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# Impact of Different Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blocker Resumption Timing on Post Acute Kidney Injury Outcomes

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**Introduction:** Evidence suggests a survival benefit from resuming angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) post acute kidney injury (AKI) compared to nonuse; however, the optimal timing and its impact on outcomes are unclear. The risks of earlier resumption, such as recurrent AKI or hyperkalemia, remain unexplored.

**Methods:** Using multiinstitutional electronic health records, we analyzed the relationship between 3 ACEI or ARB (ACEI/ARB) resumption timelines post-AKI (prior to discharge, 0–3 months, and 4–6 months postdischarge) and outcomes including all-cause mortality, major adverse cardiac and cerebrovascular events (MACCEs), dialysis initiation or end-stage renal disease (ESRD), severe hyperkalemia, and recurrent AKI with hospitalization. Cox proportional models estimated hazard ratios (HRs) for outcomes across different resumption timings, following a target trial design.

**Results:** Among 5392 AKI survivors resuming ACEI/ARB within 6 months post-AKI, earlier resumption was associated with lower mortality, MACCE, MACCE-related mortality, new dialysis initiation or ESRD ($P < 0.001$ in trend tests), without increased risks of severe hyperkalemia and re-AKI admissions. Early resumption has a lower mortality compared to 4 to 6 months postdischarge (before discharge, HR: 0.88, 95% confidence interval [CI]: 0.83–0.93; 0–3 months, HR: 0.89, 95% CI: 0.85–0.94). Subgroup analysis showed a lower mortality HR from earlier resumption among AKI survivors with prior ACEI/ARB comorbidity indications ($P < 0.001$ in trend tests; before discharge, HR: 0.85, 95% CI: 0.80–0.90; 0–3 months, HR: 0.88, 95% CI: 0.83–0.93).

**Conclusion:** Our cohort demonstrates lower risks for mortality, cardiovascular events, and ESRD with early ACEI/ARB resumption, without heightened risks of severe hyperkalemia or rehospitalization for AKI. Early resumption should be considered for patients with indications for ACEI/ARB.

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AKI, common in hospitalized patients, is linked to significant short-term and long-term mortality and morbidity.[1-3] The renin-angiotensin system blockade using ACEIs or ARBs is essential in treating diabetic kidney disease and cardiovascular disease.[4] It is recommended that ACEI/ARB should be discontinued in patients with AKI, or in those who are at risk of developing AKI.[5,6] However, post-AKI survivors often do not resume, or delay restarting ACEI/ARB because of concerns about recurrent AKI or hyperkalemia, as well as the patient's frailty.[7,8]

Despite the absence of prospective trials, extant evidence suggests that discontinuation of ACEI/ARB post-AKI is associated with adverse outcomes. Brar revealed that about 25% of stable ACEI/ARB users did not resume therapy within 6 months after AKI and this discontinuation was associated with higher mortality.[9] Other cohort studies[10-15] show ACEI/ARB use post-AKI improves survival. However, the timing points for defining ACEI/ARB resumption in these studies varied, ranging from prior to hospital discharge to 2 years postdischarge. Therefore, the optimal timing for

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resuming ACEI/ARB and whether earlier resumption might elevate the risk of recurrent AKI or hyperkalemia have not been fully examined.

We aimed to investigate the association between ACEI/ARB resumption timing after AKI and cardiovascular, renal outcomes, and patient survival. In addition, we aimed to explore the association between early ACEI/ARB resumption and risks of recurrent AKI hospitalization and severe hyperkalemia.

## METHODS

### Data Source

This retrospective cohort study utilized the Chang Gung Research Database (CGRD) from Taiwan's largest health care network, Chang Gung Memorial Hospital System, accounting for 21.2% of outpatient and 12.4% of inpatient services in Taiwan. The CGRD offers extensive clinical details, including laboratory results and hemodynamic data than claims databases and has high overall coverage of the Taiwanese population.[16–18] This study received approval from the Chang Gung Memorial Hospitals' institutional review board (IRB No. 201900835B0). Individual consent was waived because personal identification data were not included. The STROBE checklist is provided in Supplementary Table S1.

### Study Population

We used a target trial design to emulate a randomized controlled trial with routinely collected healthy electronic records[19–21] (Supplementary Table S2). Adult patients aged 20 years and older, who did not undergo dialysis or without ESRD, who had been prescribed ACEI/ARB medications prior to their index admission and subsequently developed AKI during hospitalization between January 1, 2001, and December 31, 2019, were identified. The initial AKI episode identified during hospitalization was assigned as the index AKI admission if a patient suffered from twice or more AKI events. We assessed the association between ACEI/ARB resumption timing and outcomes in patients who stopped ACEI/ARB during their initial AKI admission and resumed it just before discharge or within 6 months after discharge (Figure 1).

Exclusion criteria included a history of cancer, organ transplant, in-hospital death during index AKI, or loss to follow-up post discharge. Patients with systolic blood pressure $<$ 100 mm Hg before discharge or new ACEI/ARB users ($<$ 1-month preadmission) were also excluded, though the latter were included in sensitivity analyses. Following ACEI/ARB resumption, an as-started analysis was conducted to mimic a target trial despite potential discontinuation due to disease progression or hyperkalemia.[20]

### Baseline Renal Function and AKI Definition

Baseline renal function was defined utilizing the lowest outpatient creatinine level recorded within a span of 7 to 365 days prior to the index AKI admission. In the absence of a creatinine value within this specified

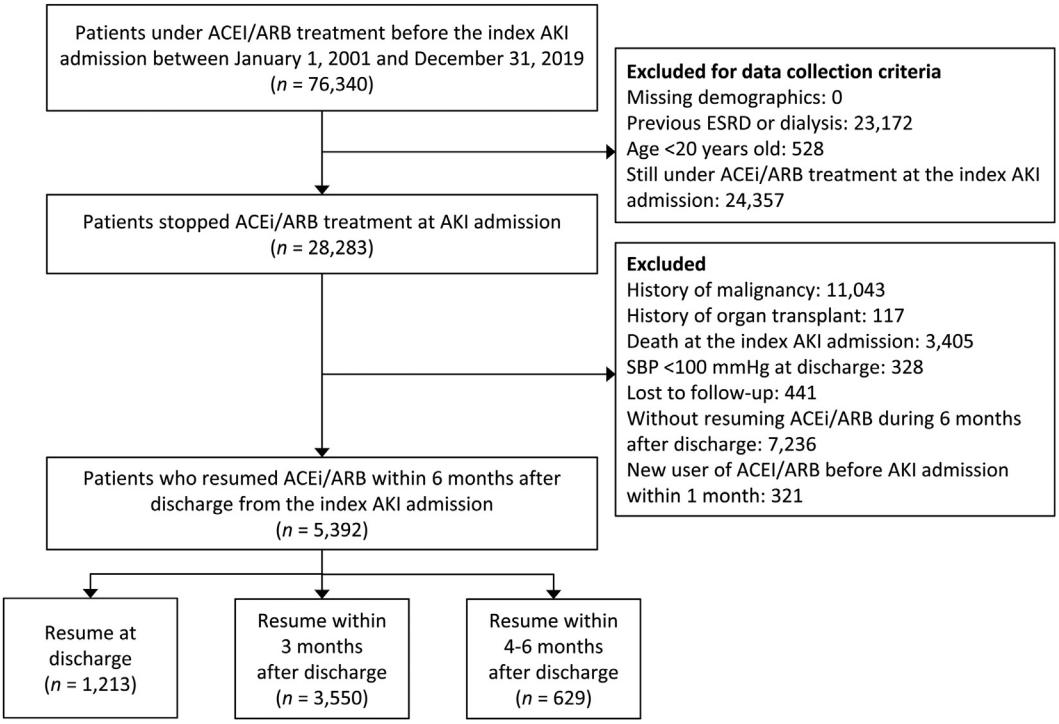


**Figure 1.** Flow diagram for the inclusion and exclusion of study patients. ACEI, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease.

timeframe, the lowest creatinine value within 7 days preceding the AKI admission, followed by the first creatinine value recorded during the index AKI admission, was adopted as the baseline creatinine value.[22] The baseline estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[23] The presence and stage classification of AKI were defined according to Kidney Disease: Improving Global Outcomes AKI criteria.[24]

## Assessment of Covariates

Baseline characteristics, including demographics, smoking status, body mass index, recent blood pressure, and laboratory values (eGFR, proteinuria, cholesterol, high-density lipoprotein, low-density lipoprotein, and mean hemoglobin) were collected. Baseline proteinuria and lipid profiles were taken from the most recent value in the past 2 years, with mean hemoglobin over past 2 years was used. Comorbidities (hypertension, diabetes mellitus [DM], coronary artery disease, peripheral arterial disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, atrial fibrillation, and liver cirrhosis) were defined using diagnostic codes (with at least 2 outpatient diagnoses or at least 1 inpatient diagnosis before the index AKI admission). Baseline cardiorenal medications and primary index AKI diagnoses were noted (Table 1). We also assessed AKI severity, first in-hospital laboratory results, ventilator and inotrope use, intensive care unit stays, hospitalization duration, and predischarge blood pressure and renal function, with details in Supplementary Tables S3 and S4.

## Exposure and Outcome Measurement

Published studies have employed various time points, such as prior hospital discharge, after discharge but within 1 month,[10] within 3 months,[12] and within 6 months,[9] to compare the effect of ACEI/ARB resumption after AKI to those without resumption following AKI. Presently, acute kidney disease guidelines utilize a 3-month period as the definitive time cutoff for determining post-AKI renal function status.[25] Therefore, in this study, we defined exposure as the different timing of ACEI/ARB resumption after AKI, categorizing participants into 3 groups as follows: (i) resumption prior to discharge (initial ACEI/ARB prescription within 2 days of discharge), (ii) within 3 months (resumption after discharge to 90 days), and (iii) between 4 and 6 months (resumption after 91 days to 6 months from discharge).

The outcome of primary interest is all-cause mortality. Outcomes of secondary interest encompassed MACCE (composite 3-point major cardiovascular events outcome [3P-major adverse cardiac event, including cardiovascular death, admission with nonfatal myocardial infarction, or admission with nonfatal stroke]), the onset of dialysis or the evolution to ESRD, cardiovascular-related mortality (Supplementary Tables S3 and S5). Information regarding the date and cause of death were cross-referenced with the Taiwan Death Registry database, which is also available in the CGRD. The safety of earlier resumption of ACEI/ARB was evaluated by severe hyperkalemia (any serum potassium $\geq$ 6.5 meq/dl)[26] and recurrent AKI admission (Supplementary Table S5). The index date is defined as day 1 postdischarge for participants who resumed ACEI/ARB prior to discharge, and the day following resumption for participants who resumed ACEI/ARB after discharge. Participants were followed-up with from the index date until the day of outcome occurrence, death, or the end of database (December 31, 2019).

## Statistical Analysis

All noted baseline discrepancies in all covariates, baseline medication, severity of AKI, and admission diagnosis (Table 1) across the 3 groups (resumption of ACEI/ARB before discharge, after discharge but within 3 months postdischarge, or between 4 to 6 months postdischarge) were balanced utilizing the inverse probability treatment weighting (IPTW) with average treatment effect based on propensity score. The propensity score was estimated using the generalized boosted modeling with 10,000 trees.[27] The equilibrium of covariates among the 3 groups before and after IPTW was assessed by the maximum absolute standardized difference, where a maximum absolute standardized difference exceeding 0.2 indicates a substantial imbalance between groups.[27] Because there were missing values, single expectation maximization imputation was employed before conducting IPTW.

The analyses regarding outcome comparisons between the study groups were made in the IPTW-adjusted and -imputed cohort. The risks associated with outcomes involving fatal events (i.e., MACCE, cardiovascular death, and all-cause death) were compared among the study groups using the Cox proportional hazard model. The incidences of other outcomes (i.e., new dialysis, hyperkalemia, and recurrent AKI admission) were compared between the study groups using the Fine and Gray subdistribution hazard model, accounting for all-cause death as a competing risk. Using the group that resumed ACEI/ARB 4 to 6 months postdischarge as the reference category, the HRs and CI of the other 2 study groups were obtained. In an alternative model, the timing of resuming AECI/ARB was treated as an ordinal variable and the

**Table 1.** Demographic and clinical characteristics before GBM-IPTW and EM imputation

| Variable | Available numbers | Total ($n$ = 5392) | Discharge resumed ($n$ = 1213) | 0–3 mo resumed ($n$ = 3550) | 4–6 mo resumed ($n$ = 629) | MASD |
|---|---|---|---|---|---|---|
| Age, yr | 5392 | 70.1 ± 13.8 | 70.2 ± 13.9 | 70.3 ± 13.6 | 69.2 ± 14.6 | 0.08 |
| Age group | 5392 | | | | | 0.02 |
| 20–65 yrs | | 1751 (32.5) | 402 (33.1) | 1146 (32.3) | 203 (32.3) | |
| > 65 yrs | | 3641 (67.5) | 811 (66.9) | 2404 (67.7) | 426 (67.7) | |
| Male | 5392 | 2703 (50.1) | 589 (48.6) | 1775 (50.0) | 339 (53.9) | 0.11 |
| Smoking | 5392 | 1144 (21.2) | 262 (21.6) | 750 (21.1) | 132 (21.0) | 0.02 |
| BMI, kg/m$^2$ | 5136 | 24.8 ± 5.1 | 25.0 ± 4.8 | 24.8 ± 5.3 | 24.2 ± 4.9 | 0.14 |
| Baseline laboratory data | | | | | | |
| eGFR, ml/min per 1.73 m$^2$ | 5149 | 76.5 ± 32.6 | 77.0 ± 32.0 | 76.2 ± 32.3 | 77.5 ± 35.3 | 0.02 |
| Proteinuria | 5392 | | | | | 0.02 |
| Negative | | 1600 (29.7) | 360 (29.7) | 1059 (29.8) | 181 (28.8) | |
| Trace | | 546 (10.1) | 107 (8.8) | 366 (10.3) | 73 (11.6) | |
| 1+ | | 653 (12.1) | 118 (9.7) | 450 (12.7) | 85 (13.5) | |
| 2+ | | 727 (13.5) | 167 (13.8) | 485 (13.7) | 75 (11.9) | |
| 3+ | | 594 (11.0) | 141 (11.6) | 367 (10.3) | 86 (13.7) | |
| 4+ | | 179 (3.3) | 53 (4.4) | 100 (2.8) | 26 (4.1) | |
| Unknown | | 1093 (20.3) | 267 (22.0) | 723 (20.4) | 103 (16.4) | |
| LDL, mg/dl | 3955 | 103.0 ± 46.6 | 104.1 ± 48.1 | 102.4 ± 45.7 | 103.6 ± 48.2 | 0.04 |
| HDL, mg/dl | 3869 | 44.2 ± 14.3 | 43.4 ± 13.7 | 44.6 ± 14.5 | 43.3 ± 14.7 | 0.07 |
| Total cholesterol, mg/dl | 4236 | 175.7 ± 50.4 | 176.0 ± 50.2 | 175.2 ± 49.7 | 178.0 ± 54.8 | 0.05 |
| Mean of baseline hemoglobin, g/dl | 4843 | 11.5 ± 2.0 | 11.5 ± 2.0 | 11.6 ± 2.0 | 11.4 ± 2.0 | 0.09 |
| Comorbidity | | | | | | |
| Hypertension | 5392 | 4848 (89.9) | 1099 (90.6) | 3195 (90.0) | 554 (88.1) | 0.08 |
| Diabetes mellitus | 5392 | 3355 (62.2) | 786 (64.8) | 2188 (61.6) | 381 (60.6) | 0.09 |
| Coronary artery disease | 5392 | 1864 (34.6) | 445 (36.7) | 1,212 (34.1) | 207 (32.9) | 0.08 |
| Peripheral arterial disease | 5392 | 580 (10.8) | 140 (11.5) | 368 (10.4) | 72 (11.4) | 0.04 |
| Cerebrovascular disease | 5392 | 1,155 (21.4) | 258 (21.3) | 761 (21.4) | 136 (21.6) | 0.01 |
| Heart failure | 5392 | 935 (17.3) | 234 (19.3) | 603 (17.0) | 98 (15.6) | 0.10 |
| Chronic obstructive pulmonary disease | 5392 | 1,254 (23.3) | 262 (21.6) | 853 (24.0) | 139 (22.1) | 0.06 |
| Atrial fibrillation | 5392 | 804 (14.9) | 191 (15.7) | 527 (14.8) | 86 (13.7) | 0.06 |
| Liver cirrhosis | 5392 | 311 (5.8) | 60 (4.9) | 227 (6.4) | 24 (3.8) | 0.11 |
| Prior admission times 1 yr before AKI | 5392 | 1.06 ± 1.27 | 1.02 ± 1.21 | 1.04 ± 1.25 | 1.26 ± 1.44 | 0.19 |
| Prior OPD times 1 yr before AKI | 5392 | 14.0 ± 10.0 | 13.6 ± 9.7 | 14.1 ± 10.0 | 14.6 ± 10.7 | 0.11 |
| Baseline medication | | | | | | |
| MRAs/spironolactone | 5392 | 835 (15.5) | 179 (14.8) | 540 (15.2) | 116 (18.4) | 0.10 |
| Loop diuretics | 5392 | 2376 (44.1) | 540 (44.5) | 1527 (43.0) | 309 (49.1) | 0.12 |
| Thiazide | 5392 | 746 (13.8) | 153 (12.6) | 485 (13.7) | 108 (17.2) | 0.13 |
| Statin | 5392 | 2285 (42.4) | 507 (41.8) | 1537 (43.3) | 241 (38.3) | 0.10 |
| Beta-blockers | 5392 | 1848 (34.3) | 440 (36.3) | 1200 (33.8) | 208 (33.1) | 0.07 |
| CCBs | 5392 | 3041 (56.4) | 687 (56.6) | 1967 (55.4) | 387 (61.5) | 0.12 |
| Aspirin | 5392 | 2420 (44.9) | 554 (45.7) | 1595 (44.9) | 271 (43.1) | 0.05 |
| Clopidogrel | 5392 | 1006 (18.7) | 234 (19.3) | 663 (18.7) | 109 (17.3) | 0.05 |
| Severity of index AKI admission | | | | | | |
| AKI stage | 5392 | | | | | 0.25 |
| 1 | | 2619 (48.6) | 668 (55.1) | 1683 (47.4) | 268 (42.6) | |
| 2 | | 1384 (25.7) | 284 (23.4) | 923 (26.0) | 177 (28.1) | |
| 3 | | 819 (15.2) | 160 (13.2) | 561 (15.8) | 98 (15.6) | |
| D-AKI | | 570 (10.6) | 101 (8.3) | 383 (10.8) | 86 (13.7) | |
| Sodium, mg/dl | 5195 | 135.9 ± 6.5 | 136.1 ± 6.2 | 135.8 ± 6.7 | 136.1 ± 6.5 | 0.05 |
| Potassium, mg/dl | 5224 | 4.3 ± 0.9 | 4.2 ± 0.9 | 4.3 ± 0.9 | 4.2 ± 0.9 | 0.09 |
| Albumin, g/dl | 2923 | 3.2 ± 0.7 | 3.2 ± 0.7 | 3.2 ± 0.7 | 3.1 ± 0.7 | 0.18 |
| Hemoglobin, g/dl | 5199 | 11.1 ± 2.5 | 11.1 ± 2.5 | 11.1 ± 2.5 | 11.0 ± 2.6 | 0.03 |
| Hospitalization days | 5392 | 12 (8, 19) | 10 (7, 15) | 12 (8, 20) | 15 (9, 26) | 0.56 |
| ICU admission | 5392 | 1007 (18.7) | 200 (16.5) | 669 (18.8) | 138 (21.9) | 0.14 |
| Ventilator | 5392 | 629 (11.7) | 107 (8.8) | 426 (12.0) | 96 (15.3) | 0.20 |
| Inotropic agents | 5392 | 636 (11.8) | 108 (8.9) | 454 (12.8) | 74 (11.8) | 0.12 |

*(Continued on following page)*

**Table 1.** (Continued) Demographic and clinical characteristics before GBM-IPTW and EM imputation

| Variable | Available numbers | Total ($n$ = 5392) | Discharge resumed ($n$ = 1213) | 0–3 mo resumed ($n$ = 3550) | 4–6 mo resumed ($n$ = 629) | MASD |
|---|---|---|---|---|---|---|
| Vital sign | | | | | | |
| SBP before AKI, mm Hg | 4045 | 138.0 ± 24.9 | 138.7 ± 24.2 | 137.3 ± 24.7 | 140.7 ± 27.4 | 0.12 |
| DBP before AKI, mm Hg | 4044 | 74.7 ± 13.9 | 74.4 ± 13.9 | 74.4 ± 13.6 | 77.1 ± 15.1 | 0.20 |
| SBP at AKI discharge, mm Hg | 5090 | 135.7 ± 19.1 | 137.3 ± 20.4 | 135.3 ± 18.6 | 135.2 ± 18.9 | 0.11 |
| DBP at AKI discharge, mm Hg | 5090 | 75.8 ± 12.0 | 75.4 ± 12.2 | 75.8 ± 12.0 | 76.1 ± 11.6 | 0.06 |
| Pre-discharge SCr, mg/dl[a] | 4976 | 1.11 (0.78–1.74) | 1.10 (0.80–1.71) | 1.11 (0.78–1.71) | 1.10 (0.72–2.00) | 0.13 |
| Pre-discharge eGFR, ml/min per 1.73 $m^2$[a] | 4976 | 66.4 (38.4–92.3) | 67.0 (39.9–91.3) | 65.9 (39.1–92.2) | 67.7 (33.1–94.2) | 0.04 |
| Primary diagnosis of index AKI admission | 5392 | | | | | 0.11 |
| Cardiac surgery (1) | | 94 (1.7) | 13 (1.1) | 65 (1.8) | 16 (2.5) | |
| Major noncardiac surgery (2) | | 738 (13.7) | 135 (11.1) | 507 (14.3) | 96 (15.3) | |
| Coronary artery disease (3) | | 184 (3.4) | 50 (4.1) | 101 (2.8) | 33 (5.2) | |
| Cerebrovascular accident (4) | | 112 (2.1) | 30 (2.5) | 70 (2.0) | 12 (1.9) | |
| Congestive heart failure (5) | | 224 (4.2) | 83 (6.8) | 114 (3.2) | 27 (4.3) | |
| Cardiac arrhythmia (6) | | 90 (1.7) | 39 (3.2) | 44 (1.2) | 7 (1.1) | |
| Acute pulmonary edema (7) | | 27 (0.5) | 8 (0.7) | 16 (0.5) | 3 (0.5) | |
| Sepsis or severe infection (8) | | 1512 (28.0) | 311 (25.6) | 1045 (29.4) | 156 (24.8) | |
| Gastrointestinal bleeding (9) | | 189 (3.5) | 43 (3.5) | 129 (3.6) | 17 (2.7) | |
| Cirrhosis and related complication (10) | | 45 (0.8) | 9 (0.7) | 32 (0.9) | 4 (0.6) | |
| Renal (CKD, AKI or electrolyte imbalance) (11) | | 619 (11.5) | 128 (10.6) | 427 (12.0) | 64 (10.2) | |
| Diabetes mellitus and related complication (12) | | 309 (5.7) | 72 (5.9) | 192 (5.4) | 45 (7.2) | |
| Respiratory failure (13) | | 133 (2.5) | 20 (1.6) | 98 (2.8) | 15 (2.4) | |
| Others (14) | | 1116 (20.7) | 272 (22.4) | 710 (20.0) | 134 (21.3) | |
| SCr at resumed ACEI/ARB, mg/dl[b] | 2063 | 1.38 (0.90–2.56) | 1.40 (1.00–2.22) | 1.39 (0.90–2.52) | 1.30 (0.80–3.20) | 0.19 |
| eGFR at resumed ACEI/ARB, mL/min/1.73$m^2$[b] | 2063 | 50.9 (24.9–84.7) | 50.5 (28.7–78.4) | 50.5 (24.9–84.0) | 52.4 (19.6–90.8) | 0.06 |
| Mean follow up yrs | 5392 | 2.5 (0.9–5.3) | 2.8 (1.1–5.5) | 2.4 (0.9–5.4) | 3.3 (2.2–0.8) | 0.12 |

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; CCBs, calcium channel blockers; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; GBM, generalized boosted modeling; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; LDL, low-density lipoprotein; MASD, maximum absolute standardized difference; MRAs, mineralocorticoid receptor antagonists; OPD, outpatient department; SBP, systolic blood pressure; SCr, serum creatinine.
[a]Did not include patients who were still under dialysis treatment at discharge.
[b]Did not include patients who were under dialysis treatment at resumed ACEI/ARBs point.
Data were presented as frequency (percentage), mean ± SD or median (25th–75th percentiles).

significance of linear trend was obtained. Additional sensitivity analysis was performed by incorporating participants who were initially prescribed within 1 month prior to the index AKI admission.

Subgroup analyses for outcomes such as MACCE, all-cause mortality, and new dialysis or ESRD were performed, stratifying patients by ACEI/ARB-certain comorbidities indication and DM. The certain comorbidities indication for ACEI/ARB was determined by any of underlying conditions such as DM, coronary artery disease, congestive heart failure, or chronic kidney disease (defined by baseline eGFR $<$ 60 or proteinuria) (Supplementary Table S3). Additional subgroup analysis was undertaken by stratifying patients based on the available eGFR at the time of ACEI/ARB resumption. Participants were categorized into 2 subgroups according to their eGFR at the timing of ACEI/ARB resumption (eGFR $\geq$ 30 or $<$ 30 ml/min per 1.73 $m^2$). The most recent creatinine value, obtained within 1 week before the deprescription of ACEI/ARB post-AKI, was employed to calculate the eGFR at the time of ACEI/ARB resumption. A 2-sided $P$ value $<$ 0.5 was considered as statistical significance. Statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Patient Inclusion

A total of 28,283 adult patients under ACEI/ARB treatment, admitted to Chang Gung Memorial Hospitals between January 1, 2001, and December 31, 2019, were identified as having been diagnosed with AKI for the first time, and had discontinued ACEI/ARB usage during their admission. After excluding participants based on set criteria (Figure 1), a total of 5392 individuals were included in the study.

### Patient Characteristics

Baseline demographic characteristics are provided (Table 1 and Supplementary Table S6). Prior to IPTW adjustment, participants who delayed ACEI/ARB resumption exhibited higher AKI severity and longer hospitalization durations. Post-IPTW adjustment, no significant differences were observed. Among the 5392 participants, the mean age was 70.1 years, with males constituting 50.1% of the cohort. Hypertension was

the most prevalent underlying disease (89.9%), followed by DM (62.2%), and coronary artery disease (34.6%). Beyond ACEI/ARB, calcium channel blockers and loop diuretics were the most commonly administered antihypertensive medications. The median duration of follow-up was 2.5 years after AKI.

### Effect of Timing of ACEI/ARB Resumption

Earlier resumption of ACEI/ARB was associated with a lower risk for MACCE ($P$ value of trend test $< 0.001$, Figure 2a), new-onset dialysis or ESRD ($P$ value of trend test $< 0.001$, Figure 2b), cardiovascular death ($P$ value of trend test $= 0.001$, Figure 2c), and all-cause mortality ($P$ value of trend test $< 0.001$, Figure 2d). No significant difference was observed regarding severe hyperkalemia and re-AKI admission in relation to the timing of ACEI/ARB resumption (Figure 2e and f).

Regarding the pairwise analysis, compared to the resumption of ACEI/ARB 4 to 6 months postdischarge, resumption before discharge was associated with a lower risk for MACCE (HR: 0.84, 95% CI: 0.78–0.90), new-onset dialysis or ESRD (HR: 0.63, 95% CI: 0.57–0.70), cardiovascular death (HR: 0.85, 95% CI: 0.77–0.94), and all-cause mortality (HR: 0.88, 95% CI: 0.83–0.93). Similarly, compared to the resumption of ACEI/ARB 4 to 6 months postdischarge, resumption 0 to 3 months postdischarge was associated with a lower HR for MACCE (HR: 0.88, 95% CI: 0.82–0.94), new-onset dialysis or ESRD (HR: 0.80, 95% CI: 0.74–0.88), cardiovascular death (HR: 0.81, 95% CI: 0.74–0.90), and all-cause mortality (HR: 0.89, 95% CI: 0.85–0.94) (Table 2). No significant difference in the risk for severe hyperkalemia and re-AKI admission was noted among the 3 groups.

### Sensitivity Analysis

We carried out a sensitivity analysis that included participants who became new ACEI/ARB users within 1 month prior to AKI admission. Upon incorporating these new users, compared to a more delayed reinitiation of ACEI/ARB, an earlier resumption of ACEI/ARB was still associated with a lower HR for new-onset dialysis or ESRD ($P$ value of trend test $< 0.001$) (Supplementary Table S7).

### Subgroup Analyses

Subgroup analyses stratified participants by ACEI/ARB indications. For those with such indications, earlier ACEI/ARB resumption versus 4 to 6 months postdischarge was associated with lower HR for MACCE, new-onset dialysis or ESRD, and all-cause mortality (trend test $P < 0.001$) (Supplementary Table S8). Diabetic participants with earlier ACEI/ARB resumption were also associated with lower HR for the primary outcome (Supplementary Table S8).

A further subgroup analysis was conducted, stratifying participants by eGFR at the time of ACEI/ARB resumption. Participants with eGFR $<$ 30 ml/min per 1.73 $m^2$ had a lower HR for new-onset dialysis or ESRD in the earlier resumption groups ($P$ value for trend test: 0.032). Participants with eGFR $\geq$ 30 ml/min per 1.73 $m^2$ had a lower HR for all-cause mortality ($P$ value for trend test $< 0.001$). For severe hyperkalemia, a higher HR was observed ($P$ value for trend test $< 0.001$) in participants with eGFR $\geq$ 30 ml/min per 1.73 $m^2$ at the time of resumption but not in participants with eGFR $<$ 30 ml/min per 1.73 $m^2$. No significant linear association was noted in the 2 eGFR subgroups concerning re-AKI admission, ACEI/ARB resumption, MACCE, and cardiovascular death (Supplementary Table S9).

### Timing of ACEI/ARB Resumption and eGFR Decline

Figure 3 reveals that during the 3-year follow up period, earlier resumption ACEI/ARB before discharge has a slower eGFR decline slope compared with resumption within 4 to 6 months after discharge.

## DISCUSSION

Our study highlights the following 4 key findings: (i) early ACEI/ARB resumption post-AKI was associated with reduced HR for MACCE, new dialysis or ESRD, and mortality without increased HR for severe hyperkalemia and recurrent AKI admission; (ii) in participants with prior ACEI/ARB indication, earlier resumption was associated with lower HR for mortality, cardiovascular event, and dialysis; (iii) participants with eGFR $<$ 30 ml/min per 1.73 $m^2$ was associated with reduced HR for dialysis or ESRD with early resumption.

Our analysis disclosed that earlier ACEI/ARB resumption correlated with lower HR for mortality, renal adverse events, and cardiovascular incidents. To our best awareness, this study pioneers in examining the relationship between different resumption timings post-AKI and cardiovascular, renal outcomes among stable ACEI/ARB users. Although the existing literature (refer to Supplementary Table S10 for a summary of major outcomes and participant enrollment from these studies) emphasizes mortality and shows that post-AKI ACEI/ARB users have a lower mortality risk compared to nonusers,[9-15,28,29] our research elaborates on these findings by including cardiovascular and renal outcomes. Our findings, in agreement with Murphy *et al.*,[13] demonstrate that earlier resumption of ACEI/ARB not only aligns with a lower HR for mortality but

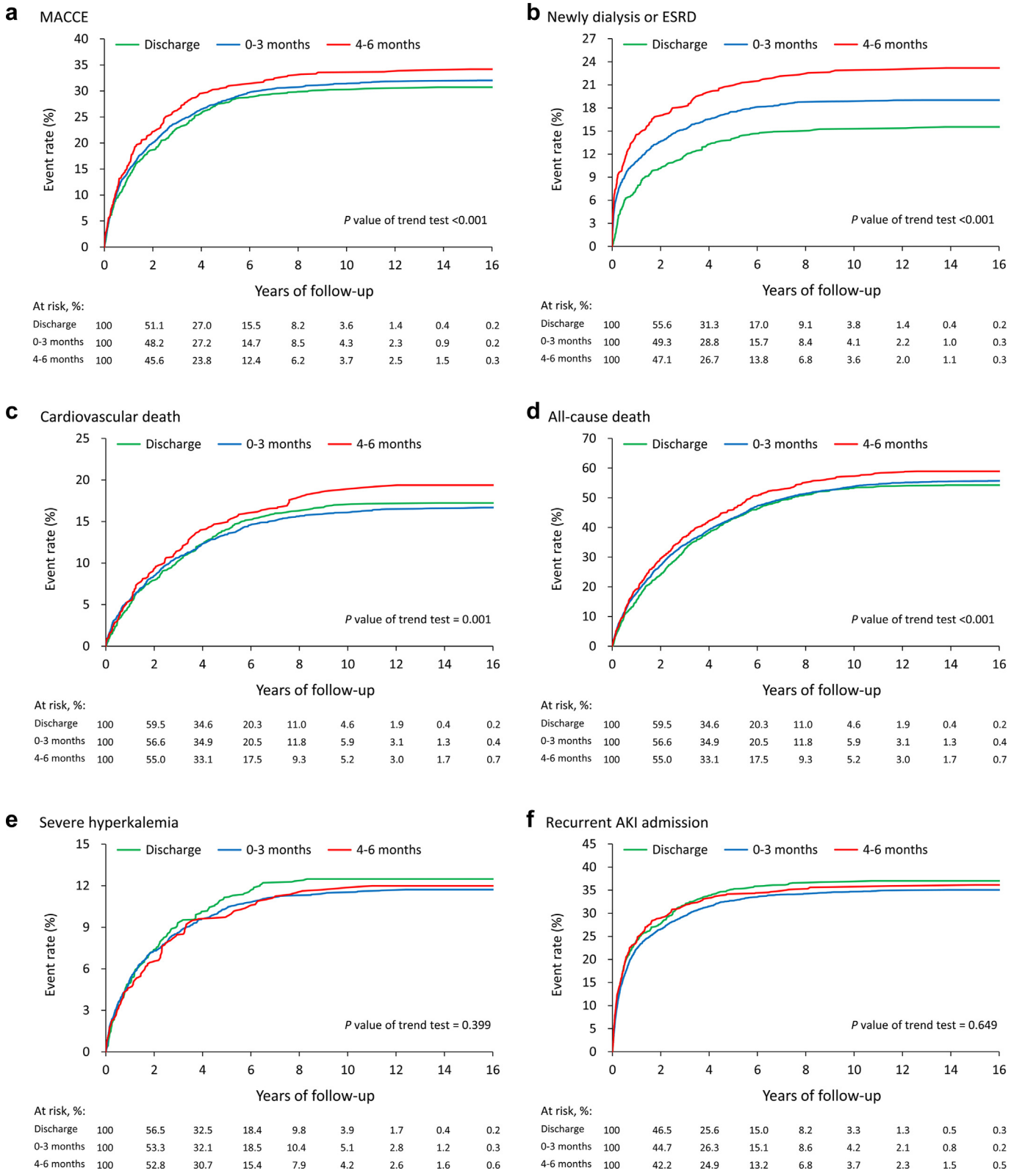


**Figure 2.** Cumulative event rates by timing of ACEI/ARB resumption: (a) MACCE, (b) new dialysis/ESRD, (c) cardiovascular death, (d) all-cause mortality, (e) severe hyperkalemia, (f) recurrent AKI admission. ACEI, angiotensin- converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events.

also associates with reduced HR for MACCE, new-onset dialysis or ESRD, and MACCE-related mortality, particularly in those indicated for ACEI/ARB.

Concerning the reinitiation of ACEI/ARB in participants with lower eGFR and the associated risks of recurrent AKI and hyperkalemia, our subgroup

**Table 2.** Follow-up outcomes after resumption of ACEI/ARB

| Outcomes | Event and event rate before GBM-IPTW[a] | | | Event rate after GBM-IPTW | | | Hazard ratio (95% CI) after GBM-IPTW | | |
|---|---|---|---|---|---|---|---|---|---|
| | Discharge resumed ($n$ = 1213) | 0–3 mo resumed ($n$ = 3550) | 4–6 mo resumed ($n$ = 629) | Discharge resumed ($n$ = 4567.0) | 0-3 mo resumed ($n$ = 5214.2) | 4-6 mo resumed ($n$ = 4410.8) | Discharge vs. 4–6 mo | 0-3 mo vs. 4–6 mo | $P$ value of trend test |
| MACCE[b] | 397 (32.7) | 1,122 (31.6) | 212 (33.7) | 30.7% | 32.0% | 34.2% | 0.84 (0.78–0.90) | 0.88 (0.82–0.94) | <0.001 |
| Newly dialysis or ESRD[c] | 174 (15.4) | 655 (18.8) | 159 (26.1) | 15.5% | 19.0% | 23.2% | 0.63 (0.57–0.70) | 0.80 (0.74–0.88) | <0.001 |
| Cardiovascular death | 227 (18.7) | 586 (16.5) | 121 (19.2) | 17.2% | 16.7% | 19.4% | 0.85 (0.77–0.94) | 0.81 (0.74–0.90) | 0.001 |
| All-cause death | 659 (54.3) | 1,980 (55.8) | 386 (61.4) | 54.3% | 55.8% | 58.9% | 0.88 (0.83–0.93) | 0.89 (0.85–0.94) | <0.001 |
| Severe hyperkalemia[d] | 143 (11.8) | 417 (11.7) | 88 (14.0) | 12.5% | 11.7% | 12.0% | 1.05 (0.94–1.18) | 0.98 (0.87–1.10) | 0.399 |
| Re-AKI admission[c] | 418 (36.9) | 1,225 (35.2) | 226 (37.0) | 36.9% | 35.1% | 36.1% | 1.02 (0.95–1.09) | 0.95 (0.89–1.02) | 0.649 |

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CI, confidence interval; ESRD, end-stage renal disease; GBM, generalized boosted modeling; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events.
[a]Data are presented as frequency (percentage).
[b]Any out of cardiovascular related death, acute myocardial infarction, and stroke.
[c]Patients who did not under dialysis when resumed ACEI/ARB were eligible for analysis.
[d]Potassium levels higher than 6.5 mg/dl.

analysis based on eGFR values at ACEI/ARB resumption time, disclosed that earlier resumption among participants with eGFR $<$ 30 ml/min per 1.73 $m^2$ did not correspond with higher risks for severe hyperkalemia and re-AKI admission. Hsu *et al.*[30] found no increased recurrent AKI risk with new ACEI/ARB use in those without congestive heart failure. Our data suggest that in patients with eGFR $<$ 30 ml/min per 1.73 $m^2$, resuming ACEI/ARB earlier is linked to reduced HR of primary outcome but not increased HR for severe hyperkalemia or re-AKI admission. This indicates that, under close monitoring, early ACEI/ARB resumption might be feasible in hemodynamically stable patients with moderate to severe impaired renal function. Compared to the STOP ACEi trial cohort, which had a mean age of 63 years and over 60% of participants without DM, our participants were relatively older and had a higher prevalence of diabetes. In the STOP ACEi trial, discontinuation of renin-angiotensin system inhibitors did not affect the decline in glomerular filtration rate.[31] In addition, *post hoc* analysis showed that continuation of ACEI, but not ARB, was associated with a lower risk for end-stage kidney disease, although the power was insufficient and the conclusion might be due to chance.[32]

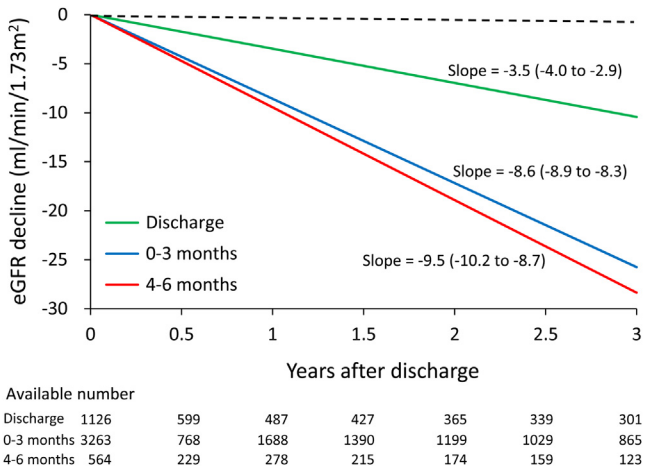


**Figure 3.** eGFR decline and slope after ACEI/ARB resumption in the IPTW-adjusted cohort. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting. The slope of eGFR decline during 3-year follow-up after discharge day from the index AKI admission in each study group were estimated using the linear mixed model which treated participants as random effect.

The strengths of our study are manifold. This study is among the first to examine how the timing of ACEI/ARB resumption after AKI affects the onset of MACCE, new dialysis or ESRD, along with the risks of severe hyperkalemia and re-AKI admission. Furthermore, we investigated whether patients needing ACEI/ARB gain more from early resumption after AKI, and examined the risks of severe hyperkalemia and recurrent AKI in patients with reduced eGFR a new perspective in post-AKI cases, already explored in stable chronic kidney disease groups.[31,33] Contrary to the study by Murphy *et al.*,[13] our research encompasses a broader participant spectrum, featuring a nearly balanced male-to-female ratio, and includes participants both with and without prior indications for ACEI/ARB, while integrating the admission diagnosis of index AKI admission into the analysis.

Our study has limitations. It is based on CGRD data from older patients (average age 70.1 years), with more comorbidities and severe conditions (20% intensive care unit admissions), so results may not apply to younger, healthier patients. Moreover, our study

design and cohort selection were driven by our hypothesis. The older age, higher prevalence of comorbidities, and single-country patient population in our cohort limit the generalizability of our results. In addition, our conclusions might not be applicable to other countries or different ethnic groups. Moreover, ACEI/ARB prescriptions outside CGRD were not considered. Immortal bias in delayed resumption groups could impact results, but not their direction. Nearly half the participants lacked follow-up eGFR values, possibly indicating sicker individuals or those under nephrology care. The impact of early ACEI/ARB resumption on severe hyperkalemia risk in healthier patients without eGFR data needs further study. Due to the observational nature of the study, residual or unmeasured confounding may still be present, even though IPTW was applied using a comprehensive set of covariates. In addition, frailty indices such as the Clinical Frailty Scale or Study of Osteoporotic Fractures were not included in the CGRD; thus, we could not analyze frailty in the included participants.

### Conclusion

Our study fills a knowledge gap about when to resume ACEI/ARB after AKI. We found high rates of dialysis, ESRD, and cardiovascular events post-AKI, highlighting the need for better post-AKI care. Early ACEI/ARB resumption during acute kidney disease stage linked to lower HR of mortality, new dialysis, ESRD, and cardiovascular events. Future large-scale trials should investigate ACEI/ARB's protective effects post-AKI and identify patients who could benefit from early resumption.

## DISCLOSURE

All the authors declared no competing interests.

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## DATA AVAILAIBILITY STATEMENT

Data cannot be directly shared publicly because of the regulation of Chang Gung Research Database policy. The data are provided, maintained, and managed by the Chang Gung Medical Foundation. Researchers interested in accessing this data set can submit a formal application to request access (Chang Gung Memorial Hospital, No. 5, Fuxing St., Guishan Dist., Taoyuan City 33305, Taiwan; E-mail: ccling999@gmail.com, +886-03-328120-7721).

## AUTHOR CONTRIBUTIONS

Concept and design were by C-HC and J-JC. Acquisition, analysis, or interpretation of data was by J-JC, C-CL, C-LY, and P-CF. Drafting of the manuscript was by J-JC and M-JC. Critical revision of the manuscript was by T-YT, Y-CC, and C-WY. Editing and table formation was by J-JC and M-JC. Statistical analysis was done by T-YT and M-JC. Supervision and funding were by C-HC, Y-CC, and C-WY.

## SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

**Table S1.** STROBE checklist.

**Table S2.** Specification and emulation of a target trial evaluating the effect of timing of ACEI/ARB resumption on hazards of outcomes using real-world data from CGRD.

**Table S3.** ICD codes for diseases mentioned in this study.

**Table S4.** Admission diagnosis classification.

**Table S5.** Outcomes and procedures definition.

**Table S6.** Demographic and clinical characteristics of patients after GBM-IPTW and EM imputation.

**Table S7.** Follow-up outcomes of patients with difference resumption timings for ACEI/ARB in the GBM-IPTW adjusted cohort, including patients who were newly prescribed with ACEI/ARB the index AKI admission within 1 month.

**Table S8.** Subgroup analysis on selected outcomes according to ACEI/ARB indication in the GBM-IPTW adjusted cohort.

**Table S9.** Subgroup analysis on renal outcomes according to eGFR when resuming ACEI/ARB in the GBM-IPTW adjusted cohort.

**Table S10.** Summary of prior studies examine the association between post-AKI ACEI/ARB prescription and outcomes.

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