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Original Article

Long-Term Renal Outcomes of ACEI or ARB Use after Recovery from Dialysis-Requiring Acute Kidney Injury: A Population-Based Cohort Study

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SUMMARY

Background: Limited evidence suggests strategies to improve long-term outcomes in patients recovering from dialysis-requiring acute kidney injury (AKI-D). We aimed to evaluate whether the post-discharge use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is associated with improved outcomes in these patients.

Methods: This cohort study used data from Taiwan's National Health Insurance database. Between 2001 and 2014, we included hospitalized patients aged ≥ 18 years who recovered from AKI-D and survived 180 days after discharge. Patients taking ACEI/ARB within 180 days of discharge were matched 1:1 to nonusers using propensity score methods. The outcomes of interest were all-cause mortality and end-stage renal disease (ESRD). We used Cox proportional hazards regression models to analyze the associations between ACEI/ARB use and the outcomes.

Results: A total of 8,463 matched pairs of ACEI/ARB users and nonusers were analyzed. After a median follow-up of 4 years, post-discharge ACEI/ARB was associated with lower all-cause mortality (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.90–1.00; p = 0.04), but not with ESRD. When considering the dispensing timing, ACEI/ARB use within 90 days of discharge, as compared with nonusers, was associated with lower risks for all-cause mortality (HR, 0.93; 95% CI, 0.88–0.98; p = 0.01) and ESRD (HR, 0.92; 95% CI, 0.85–0.99; p = 0.02).

Conclusion: Our results suggest the potential benefits of post-discharge use of ACEI/ARB in patients surviving AKI-D, plausibly in the window of 3 months after discharge.

1. Introduction

Acute kidney injury (AKI) is independently associated with increased long-term risks of *de novo* or progression of chronic kidney disease (CKD), end-stage renal disease (ESRD), and death.[1,2] The increased risks of morbidity and mortality is partly attributed to the activation of the intra-renal renin-angiotensin-aldosterone system (RAAS) after AKI.[3] Nowadays, there is increasing attention on the aftercare of AKI.[4,5] Although angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have proven efficacy in the management of CKD due to their beneficial effects on preserving heart and kidney function,[6–8] their roles in patients recovering from dialysis-requiring AKI (AKI-D), the most severe form of AKI, remain limitedly explored.

Hemodynamically, ACEI/ARB reduces intraglomerular pressure and renal filtration fraction through predominantly dilating efferent arterioles,[9] and thus functional AKI may ensue. Some debates are raised about the use of ACEI/ARB in the setting of AKI,[10,11] and it is common to see the clinicians withholding ACEI/ARB during or shortly after AKI for the fear that ACEI/ARB may deteriorate renal function. Despite so, once renal function gets stable after AKI, judicious use of ACEI/ARB should be considered. Because patients recovering from AKI-D follow different renal trajectories, the optimal timing of initiating ACEI/ARB remains controversial, and some clinicians may prefer to follow up renal function for an extended period to determine ACEI/ARB use or not. We therefore sought to evaluate whether the use of ACEI/ARB following discharge would also benefit patients with AKI-D. Specifically, we hypothesized that ACEI/ARB use in the first 6 months after discharge would reduce long-term mortality and the development of ESRD in patients recovering from AKI-D.

2. Materials and methods

2.1. Data source

This study used deidentified records from Taiwan's National Health Insurance (NHI) Research Database. NHI covers almost the entire Taiwanese population of 23 million and contains comprehensive healthcare utilization information.[12] Since the included patients were anonymous, this study was exempt from a full ethical review by the institutional review board of MacKay Memorial Hospital (IRB No. 20MMHIS112e).

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2.2. Design and study population

This study included patients aged ≥ 18 years who developed *de novo* AKI-D during their index admissions between 2001 and 2014, and were alive and off dialysis for > 180 days after discharge. The modalities of dialysis during AKI included hemodialysis, continuous renal replacement therapy, and prolonged intermittent renal replacement therapy. We excluded patients who had ESRD or previous AKI within one year prior to admission, those who were renal transplant recipients, those who underwent vascular access creation or peritoneal dialysis catheter implantation during the index hospitalization, and those who had a prolonged hospitalization for > 180 days. ESRD was defined as a status of dialysis-dependence for ≥ 3 months. Patients having at least one prescription of ACEI/ARB for ≥ 7 days and those who never received ACEI/ARB within 180 days after discharge were identified and matched by the propensity score approach at a 1:1 ratio to minimize the baseline differences.

2.3. Research variables

Detailed information was obtained on demographics, pre-admission baseline and in-hospital acute comorbidities, and prescription records. Baseline comorbidities were identified from at least three outpatient visits or one inpatient claim within one year prior to the index admission. All diagnoses were defined by the codes of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). We calculated the Charlson comorbidity index by weighting baseline comorbidities.[13] The prescription information for ACEIs, ARBs, beta blockers, aspirin, clopidogrel, and statins was identified within 90 days prior to and 180 days after the index hospitalization. Drug users were defined as patients who received at least one prescription for ≥ 7 days in the corresponding period.

2.4. Outcome measures

The outcomes of interest were all-cause mortality and the development of ESRD. Each patient was followed from the date of discharge to the commencement of ESRD, and was censored at death or the end of the study (December 31, 2014), whichever occurred first.

2.5. Statistical analysis

Data are represented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and as frequencies (proportions) for categorical ones. Categorical variables between groups were compared using the Chi-square test. To yield a balanced covariate distribution between post-discharge ACEI/ARB treated and untreated groups, a multivariate logistic regression model that included age, gender, year of admission, pre-admission drug prescriptions, and pre-admission baseline and in-hospital acute comorbidities was used to estimate the probability of being treated with an ACEI/ARB within 180 days after discharge. We matched the ACEI/ARB treated and untreated groups at a 1:1 ratio without replacement based on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score.[14] The absolute value of the standardized mean difference of less than 0.1 was considered a negligible covariate difference between the two groups.[15]

All analyses were conducted on an intention-to-treat basis. Multivariate Cox proportional hazards regression models were used to evaluate the associations between post-discharge use of ACEI/ ARB and the outcomes of interest, with adjustment for prognostic variables.

2.6. Subgroup analysis

We tried to elucidate the optimal timing of post-AKI ACEI/ARB treatment by comparing the outcomes in patients who started ACEI/ARB within 90 days of discharge versus after 90 days. The probability of event-free survival was assessed using a Kaplan-Meier plot. Furthermore, we categorized ACEI/ARB users into three groups: continued use (drug use within 90 days before and 180 days after the index admission), prior use (no more post-discharge prescription), and new use (no prior prescription before admission), and repeated the analyses using nonuse as the control group.

2.7. Sensitivity analysis

Death was considered a competing risk using cause-specific hazards models to analyze the effect of post-discharge ACEI/ARB on ESRD. Finally, to substantiate the impact of ACEI/ARB on the outcomes, we redefined the ACEI/ARB users as those who had drug prescription for ≥ 28 days after discharge and redid the Cox proportional hazards regression models and Kaplan-Meier analyses.

All analyses were performed using SAS/STAT software, version 9.4 of the SAS System for Windows (SAS Institute, Inc., Cary, NC, U.S.A.) and STATA, version 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). A two-sided p value < 0.05 was considered significant.

3. Results

3.1. Patient characteristics

Among the 204,556 patients with AKI-D, 104,711 (51.2%) not surviving 180 days and 71,708 (35.1%) requiring at least one session of dialysis within 180 days of discharge were excluded (Figure 1).

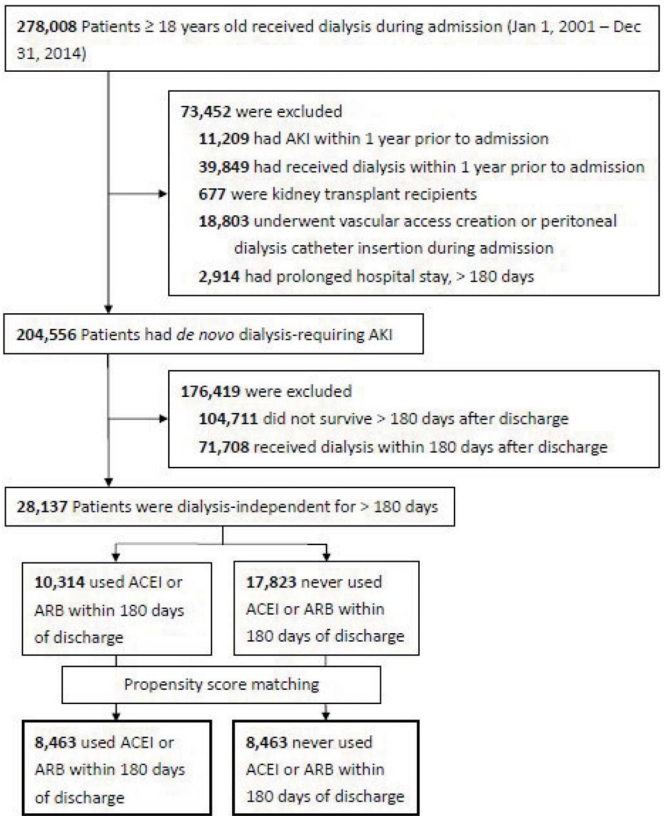

Figure 1. Flowchart for enrollees.

Among the remaining 28,137 patients, only 10,314 (36.7%) had an ACEI/ARB prescription within 180 days of discharge. After propensity score matching, 8,463 matched pairs of ACEI/ARB users and nonusers were analyzed (Table 1). The standardized mean differences were all < 0.1, suggesting a balanced distribution of covariates in both groups. The average age was 66.6 ± 14.6 years, 7419 (43.8%) patients were male, and the Charlson comorbidity index was 2.8 ± 2.3. Of the baseline comorbidities, diabetes mellitus (73.7%), hypertension (68.6%), and CKD (33.3%) were common. More than half of patients (56.0%) had already been prescribed an ACEI/ARB before the

Table 1
Characteristics of ACEI/ARB users and nonusers.

	Before PSM			After PSM		
	ACEI/ARB users (N = 10,314)	ACEI/ARB nonusers (N = 17,823)	SMD	ACEI/ARB users (N = 8,463)	ACEI/ARB nonusers (N = 8,463)	SMD
Gender (Male)	5645 (54.7%)	10780 (60.5%)	0.12	3752 (44.3%)	3667 (43.3%)	0.02
Age (year)	66.7 ± 14.2	62.8 ± 17.6	0.25	66.3 ± 14.6	66.9 ± 14.6	0.05
Year of admission						
2001–2005	2455 (23.8%)	4963 (27.8%)	0.09	2073 (24.5%)	2052 (24.2%)	0.01
2006–2010	4040 (39.2%)	6437 (36.1%)	0.06	3230 (38.2%)	3229 (38.2%)	0.00
2011–2014	3819 (37.0%)	6423 (36.0%)	0.02	3160 (37.3%)	3182 (37.6%)	0.01
Length of hospital stay (day)	20 (11,37)	23 (12,44)	N/A	20 (11,38)	21 (12,42)	N/A
Pre-admission comorbidities						
Charlson comorbidity index	2.9 ± 2.3	2.3 ± 2.4	0.25	2.8 ± 2.3	2.8 ± 2.3	0.00
0	1700 (16.5%)	5621 (31.5%)	0.36	1589 (18.8%)	1600 (18.9%)	0.00
1–2	3440 (33.4%)	5435 (30.5%)	0.06	2813 (33.2%)	2861 (33.8%)	0.01
> 2	5174 (50.2%)	6767 (38.0%)	0.25	4061 (48.0%)	4002 (47.3%)	0.01
Myocardial infarction	540 (5.2%)	510 (2.9%)	0.12	406 (4.8%)	398 (4.7%)	0.00
Congestive heart failure	2372 (23.0%)	2470 (13.9%)	0.24	1814 (21.4%)	1812 (21.4%)	0.00
Peripheral vascular disease	349 (3.4%)	437 (2.5%)	0.06	278 (3.3%)	283 (3.3%)	0.00
Cerebrovascular disease	1851 (17.9%)	2409 (13.5%)	0.12	1501 (17.7%)	1491 (17.6%)	0.00
Dementia	364 (3.5%)	722 (4.1%)	0.03	329 (3.9%)	343 (4.1%)	0.01
Chronic obstructive pulmonary disease	1476 (14.3%)	2275 (12.8%)	0.05	1220 (14.4%)	1211 (14.3%)	0.00
Rheumatologic disease	236 (2.3%)	316 (1.8%)	0.04	189 (2.2%)	192 (2.3%)	0.00
Peptic ulcer	1626 (15.8%)	2694 (15.1%)	0.02	1343 (15.9%)	1355 (16.0%)	0.00
Mild liver disease	974 (9.4%)	2165 (12.1%)	0.09	836 (9.9%)	830 (9.8%)	0.00
Moderate or severe liver disease	102 (1.0%)	442 (2.5%)	0.11	99 (1.2%)	92 (1.1%)	0.01
Diabetes mellitus without complications	5030 (48.8%)	5326 (29.9%)	0.39	3775 (44.6%)	3738 (44.2%)	0.01
Diabetes mellitus with complications	3371 (32.7%)	3354 (18.8%)	0.32	2496 (29.5%)	2459 (29.1%)	0.01
Hemiplegia	194 (1.9%)	268 (1.5%)	0.03	146 (1.7%)	150 (1.8%)	0.00
Renal disease	2651 (25.7%)	3658 (20.5%)	0.12	2139 (25.3%)	2206 (26.1%)	0.02
Malignancy	750 (7.3%)	1711 (9.6%)	0.08	661 (7.8%)	632 (7.5%)	0.01
Metastatic carcinoma	91 (0.9%)	320 (1.8%)	0.08	88 (1.0%)	83 (1.0%)	0.01
Hypertension	7496 (72.7%)	8257 (46.3%)	0.56	5749 (67.9%)	5855 (69.2%)	0.03
Dyslipidemia	2737 (26.5%)	2753 (15.4%)	0.28	2020 (23.9%)	2025 (23.9%)	0.00
In-hospital acute comorbidities						
ICU admission	7571 (73.4%)	13082 (73.4%)	0.08	6245 (73.8%)	6233 (73.7%)	0.00
Acute organ dysfunction						
Cardiovascular	1270 (12.3%)	2547 (14.3%)	0.06	1098 (13.0%)	1058 (12.5%)	0.01
Respiratory	5208 (50.5%)	9623 (54.0%)	0.07	4356 (51.5%)	4394 (51.9%)	0.01
Hepatic	167 (1.6%)	499 (2.8%)	0.08	153 (1.8%)	123 (1.5%)	0.03
Neurologic	179 (1.7%)	413 (2.3%)	0.04	154 (1.8%)	154 (1.8%)	0.00
Hematologic	145 (1.4%)	329 (1.8%)	0.04	130 (1.5%)	137 (1.6%)	0.01
Operation categories						
Cardiothoracic	1055 (10.2%)	1432 (8.0%)	0.08	854 (10.1%)	857 (10.1%)	0.00
Upper gastrointestinal	89 (0.9%)	216 (1.2%)	0.03	79 (0.9%)	75 (0.9%)	0.01
Lower gastrointestinal	146 (1.4%)	425 (2.4%)	0.07	135 (1.6%)	118 (1.4%)	0.02
Hepatobiliary	130 (1.3%)	400 (2.2%)	0.08	117 (1.4%)	107 (1.3%)	0.01
Associated condition						
Severe sepsis	3023 (29.3%)	6185 (34.7%)	0.12	2598 (30.7%)	2642 (31.2%)	0.01
Shock	1251 (12.1%)	2515 (14.1%)	0.06	1083 (12.8%)	1043 (12.3%)	0.01
Myocardial infarction	963 (9.3%)	968 (5.4%)	0.15	725 (8.6%)	708 (8.4%)	0.01
Hepatorenal syndrome	12 (0.1%)	52 (0.3%)	0.04	12 (0.1%)	12 (0.1%)	0.00
Obstructive uropathy	213 (2.1%)	668 (3.7%)	0.10	197 (2.3%)	186 (2.2%)	0.01
Contrast exposure	2938 (28.5%)	4979 (27.9%)	0.01	2405 (28.4%)	2377 (28.1%)	0.01
Medication within 90 days prior to admission						
ACEI/ARB	6623 (64.2%)	4778 (26.8%)	0.81	4774 (56.4%)	4711 (55.7%)	0.02
Beta-blocker	3998 (38.8%)	4375 (24.5%)	0.31	3037 (35.9%)	3039 (35.9%)	0.00
Aspirin/clopidogrel	3684 (35.7%)	3785 (21.2%)	0.33	2807 (33.2%)	2780 (32.8%)	0.01
Statin	2522 (24.5%)	2315 (13.0%)	0.30	1819 (21.5%)	1799 (21.3%)	0.01

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ICU, intensive care unit; N/A, not applicable; PSM, propensity score matching; SMD, standardized mean difference.

index admission. The in-hospital treatment course was complicated with acute respiratory failure (51.7%), severe sepsis (31.0%), surgery (13.8%), and shock (12.6%).

3.2. Primary outcomes

The median follow-up duration was 4.12 (interquartile range, 2.08–6.89) years in ACEI/ARB users and 3.96 (interquartile range, 1.88–6.88) years in the nonusers. The crude incidence rates of all-cause death in ACEI/ARB users and nonusers were 11.11 and 12.29 per 1,000 patient-years (p < 0.001) and those of the development of ESRD were 6.51 and 6.67 per 1,000 patient-years (p = 0.43), respectively (Table 2). The numbers needed to treat (NNT) to prevent one occurrence of death and ESRD were 858 and 6289, respectively. Using multivariate Cox-regression models, the risk for all-cause mortality was lower among ACEI/ARB users versus nonusers (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.90–1.00; p = 0.04). The risk for ESRD development (HR, 0.94; 95% CI, 0.87–1.01; p = 0.08) was not significantly different between ACEI/ARB users and nonusers (Table 2).

3.3. Subgroup analysis

Among 8,463 ACEI/ARB users, the majority (n = 7,146; 84.4%) started ACEI/ARB use within 90 days of discharge. Further analyses concerning the dispensing timing showed that patients starting ACEI/ARB within 90 days of discharge had reduced risks for all-cause mortality (HR, 0.93; 95% CI, 0.88–0.98; p = 0.01) and ESRD (HR, 0.92; 95% CI, 0.85–0.99; p = 0.02) as compared with nonusers (Figure 2). The corresponding NNTs for death and ESRD were 792 and 5138, respectively. Patients taking ACEI/ARB after 90 days of discharge had similar risks for all-cause mortality and ESRD as nonusers.

Compared with nonuse of ACEI/ARB prior to and after the index admission, continued use of ACEI/ARB was associated with a most pronounced risk of lower mortality (HR, 0.91; 95% CI, 0.84–0.99; p = 0.02). The prescription status of ACEI/ARB prior to and after the index admission was not significantly related to the development of ESRD (Table 3).

3.4. Sensitivity analysis

When death was considered a competing risk for ESRD (Supplementary Tables 1 and 2), and when only including patients whose post-discharge prescription of ACEI/ARB was ≥ 28 days (Supplementary Table 3 and Supplementary Figure 1), the findings of the effects of ACEI/ARB were similar, as previously elaborated.

4. Discussion

This nationwide population-based cohort study demonstrates that post-discharge ACEI/ARB use is associated with a reduced risk of long-term mortality in patients surviving 180 days after an AKI-D episode. Patients with AKI surviving hospitalization are at risks for subsequent unplanned hospital readmission and death, with the highest risk observed within 90 days of discharge and decreasing risk after that.[16,17] AKI-D is the most severe form of AKI and previous studies reported a high mortality rate of 31.7–76.0% in the first 6 months after discharge.[18,19] In our cohort, 51.2% of the patients did not survive 180 days and were excluded before the final analysis. We focused on relatively well patients who recovered their renal function

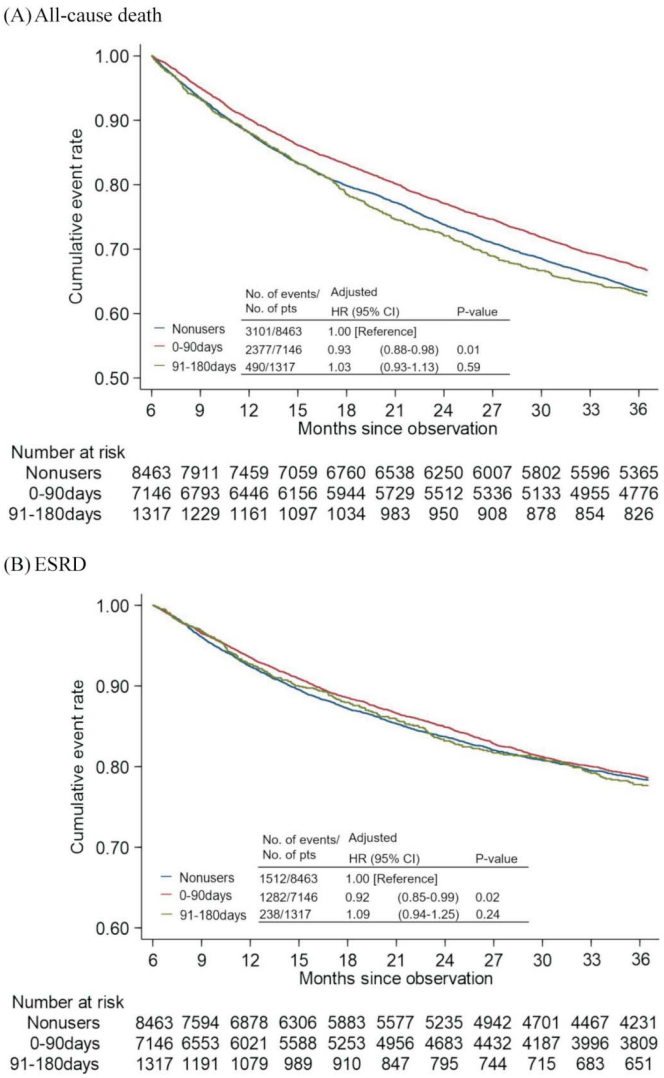

Figure 2. Kaplan-Meier curves for long-term event-free survivals. All hazard ratios were shown after adjustment for age, gender, baseline comorbidities, acute diseases, and drugs within 3 months prior to and 6 months after discharge.

Table 2
Outcomes associated with post-discharge ACEI/ARB use.

	Events	Person-years	Incidence rate (per 1,000 person-years)	Hazard ratio (95% confidence interval)			
				Crude	p-value	Adjusted*	p-value
All-cause mortality					< 0.001		0.04
Nonusers	3,101	252,344	12.29	1 [Reference]		1 [Reference]	
ACEI/ARB users	2,867	258,061	11.11	0.90 (0.86–0.95)		0.95 (0.90–1.00)	
ESRD					0.42		0.08
Nonusers	1,512	226,723	6.67	1 [Reference]		1 [Reference]	
ACEI/ARB users	1,520	233,308	6.51	0.97 (0.91–1.04)		0.94 (0.87–1.01)	

* Adjusted for age, gender, baseline comorbidities, acute diseases, and drugs within 3 months prior to and 6 months after discharge.

Table 3
Outcomes associated with continued use, prior use, and new use of ACEI/ARB.

ACEI/ARB use	No. of events/ No. of patients	Adjusted hazard ratio (95% confidence interval)*	p-value
All-cause mortality			
Nonuser	1214/3752	1 [Reference]	
Continued use	1699/4774	0.91 (0.84–0.99)	0.02
Prior use	1887/4711	0.98 (0.91–1.06)	0.66
New use	1168/3689	0.97 (0.89–1.05)	0.45
ESRD			
Nonuser	599/3752	1 [Reference]	
Continued use	969/4774	0.90 (0.81–1.00)	0.05
Prior use	915/4711	0.99 (0.88–1.10)	0.79
New use	552/3689	0.99 (0.88–1.11)	0.85

* Adjusted for age, gender, baseline comorbidities, acute diseases, and drugs within 3 months prior to and 6 months after discharge.

and had a life expectancy of $\geq$ 6 months after discharge, in whom prompt ACEI/ARB treatment could be beneficial.

RAAS is believed to play a pivotal role in AKI-CKD transition.[3] Prolonged RAAS activation after AKI results in the constriction of efferent arterioles, glomerular hypertension and sclerosis, the activation of inflammatory pathways, an influx of inflammatory cells into the glomerulus and tubulointerstitium, and eventually renal fibrosis.[3,9,20,21] Clinical studies supporting the post-AKI use of ACEI/ARB with respect to renal outcomes are nevertheless scarce. A small-scale retrospective study involving 587 patients reported that users of RAAS inhibitors following functional recovery from coronary surgery-associated AKI had lower rates of ensuing CKD.[22] Among 46,253 enrollees, Brar et al. did not find an improvement in ESRD risk by post-AKI use of ACEI/ARB,[23] which could be due to a short follow-up duration (2 years) and low event rates in patients with relatively preserved renal function (only 2.1% experienced AKI-D, as compared to 100% in our cohort). Our study showed that ACEI/ARB was associated with a reduced long-term risk of ESRD development after AKI-D, but only when dispensed within 90 days of discharge. The timing of ACEI/ARB prescription after AKI has rarely been explored. The benefit of early ACEI/ARB use is plausible as it may nip the AKI-CKD transition in the bud, but more studies are needed to substantiate this notion. Hyperkalemia and AKI accompanied by ACEI/ARB treatment is another concern. Brar et al. reported that post-AKI ACEI/ARB was associated with a higher risk of hospitalization for a renal cause, mainly acute renal failure and hyperkalemia;[23] however, Hsu et al. argued that ACEI/ARB was not associated with recurrent hospitalized AKI in AKI survivors without heart failure.[24] In either case, careful monitoring of electrolytes and renal function in patients receiving ACEI/ARB treatment is required.

Our study showed a robust result that ACEI/ARB was associated with a lower risk for all-cause mortality, particularly when ACEI/ARB therapy was started within 90 days of discharge. Similar to our findings, Brar et al. demonstrated that post-discharge use of ACEI/ARB was associated with an improved two-year survival (HR, 0.85; 95% CI, 0.81–0.89).[23] Two more studies investigated the long-term effects of ACEI/ARB treatment after AKI at the time of intensive care unit discharge. One reported a one-year survival benefit (HR, 0.48; 95% CI, 0.27–0.85),[25] while the other found no difference in survival after two years (HR, 1.71; 95% CI, 0.71–3.90).[26] Despite the observational nature of these studies, these results shed light on the effectiveness of ACEI/ARB at improving post-AKI survival.

4.1. Strengths and limitations

Our study has several strengths, including a large cohort size, nationally representative data, evaluation of hard outcomes, and rigorous study design to control confounding. However, care should be taken when interpreting our results. The most important concern stems from the observational and retrospective nature of the administrative data. The use of ACEI/ARB may be confounded by the indication bias, and patients taking ACEI/ARB may have more stable renal function and hemodynamic condition than nonusers. We used the propensity score approach to minimize confounding; however, residual confounders might exist. Also, although significant associations between ACEI/ARB and outcomes were identified, we could not confirm the causality. Because the NNTs for death and ESRD were large, these findings may not be clinically significant. Second, our database does not contain records of blood pressure and laboratory data such as serum creatinine, glycated hemoglobin/albumin, and proteinuria, which are known risk factors for morbidity and mortality in CKD patients.[27,28] Finally, the compliance of ACEI/ARB therapy was uncertain. However, nonadherence would tend to bias the results toward the null.

In conclusion, our study provides evidence that post-discharge use of ACEI/ARB was associated with improved long-term outcomes in patients surviving 180 days after AKI-D. Notably, lower risks for all-cause mortality and ESRD were observed when ACEI/ARB was started within 90 days of discharge versus after 90 days. Prompt (probably best within 3 months of discharge) use of ACEI/ARB and a judicious monitoring strategy may help optimize the AKI aftercare; however, the clinical benefits in real world might be limited due to large NNTs. More studies are needed to substantiate the observations.

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None.

Conflicts of interest

None.

Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=33.

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