{interaction} = 0.06$) and in patients without any cardiovascular indication for ACEi/ARB initiation (2.1 mL/min/1.73 m^2/month; 95% CI, 1.0-3.2; $P_{interaction} = 0.001$).

Concerning long-term post-AKI kidney function outcomes (Table 3), we did not observe any significant association of post-AKI use of ACEi/ARB with eGFR decline (−0.8 mL/min/1.73 m^2/year; 95% CI, −2.0 to 0.3; $P = 0.17$) in the overall cohort. While there was a trend toward a nephroprotective effect of post-AKI ACEi/ARB use in a subgroup of patients with KDIGO 2 AKI compared to KDIGO 1 AKI (KDIGO 2: 3.2 mL/min/1.73 m^2/year; 95% CI, −0.1 to 6.4; $P_{interaction} = 0.02$) and a greater eGFR decline in patients without any cardiovascular indication for ACEi/ARB initiation (−2.2 mL/min/1.73 m^2/year; 95% CI, −3.9 to −0.4; $P_{interaction} = 0.002$), the eGFR outcomes in these subgroups were not statistically significant after correction for multiple comparisons.

DISCUSSION

AKI is a risk factor for long-term cardiovascular events and mortality,[7,31-34] even in patients who have kidney function recovery post-AKI.[33,34] Although ACEi/ARBs are one of the leading secondary prevention therapeutic strategies in patients with high cardiovascular risks or coronary artery disease,[35] it is uncertain whether post-AKI use of ACEi/ARB would improve long-term mortality post-AKI. In our study, we observed a novel and significant association of post-AKI use of ACEi/ARB with reduced risk of mortality in patients with KDIGO 3 AKI, a cohort which otherwise experiences the worst adverse outcomes compared to patients with less severe AKI.[31,32] Although one study suggested that ACEi/ARB use was associated with lower risk of post-AKI mortality independent of kidney function recovery,[15,36] the interaction of AKI severity with the effect of post-AKI use of ACEi/ARB on long-term kidney outcomes is poorly understood. Our observed association with lower mortality risk is unlikely to be related to post-AKI kidney function recovery[1,15] or duration of AKI,[37] because we did not observe any significant association of post-AKI use of ACEi/ARB with long-term (>180 days) eGFR decline or MAKE in patients with KDIGO 3 AKI.

Our findings are contrary to previous studies that observed reduced mortality risk in the general cohort of patients with AKI using ACEi/ARBs.[12,13,15] In these studies, there were higher proportions of patients with cardiovascular risk factors (eg, one study had 75.9% of patients with hypertension and 29% with heart failure,[12] whereas another study included patients with diabetic kidney disease[15]) for whom ACEi/ARB would be indicated[35] or included patients admitted to the ICU.[13] Cessation of or intolerance to ACEi/ARB post-AKI in these groups may inadvertently confer worse mortality. In comparison, our study had a relatively lower proportion of patients with hypertension (27.5%), diabetes mellitus (15.4%), heart failure (8.2%), and ischemic heart disease (10.3%). Thus, 2 possible explanations for the discrepancy between our findings and those of previous studies include the cardioprotective effects of ACEi/ARB in patients with severe AKI who have the highest cardiovascular risks and the different cardiovascular risk profiles in our cohort compared with previously studied cohorts. Further studies are warranted to understand how ACEi/ARB use could reduce long-term cardiovascular events and mortality in patients with AKI and to address the heterogeneity of patients with AKI and cardiovascular risk factors.

Concerning long-term post-AKI sequelae, longitudinal data on post-AKI kidney outcomes are lacking. Although AKD[13,14] and progression to end-stage kidney disease[12] have been studied, these clinical endpoints do not characterize post-AKI kidney function trajectories (ie, progression of AKI to AKD and CKD) comprehensively. To our knowledge, our study is the first observational cohort study that addresses this question. Consistent with other studies, we observed significant associations between post-AKI use of ACEi/ARB and increased risk of progression to AKD in patients with KDIGO 2 or 3 AKI or with prior ACEi/ARB use. Unexpectedly, in patients with KDIGO 2 AKI or with prior ACEi/ARB use, a transient and delayed nephroprotective effect was seen in 91-180 days as AKD transitioned to CKD. Similarly, we did not observe any increase in MAKEs in these subgroups. Overall, our findings are more consistent with a large cohort study of higher AKD rates in patients with post-AKI use of ACEi/ARB[13] and differ from those of a smaller cohort study of 345 patients, which observed no increased risk of AKD with ACEi/ARB initiation post-AKI.[38]

Unexpectedly, we observed a significant association of post-AKI use of ACEi/ARB with increased risk of long-term MAKEs in patients without any cardiovascular indication for ACEi/ARB initiation. Although a greater eGFR decline in the first 90 days post-AKI was observed, it was otherwise not related to longer-term eGFR decline. The discrepancy between the analyses of MAKE outcomes and long-term eGFR decline outcomes could be attributed to our study methodology of censoring patients with sustained RRT in our analysis of eGFR decline. Another possibility is that ACEi/ARB use was initiated for cardiovascular disease or proteinuric CKD; hence, patients on ACEi/ARB post-AKI were more predisposed to MAKEs. Overall, our findings are consistent with those of a previous study that reported no association of ACEi/ARB initiation-related eGFR decline with long-term kidney function outcomes.[39] Our study reinforces the need for judicious ACEi/ARB initiation in AKI patients based on cardiovascular indications.

Strengths and Limitations

Strengths of our study include the following: (1) the large sample size of 3,289 patients with a long follow-up time of a median of 4.4 years and (2) the inclusion of quantitative long-term kidney function outcomes post-AKI,

defined by either eGFR decline or a composite outcome of eGFR decline and RRT. Limitations of our study include the following: (1) the use of data on prescription of ACEi/ARB using electronic health records, from which we were unable to ascertain medication compliance; (2) the AKI definition was limited to calculations from sCr, instead of including urine output; (3) the nature of a retrospective observational cohort study, which precludes deriving causality of ACEi/ARB use with mortality and MAKE outcomes; and (4) the lack of randomization of patients to ACEi /ARB post-AKI; hence, the results could be confounded by other indications for which the patients were prescribed ACEi/ARB post-AKI.

We attempted to overcome these limitations by performing inverse propensity of treatment weighting with covariates and accounting for various potential indications for ACEi/ARB use by introducing interaction terms, thus minimizing these confounding effects. Future prospective longitudinal studies are warranted to ascertain our observed association of reduced mortality risks with post-AKI use of ACEi/ARB.

CONCLUSIONS

Post-AKI use of ACEi/ARB was associated with lower long-term mortality in the subgroup of patients with initial AKI of KDIGO 3 severity but more MAKEs in AKI patients without cardiovascular indications for ACEi/ARB initiation. Although post-AKI use of ACEi/ARB was associated with a higher risk of AKD, it was otherwise not related to longer-term eGFR decline. Future studies are warranted to establish the causality of post-AKI use of ACEi/ARB with mortality outcomes and MAKE in these patient subgroups.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: ICD-9-CM and ICD-10-CM Diagnosis and Procedure Codes.

Table S2: List of Medications.

Table S3: Demographics of the AKI Cohort and Weighted on Measured Covariates.

Table S4: Demographics of the Patient Subgroup With AKI Defined by Pre-Admission Serum Creatinine Weighted on Measured Covariates.

Table S5: Demographics of Patients Prescribed ACEi/ARB More Than 180 Days Post-AKI.

Table S6: Baseline Characteristics of the Patient Subgroup With AKI Defined Solely by Pre-Admission Serum Creatinine.

Table S7: Effect of Post-AKI Use of ACEi/ARB on Mortality and MAKE, Without Correction for AKI Recovery Duration.

Table S8: Effect of Post-AKI Use of ACEi/ARB on Mortality and MAKE in a Subgroup of Patients With AKI Defined Solely by Pre-Admission Serum Creatinine.

Table S9: Effect of Post-AKI Use of ACEi/ARB on eGFR Decline, Without Correction for AKI Recovery Duration.

Table S10: Effect of Post-AKI Use of ACEi/ARB on eGFR Decline in a Subgroup of Patients With AKI Defined Solely by Pre-Admission Serum Creatinine.

Figure S1: Cumulative incidence curves of MAKE and mortality in patients without or with pre-AKI use of ACEi/ARB.

Figure S2: Composite outcome of MAKE and mortality in patients without or with pre-AKI use of ACEi/ARB.

Figure S3: Time-dependent hazard ratio of the effect of post-AKI use of ACEi/ARB on MAKE.

Figure S4: Time-dependent hazard ratio of the effect of post-AKI use of ACEi/ARB on the composite outcome of MAKE and mortality.

Figure S5: Time-dependent hazard ratio of the effect of post-AKI use of ACEi/ARB on MAKE, without correction for AKI recovery duration.

Figure S6: Time-dependent hazard ratio of the effect of post-AKI use of ACEi/ARB on the composite outcome of MAKE and mortality without correction for AKI recovery duration.

Figure S7: Cumulative incidence curves of MAKE and mortality in patients without or with pre-AKI use of ACEi/ARB in the subgroup of patients with AKI defined using pre-admission serum creatinine.

Figure S8: MAKE and mortality outcomes in patients with and without post-AKI use of ACEi/ARB, in the subgroup of patients with AKI defined solely by pre-admission serum creatinine.

Figure S9: Composite outcome of MAKE and mortality in patients without or with pre-AKI use of ACEi/ARB, in the subgroup of patients with AKI defined using pre-admission serum creatinine.

Figure S10: Time-dependent hazard ratio of the effect of post-AKI use of ACEi/ARB on MAKE, in the subgroup of patients with AKI defined using pre-admission serum creatinine.

Figure S11: Time-dependent hazard ratio of the effect of post-AKI use of ACEi/ARB on composite outcome of MAKE and mortality, in the subgroup of patients with AKI defined solely by pre-admission serum creatinine.

ARTICLE INFORMATION

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