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Citation	Journal of the American Society of Nephrology. 2024, 35(10), p. 1391-1401
Version Type	AM
URL	https://hdl.handle.net/11094/97749
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Estimated Effect of Restarting Renin-Angiotensin System Inhibitors after Discontinuation on Kidney Outcomes and Mortality

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Key Points

- Restarting renin-angiotensin system inhibitor after discontinuation was associated with a lower risk of kidney outcomes and mortality but not related to hyperkalemia.
- Our findings support a proactive approach to restarting renin-angiotensin system inhibitor among patients with CKD.

Abstract

Background While renin-angiotensin system inhibitors (RASi) have been the mainstream treatment for patients with CKD, they are often discontinued because of adverse effects such as hyperkalemia and AKI. It is unknown whether restarting RASi after discontinuation improves clinical outcomes.

Methods Using the Osaka Consortium for Kidney disease Research database, we performed a target trial emulation study including 6065 patients with an eGFR of 10–60 ml/min per 1.73 m² who were followed up by nephrologists and discontinued RASi between 2005 and 2021. With a clone-censor-weight approach, we compared a treatment strategy for restarting RASi within a year after discontinuation with that for not restarting RASi. Patients were followed up for 5 years at maximum after RASi discontinuation. The primary outcome was a composite kidney outcome (initiation of KRT, a $\geq 50\%$ decline in eGFR, or kidney failure [eGFR < 5 ml/min per 1.73 m²]). Secondary outcomes were all-cause death and incidence of hyperkalemia (serum potassium levels ≥ 5.5 mEq/L).

Results Among those who discontinued RASi (mean [SD] age 66 [15] years, 62% male, mean [SD] eGFR 40 [26] ml/min per 1.73 m²), 2262 (37%) restarted RASi within a year. Restarting RASi was associated with a lower hazard of the composite kidney outcome (hazard ratio [HR], 0.85; 95% confidence intervals [CIs], 0.78 to 0.93) and all-cause death (HR, 0.70; 95% CI, 0.61 to 0.80) compared with not restarting RASi. The incidence of hyperkalemia did not differ significantly between the two strategies (HR, 1.11; 95% CI, 0.96 to 1.27).

Conclusions Restarting RASi after discontinuation was associated with a lower risk of kidney outcomes and mortality but not related to the incidence of hyperkalemia.

JASN 00: 1–11, 2024. doi: <https://doi.org/10.1681/ASN.0000000000000425>

Introduction

Renin-angiotensin system inhibitors (RASi), including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are cornerstone drugs for the management of patients with CKD. Randomized controlled trials (RCTs) have shown their efficacy in slowing the progression of CKD and reducing cardiovascular risks and mortal-

ity.^{1–4} Accordingly, the Kidney Disease Improving Global Outcomes guideline recommends RASi for CKD patients with proteinuria to improve their prognosis.⁵

Despite the established benefit of RASi, however, they are often discontinued owing to adverse effects such as hyperkalemia and AKI. According to a large community-based cohort study, nearly half of patients with CKD who

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Received: January 3, 2024 **Accepted:** June 12, 2024

Published Online Ahead of Print: June 18, 2024

initiated RASi eventually discontinued these drugs.⁶ Notably, discontinuing RASi was associated with a higher risk of cardiovascular events and mortality,^{7–10} although its effect on hard kidney outcomes remains debated.^{11,12}

Given the proven efficacy of RASi for clinical outcomes in CKD, it may be preferable to restart these drugs even if they are temporarily discontinued. However, only about half of the patients who discontinued RASi restarted them thereafter.^{11,12} Such a passive approach may be attributable to a lack of robust evidence regarding the clinical consequences of restarting RASi. Because patients discontinuing RASi are potentially at a high risk of cardiovascular events and CKD progression,^{7–11} it is valuable to determine the risk-benefit ratio of restarting RASi in such a vulnerable patient population.

To address this knowledge gap, we conducted a target trial emulation study to compare the treatment strategy of restarting RASi after discontinuation versus not restarting RASi among patients with CKD.

Methods

Target Trial Emulation

Target trial emulation is a framework for analyzing observational data to closely emulate a target trial while avoiding potential biases, such as immortal time bias and depletion of susceptible bias.^{13–15} Despite being based on observational data, this study design provides equivalent estimates obtained from actual RCTs.¹⁶ We used a censor-weight approach to compare the treatment strategies of restarting RASi within a year after discontinuation versus not restarting RASi with respect to kidney outcomes and death. Details about our target trial protocol are summarized in [Supplemental Table 1](#).

This study adhered to the principles of the Declaration of Helsinki. The Ethics Committees at each hospital approved the study protocol. Owing to the retrospective nature of the study design, the need for informed consent was waived (approval number: 21513).

Date Sources

All data used in this study were collected from the Osaka Consortium for Kidney disease Research database. Osaka Consortium for Kidney disease Research is a retrospective multicenter cohort study including patients who were followed up by nephrologists at the outpatient departments of nephrology at five hospitals in Osaka, Japan, from January 2005 to December 2021: Ikeda City Hospital, Osaka General Medical Center, Osaka University Hospital, Sakai City Medical Center, and Toyonaka Municipal Hospital. An electronic data capture (EDC) system, integrated with electronic medical records (EMRs) in each hospital, was used to extract demographic, laboratory, and prescription data from outpatient and inpatient settings.^{17–19}

Target Trial Eligibility and Exclusion Criteria

The eligible patients were those (1) aged 20 years or older, (2) who had an eGFR of 10–60 ml/min per 1.73 m², and (3) who discontinued RASi. We excluded patients (1) who had undergone KRT or (2) who received RASi for <30 days before discontinuation.

Treatment Assignment

Treatment assignment was determined based on whether RASi were restarted (Restart group) or not (non-Restart group) after ≥30 days of RASi discontinuation. To align with real-world clinical practice, we allowed a 1-year grace period from discontinuation to restart of RASi.

Definitions of Discontinuation and Restart of RASi

Discontinuation of RASi was defined as an absence of a RASi prescription for ≥30 days from the index visit (baseline visit), which was prescribed for ≥30 days before the index visit ([Supplemental Figure 1](#)). The time-to-event analysis began after the index visit, as described below. In Japan, a prescription refilling system was not yet operational during the study period. Thus, physicians generally prescribed the required number of medicines until the next visit. All information about patients' visits and prescriptions were extracted from the EDC system.

Restarting RASi was defined as a represcription of RASi for ≥30 days within a year after the index visit that should be continued at least until 1 year after the index visit.

Follow-Up and Study Outcomes

Patients were followed up from the index visit when RASi were discontinued until the first outcome event, loss to follow-up, the end of the study period (December 31, 2021), or 5 years after the index visit.

The primary outcome was a composite kidney outcome, defined as the initiation of KRT, a ≥50% decline in eGFR from the index visit, or kidney failure (eGFR <5 ml/min per 1.73 m²). All patients initiating KRT were registered at each hospital and documented in a record of incident dialysis patients. KRT initiation was ascertained through this list. A few patients in our cohort initiated KRT outside our hospitals. Secondary outcomes included all-cause death and hyperkalemia (serum potassium levels ≥5.5 mEq/L). Deaths were extracted through EMRs using the EDC system, which included both in-hospital and out-of-hospital deaths.

Baseline and Time-Varying Covariates

Baseline covariates included age, sex, body mass index, diabetes mellitus, history of hyperkalemia (serum potassium levels ≥5.5 mEq/L during the 0–90 days before the index visit), eGFR declines during the 0–90 days before the index visit, laboratory measurements (serum creatinine, sodium, and potassium, venous bicarbonate, and urine protein-to-creatinine ratio [UPCR]), and prescriptions (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, α -blockers, β -blockers, loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists, potassium binders, and sodium bicarbonate). Diabetes mellitus was defined as baseline hemoglobin A1c ≥6.5% or use of glucose-lowering drugs at baseline. eGFR was calculated using a Japanese standard formula: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (if female, $\times 0.739$).²⁰ The eGFR decline was calculated using the baseline and maximum eGFR values during the 0–90 days before the index visit: $(\text{baseline eGFR} - \text{maximum eGFR}) \times 100 / \text{maximum eGFR}$. The eGFR declines were categorized into three groups: 1 (<−30%), 2 (−30% ≤, <−10%), and 3 (−10% ≤).

Laboratory tests were usually performed every 1–3 months. We collected these data on a monthly basis and imputed missing data using the last observation carried forward method.

In-Depth Chart Review

An in-depth chart review of the EMR was performed to verify data accuracy of RASi discontinuation. One of the study researchers reviewed the EMR, including referrals from and to other hospitals, among randomly selected 150 per 1161 patients from one study facility. The sample size of this random sampling was determined based on the San Diego Approach for Variable Validation,²¹ with an anticipated positive predictive value of 0.90, a confidence lower bound of 0.86, and a one-sided alpha error of 0.05. The positive predictive value for RASi discontinuation, defined as the number of patients whose RASi discontinuation was assured by this chart review divided by the total number of patients inspected, was 87%.

Statistical Analysis

To emulate the target trial comparing the Restart and non-Restart groups, we executed three steps: cloning, censoring, and weighting (Supplemental Figure 2).^{22–28} The details of this analytical method are described in the Supplemental Methods. First, each patient was cloned into two identical replicates, one of which was assigned to the Restart group and another to the non-Restart group. Second, replicates were artificially censored when deviated from the assigned treatment strategies. Finally, we used inverse probability of censoring weights (IPCW) to deal with selection bias induced by artificial censoring. The average IPCW are described in Supplemental Table 2.

To estimate the association between the treatment strategies and outcomes that occurred after the index visit, we fitted IPCW-weighted pooled logistic regression models with a robust variance estimator, which included an indicator for the treatment strategy, time (linear and quadratic terms), and baseline covariates. This model provides equivalent estimates for hazard ratios (HRs) and 95% confidence intervals (CIs) based on a Cox model.^{29,30} Time zero of this analysis was the index visit when RASi were discontinued. Using the predicted probabilities obtained from this logistic model, we estimated the absolute risk and risk difference at 5 years for each outcome to produce a weighted cumulative incidence curve.²⁷

We imputed missing data at baseline by multiple imputation by chained equations with ten iterations using fully conditional specification, assuming that the data are missing at random.³¹ The imputation model included all baseline and outcome variables. Because all missing data were continuous (*i.e.*, body mass index, venous bicarbonate, sodium, potassium, and UPCR), we used linear regression imputation. We first performed multiple imputation to generate five imputed datasets. For each imputed dataset, 100 bootstrap samples were drawn. Then, IPCW-weighted pooled logistic regression models were performed in each of 5×100 datasets. 95% CIs were calculated on the basis of the 2.5th and 97.5th percentile of the pooled distribution of the bootstrap point estimates.³²

Subgroup and Sensitivity Analyses

Subgroup analyses were performed according to age (70 years or younger versus older than 70 years), sex, diabetes mellitus, history of hyperkalemia, baseline eGFR (<30 versus ≥30 ml/min per 1.73 m²), UPCR (<1 versus ≥1 g/gCre), percent changes in UPCR after RASi discontinuation (<100% versus ≥100%), and eGFR declines and AKI before RASi discontinuation. The percent change in UPCR was calculated as follows: (the maximum UPCR during a year after discontinuation – the maximum UPCR during a year before discontinuation)/the maximum UPCR during a year before discontinuation. The cutoff value (*i.e.*, 100%) was based on the median percent change in UPCR. We detected AKI based on the National Health Service England AKI algorithm. This algorithm was validated to capture AKI from electronic health care records with a high sensitivity. Specifically, baseline AKI was identified when one of the following three criteria was met: a serum creatinine level at the index date was (1) >0.3 mg/dl higher than the lowest creatinine within 48 hours, (2) ≥1.5 times higher than the lowest creatinine within 7 days, or (3) ≥1.5 times higher than the median of all creatinine values 8–365 days ago.^{33,34} The interaction term between the treatment strategies and these potential effect modifiers was entered into the IPCW-weighted pooled logistic regression models. The details of sensitivity analyses are described in the Supplemental Methods.

All statistical analyses were performed using Stata/IC 17.0 software (Stata Corp, College Station, TX). A *P* value of < 0.05 was considered statistically significant.

Results

Study Population

Of 11,469 patients who had received RASi, 6065 (53%) discontinued RASi (Figure 1). The median duration of RASi usage before discontinuation was 308 days (interquartile range, 110–824). Among them, 2262 (37%) restarted RASi within a year after discontinuation, while 3803 (63%) did not restart within a year. The median duration from discontinuation to restart of RASi was 154 days (interquartile range, 91–299). Table 1 presents baseline characteristics of these patients.

Factors Associated with Not Restarting RASi in LASSO

In logistic LASSO, older age and rapid eGFR declines (<–30% before RASi discontinuation) were significantly related to not restarting RASi (Table 2). Neither serum potassium levels at baseline nor history of hyperkalemia was selected as a significant factor.

Composite Kidney Outcome

In the emulated trial, 1942 replicates reached the composite kidney end point. The weighted 5-year absolute risk was 63.2% (95% CI, 59.3 to 67.1) and 69.9% (95% CI, 67.0 to 72.8) in the Restart and non-Restart groups, respectively (absolute risk difference, –6.6%; 95% CI, –11.3 to –2.0) (Figure 2, Table 3). The Restart group showed a 15% lower hazard of the composite kidney outcome than the non-

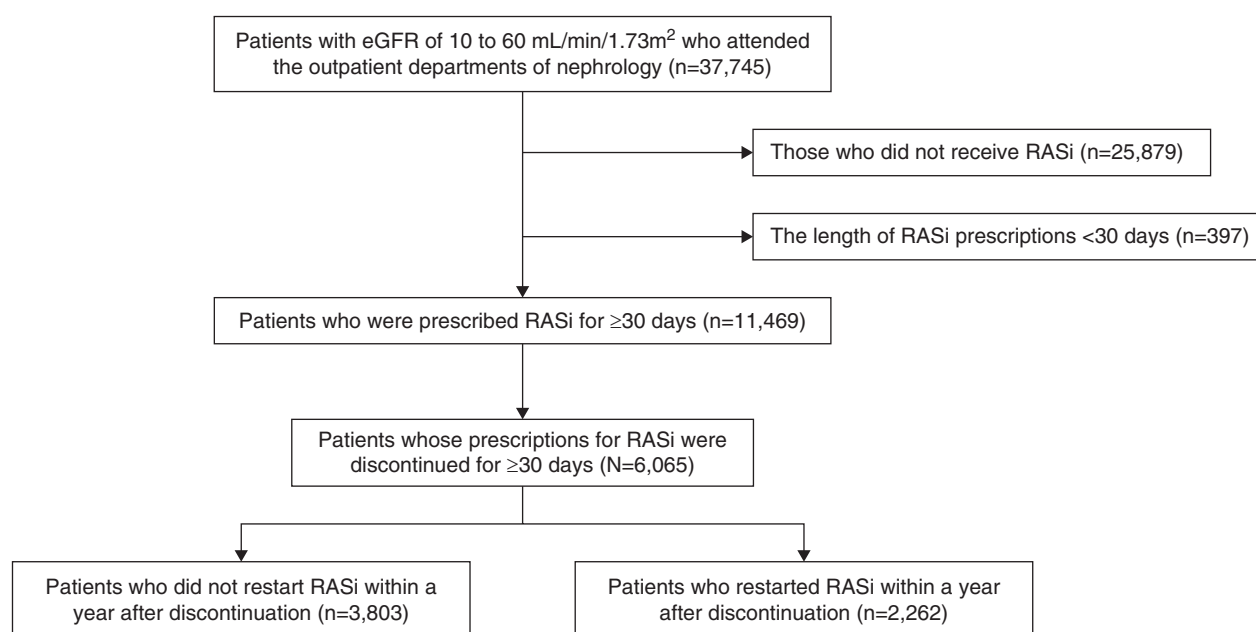


Figure 1. Flow diagram of the study participants. RASi, renin-angiotensin system inhibitors.

Restart group (HR, 0.85; 95% CI, 0.78 to 0.93). Similar trends were observed for individual components of the kidney composite outcome.

All-Cause Death

A total of 903 replicates died during follow-up. The weighted 5-year absolute risk in the Restart group was

Table 1. Patient characteristics at the time of renin-angiotensin system inhibitors discontinuation

Characteristics	Missing Data <i>n</i> (%)	Overall <i>N</i> =6065	Non-Restart Group <i>n</i> =3803 (63%)	Restart Group <i>n</i> =2262 (37%)
Demographics				
Age, yr	0	66 (15)	68 (15)	64 (15)
Male, <i>n</i> (%)	0	3749 (62)	2334 (61)	1415 (63)
BMI, kg/m ²	456 (8)	22.9 (4.6)	22.9 (4.7)	22.9 (4.5)
Diabetes mellitus, <i>n</i> (%)	0	2358 (39)	1503 (40)	855 (38)
History of hyperkalemia, <i>n</i> (%)	0	839 (14)	629 (17)	210 (9)
AKI, <i>n</i> (%)	0	1381 (23)	941 (25)	440 (19)
Prescriptions, <i>n</i> (%)				
Calcium channel blockers	0	1613 (27)	1053 (28)	560 (25)
α-blockers	0	921 (15)	640 (17)	281 (12)
β-blockers	0	276 (5)	152 (4)	124 (5)
Loop diuretics	0	1088 (18)	813 (21)	275 (12)
Thiazide diuretics	0	351 (6)	247 (6)	104 (5)
MRAs	0	380 (6)	268 (7)	112 (5)
Sodium bicarbonate	0	423 (7)	303 (8)	120 (5)
Potassium binders	0	278 (5)	178 (5)	100 (4)
Laboratory values				
eGFR, mL/min per 1.73 m ²	0	40 (26)	39 (26)	43 (25)
eGFR declines before RASi discontinuation, <i>n</i> (%)				
−10%≤	0	2979 (49)	1657 (44)	1322 (58)
−30%≤, <−10%	0	1113 (18)	1152 (30)	714 (32)
<−30%	0	1220 (20)	994 (26)	226 (10)
Serum sodium levels, mEq/L	15 (0.2)	140 (3)	139 (3)	140 (3)
Serum potassium levels, mEq/L	9 (0.1)	4.4 (0.6)	4.4 (0.6)	4.4 (0.5)
UPCR, g/gCre	743 (12)	1.5 (2.8)	1.5 (2.8)	1.5 (2.8)
Venous bicarbonate levels, mEq/L	3146 (52)	25 (4)	25 (4)	26 (4)

Data are presented as mean (SD) or number (%). BMI, body mass index; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitors; UPCR, urine protein-to-creatinine ratio.

Table 2. Baseline covariates associated with restarting renin-angiotensin system inhibitors on the basis of the logistic LASSO

Selected Covariates	Standardized OR (95% CI)
Age	0.80 (0.75 to 0.85)
eGFR declines of <−30% (versus −30%≤)	0.35 (0.31 to 0.41)
Older age and eGFR declines of <−30% before renin-angiotensin system inhibitor discontinuation were selected as a significant factor for a lower likelihood of restarting renin-angiotensin system inhibitor. The following baseline covariates were included in a LASSO logistic regression model: age, sex, body mass index, diabetes mellitus, history of hyperkalemia, eGFR declines before renin-angiotensin system inhibitor discontinuation, calcium channel blockers, α -blockers, β -blockers, loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists, sodium bicarbonate, potassium binders, eGFR, serum sodium levels, serum potassium levels, urine protein-to-creatinine ratio, and venous bicarbonate levels. The optimal λ that minimized the out-of-sample mean squared error was 0.033. CI, confidence interval; OR, odds ratio.	

22.7% (95% CI, 20.5 to 24.9) compared with 29.7% (95% CI, 27.7 to 31.7) in the non-Restart group (absolute risk difference, −7.0%; 95% CI, −9.7 to −4.2) (Figure 2, Table 4). The HR for the Restart group versus non-Restart group was 0.70 (95% CI, 0.61 to 0.80). A similar association was found when combining the composite kidney outcome with all-cause death (Table 4).

Hyperkalemia

Hyperkalemia occurred in 1508 replicates. The weighted 5-year absolute risk was 46.9% (95% CI, 43.9 to 49.9) and 45.1% (95% CI, 41.9 to 48.3) in the Restart and non-Restart groups, respectively (absolute risk difference, 1.8%, 95% CI, −1.8 to 5.3) (Figure 2). The HR for the Restart group versus non-Restart group was NS (HR, 1.11; 95% CI, 0.96 to 1.27) (Table 4).

Subgroup Analysis

The Restart group consistently showed a lower hazard of the composite kidney outcome and all-cause death than the non-Restart group across prespecified subgroups, except for a subgroup of eGFR declines before RASi discontinuation ($P_{\text{interaction}}$ for both the composite kidney outcome and all-cause death without adjustment for multiple comparisons were 0.004) (Figures 3 and 4); the associations of RASi restart with these outcomes were attenuated as eGFR declines before RASi discontinuation became larger and almost null in patients with eGFR declines of <−30%. Similar findings were obtained in the subgroup of AKI. The Restart group showed a trend toward a slightly higher risk of hyperkalemia in the subgroup of patients with a history of hyperkalemia, although the interaction term between the history of hyperkalemia and RASi restart was NS (Figure 5).

Sensitivity Analyses

Similar results were yielded when (1) analyzing data in a per-protocol manner (Supplemental Tables 3 and 4); (2) redefining the length of RASi discontinuation from ≥ 30 to ≥ 90 days (Supplemental Table 5); (3) the length of the grace period was shortened to 6 months or extended to 2 years (Supplemental Tables 6 and 7); (4) redefining the index date as the 30th day after RASi discontinuation (Supplemental Table 8); (5) redefining the baseline eGFR as the value recorded 90 days after the index date (Supplemental Table 9); (6) adding serum albumin levels and C-reactive protein to the multivariable model (Supplemental Table 10); (7) modifying the definition of hyperkalemia to serum potassium levels ≥ 6.0 mEq/L (Supplemental Table 11); and (8) adding facilities to the multivariable models as a baseline covariate (Supplemental Table 12). Finally, the risk of hyperkalemia was not significantly different between the Restart versus non-Restart groups after classifying patients who restarted RASi but discontinued during the grace period into the Restart group (HR, 1.11; 95% CI, 0.97 to 1.27; Figure 5).

Table 3. Intention-to-treat analyses for the composite kidney outcome

Outcomes	Treatment Strategies	No. of Events in the Emulated Trial	5-yr Absolute Risk, % (95% CI)	Absolute Risk Difference, % (95% CI)	HR (95% CI)
Composite kidney outcome	Non-restart group	1043	69.9 (67.0 to 72.8)	Reference	Reference
	Restart group	899	63.2 (59.3 to 67.1)	−6.6 (−11.3 to −2.0)	0.85 (0.78 to 0.93)
KRT	Non-restart group	345	20.5 (18.2 to 22.8)	Reference	Reference
	Restart group	298	17.4 (15.5 to 19.4)	−3.1 (−6.0 to −0.2)	0.84 (0.72 to 0.99)
$\geq 50\%$ decline in eGFR	Non-restart group	741	40.0 (37.2 to 42.8)	Reference	Reference
	Restart group	616	36.2 (33.7 to 38.8)	−3.8 (−7.2 to −0.4)	0.86 (0.77 to 0.96)
eGFR <5 ml/min per 1.73 m ²	Non-restart group	458	29.4 (27.2 to 31.8)	Reference	Reference
	Restart group	384	24.6 (22.2 to 27.2)	−4.8 (−7.9 to −1.7)	0.82 (0.72 to 0.94)

Models were adjusted through the inverse probability of censoring weights that were estimated from age, sex, body mass index, diabetes mellitus, history of hyperkalemia, eGFR declines before renin-angiotensin system inhibitor discontinuation, calcium channel blockers, α -blockers, β -blockers, loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists, sodium bicarbonate, potassium binders, eGFR, serum sodium levels, serum potassium levels, urinary protein-to-creatinine ratio, and venous bicarbonate levels. 95% confidence intervals were calculated using a nonparametric bootstrap on the basis of 100 resamples. CI, confidence interval; HR, hazard ratio.

Table 4. Intention-to-treat analyses for all-cause death and hyperkalemia

Outcomes	Treatment Strategies	No. of Events in the Emulated Trial	5-yr Absolute Risk, % (95% CI)	Absolute Risk Difference, % (95% CI)	HR (95% CI)
All-cause death	Non-restart group	561	29.7 (27.7 to 31.7)	Reference	Reference
	Restart group	342	22.7 (20.5 to 24.9)		
Composite of kidney outcomes and death	Non-restart group	1400	80.1 (78.0 to 82.2)	Reference	Reference
	Restart group	1143	70.2 (67.2 to 73.3)		
Hyperkalemia	Non-restart group	752	45.1 (41.9 to 48.3)	Reference	Reference
	Restart group	756	46.9 (43.9 to 49.9)		

Models were adjusted through the inverse probability of censoring weights that were estimated from age, sex, body mass index, diabetes mellitus, history of hyperkalemia, eGFR declines before renin-angiotensin system inhibitor discontinuation, calcium channel blockers, α -blockers, β -blockers, loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists, sodium bicarbonate, potassium binders, eGFR, serum sodium levels, serum potassium levels, urinary protein-to-creatinine ratio, and venous bicarbonate levels. 95% confidence intervals were calculated using a nonparametric bootstrap on the basis of 100 resamples. CI, confidence interval; HR, hazard ratio.

Discussion

While the efficacy of RASi for improving kidney prognosis is well recognized, they are often discontinued during CKD progression. In our study, only about one third of patients who discontinued RASi restarted them within a year. Using a clone-censor-weighting design, we found

that restarting RASi within a year after discontinuation was associated with a 15% lower hazard of kidney outcomes and a 30% lower hazard of mortality than not restarting RASi. Although these associations were robust across most of the subgroups, they were attenuated in subgroups of patients with rapid eGFR declines and

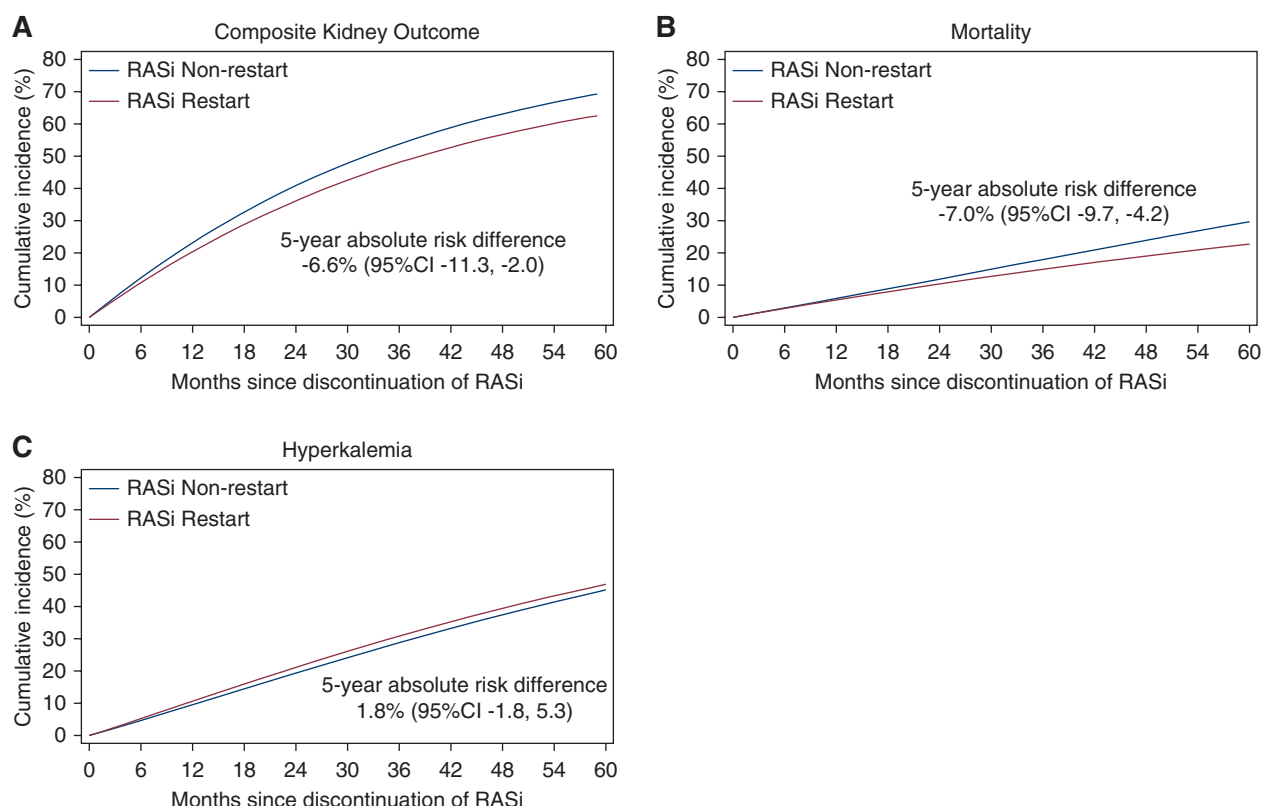


Figure 2. RASi restarting is associated with a lower risk of kidney outcomes and mortality but not related to hyperkalemia. Weighted cumulative incidence curves for (A) composite kidney outcome, (B) mortality, and (C) hyperkalemia in the target trial emulation. Weighted cumulative incidence rates at 5 years were estimated using pooled logistic regression models. The risk difference was calculated as the difference in cumulative risks between the Restart and non-Restart groups at 5 years, with 95% CIs derived from a nonparametric bootstrap method based on 100 resamples. CI, confidence interval.

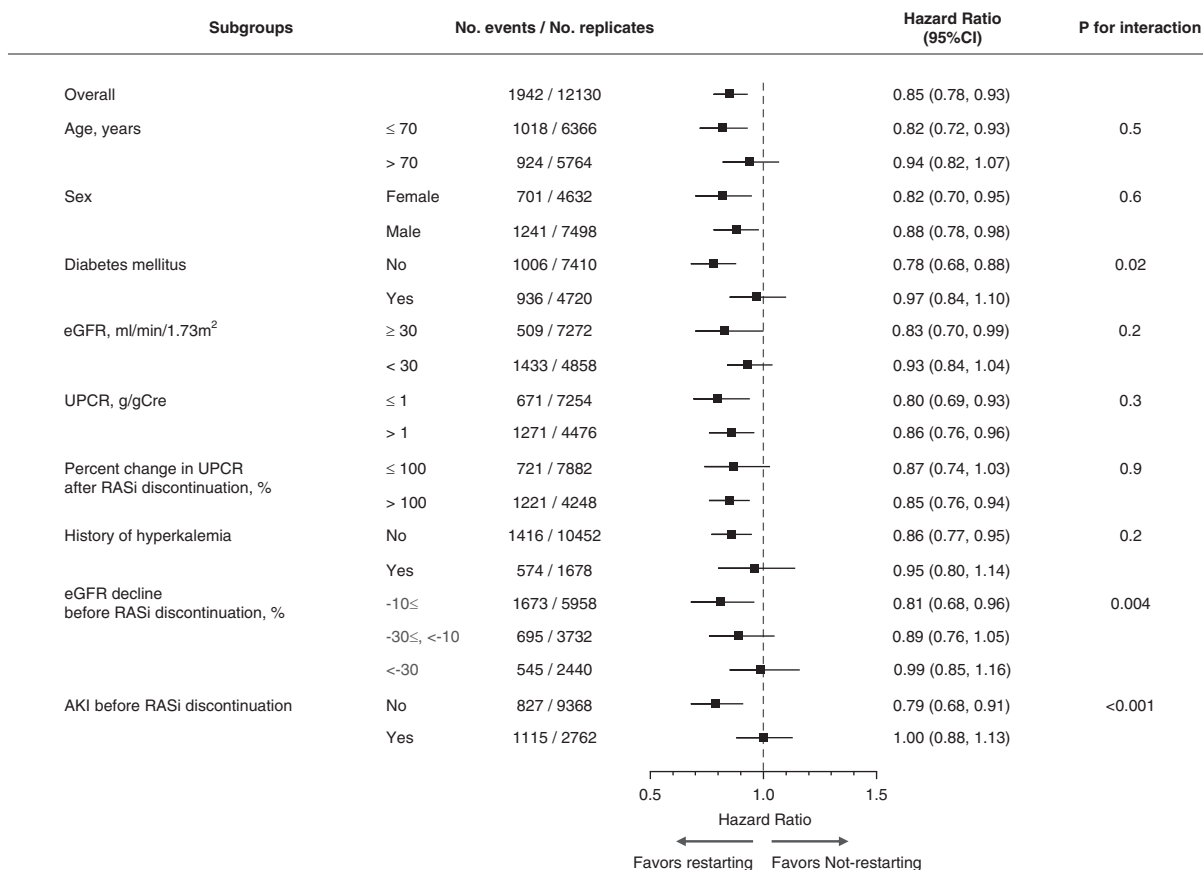


Figure 3. Subgroup analysis for the composite kidney outcome. HR for the composite kidney outcome in the Restart group versus the non-Restart group were analyzed according to the prespecified subgroups. Note that there was a significant effect modification by eGFR declines and AKI before RASi discontinuation on the association between RASi restart and the kidney outcome. Bars represent 95% CI. HR, hazard ratio; UPCR, urine protein-to-creatinine ratio.

AKI before discontinuation. Risk of hyperkalemia was similar between two strategy groups. Sensitivity analyses yielded consistent results. These findings suggest that the benefit of restarting RASi for hard kidney outcomes and mortality surpasses its risk, supporting a proactive stance toward RASi restart even if they are discontinued once.

Consistent with previous real-world data,^{11,12} we found that only 37% of patients restarted RASi within a year after discontinuation, even under the specialized management by nephrologists. LASSO identified older age as a key factor for a lower likelihood of restarting RASi. This might reflect the cautiousness of physicians against restarting RASi for such a vulnerable population who are more susceptible to adverse events. However, in our subgroup analysis, restarting RASi showed a trend toward better kidney prognosis and survival across age subgroups but was unrelated to hyperkalemia. Thus, we would emphasize that older age alone should not hamper the restart of RASi. It should be recognized, however, that our patients received close monitoring by nephrologists, which could have contributed to reducing the incidence of adverse events after restarting RASi. Thus, the risk-benefit ratio may vary in different health care circumstances.

Another key factor related to not restarting RASi was rapid eGFR declines before RASi discontinuation. Notably,

in a subgroup of patients with rapid eGFR declines (eGFR declines of $<-30\%$), the effect of restarting RASi was null on kidney outcomes and largely attenuated on mortality, although this finding should be interpreted cautiously given that the significance threshold was not adjusted for multiple comparisons. Similar findings were observed for the subgroup of patients with AKI before RASi discontinuation. These results align with a population-based cohort study including 46,253 hospitalized patients with AKI, showing that RASi use after discharge exhibited a neutral association with the risk of kidney failure but a higher risk for subsequent AKI.⁸ Thus, it can be speculated that, for those who are at a high risk of AKI, the potential benefit of RASi is offset by a negative effect attributable to AKI. Prevention strategies for AKI among RASi users, for example, through coadministration of sodium-glucose cotransporter-2 inhibitors,^{35,36} might contribute to maximize the benefit of RASi. The optimal timing and appropriate population for restarting RASi after AKI should be determined in future detailed studies.

Several target trial emulation studies have examined the association between RASi discontinuation and kidney outcomes among patients with advanced CKD.^{9,11,12} Using a propensity score overlap-weighting method, Yang *et al.* reported that patients with type 2 diabetes

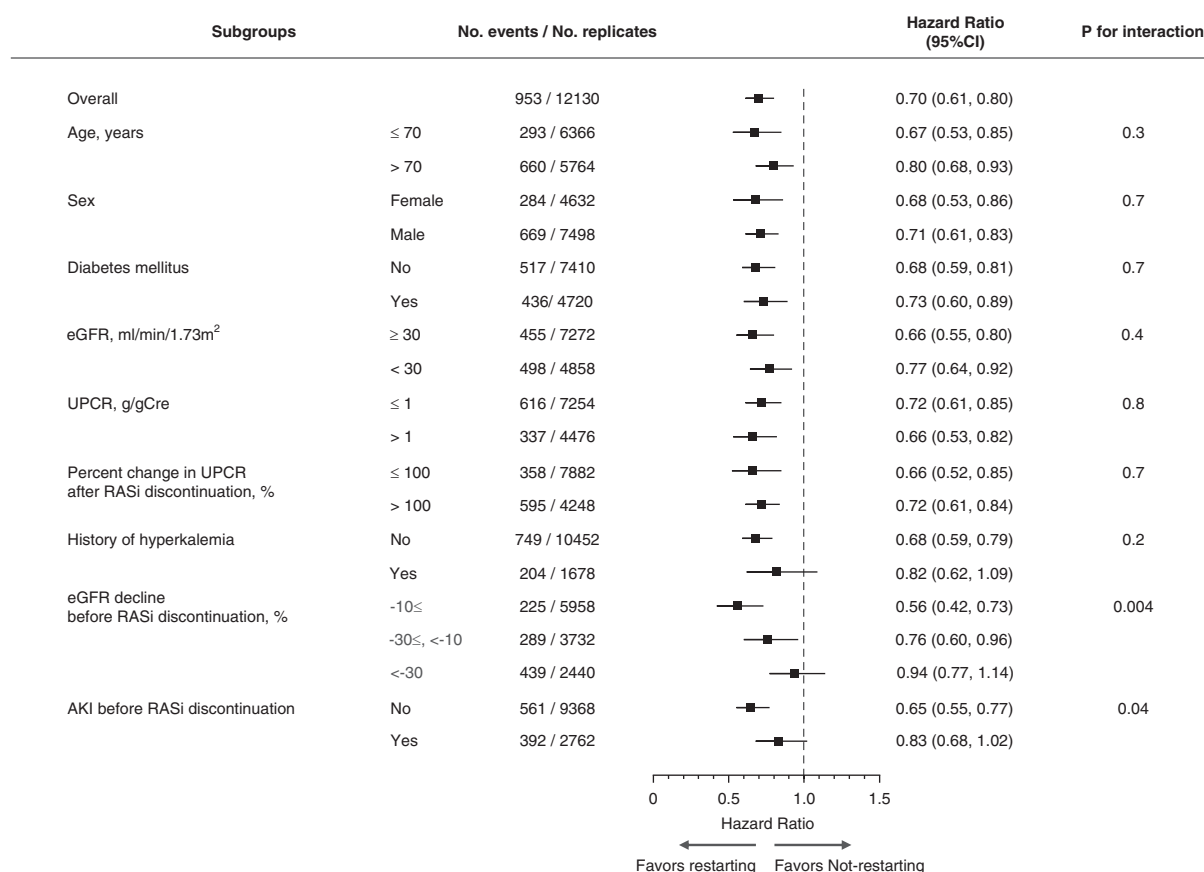


Figure 4. Subgroup analysis for all-cause death. HR for all-cause death in the Restart group versus the non-Restart group were analyzed according to the prespecified subgroups. Note that there was a significant effect modification by eGFR declines and AKI before RASi discontinuation on the association between RASi restart and all-cause death. Bars represent 95% CI.

who discontinued RASi within 6 months after reaching eGFR <30 ml/min per 1.73 m² showed a 30% higher risk of kidney failure than those who continued RASi.¹¹ Similarly, Qiao *et al.* reported a 19% higher, albeit NS, risk of kidney failure among those who discontinued RASi within 6 months after reaching eGFR <30 ml/min per 1.73 m².⁹ By contrast, with the clone-censor-weighting method, Fu *et al.* reported that stopping RASi after reaching eGFR <30 ml/min per 1.73 m² was associated with a 8.3% lower absolute risk of KRT initiation than continuing RASi.¹² Although the latter finding may somewhat contradict our result, the study by Fu *et al.* was not designed to assess the impact of restart because those who restarted RASi after discontinuation were censored in their study. Finally, in the STOP-ACEi trial, an open-label RCT including patients with eGFR <30 ml/min per 1.73 m², RASi discontinuation conferred a numerically higher risk of kidney failure than RASi continuation (HR, 1.28; 95% CI, 0.99 to 1.65).³⁷ Importantly, in these studies, RASi were discontinued in a protocol-driven manner based on a particular eGFR value. By contrast, in our real-world study, RASi were discontinued in a clinical context-driven manner, predominantly as a result of adverse effects, where restart could be a more clinically relevant issue. Therefore, the implication of RASi discontinuation, as well as restart, of our study is totally

different from the above studies and thus should be interpreted appropriately.

Although hyperkalemia is a major concern in restarting RASi, the risk of hyperkalemia was not elevated in those who restarted RASi compared with those who did not. This may be explained by the fact that our patients were closely monitored by nephrologists, highlighting that appropriate care for hyperkalemia, including dietary therapy, correction of metabolic acidosis, and use of potassium binders, may help to suppress the risk of hyperkalemia even among RASi users. Thus, it is uncertain whether our findings can be generalized to other health care settings. Moreover, there was a trend toward a slightly higher risk of hyperkalemia with RASi restart in those with a history of hyperkalemia, though not statistically significant. Careful monitoring and appropriate management for hyperkalemia are required after restarting RASi, especially for those with a history of hyperkalemia.

Our study has several limitations. Because treatment assignment was not truly randomized, residual confounding and bias may exist despite implementing a clone-censor-weight approach. BP levels were unavailable in our database. Precise reasons for RASi discontinuation were unknown, preventing us from analyzing the reason-specific risk-benefit ratio of RASi restart. Nevertheless, we

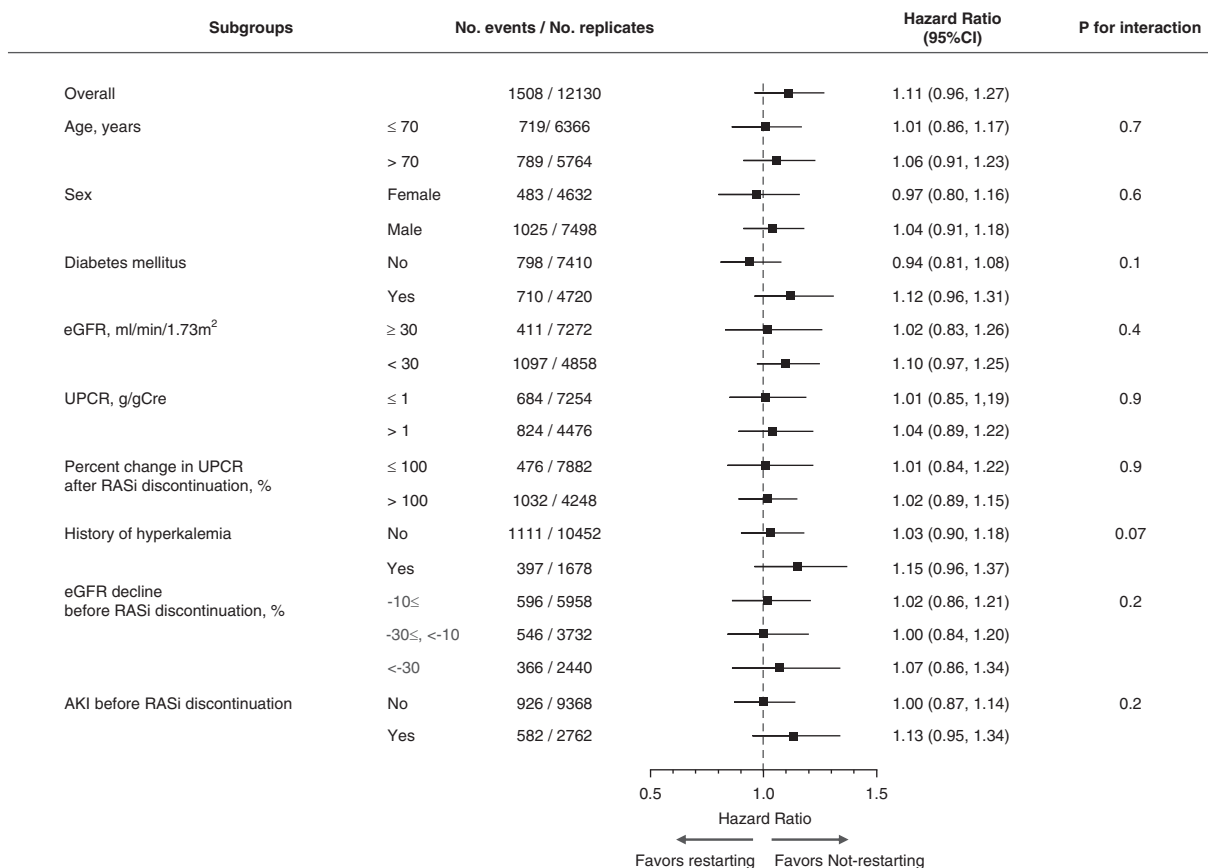


Figure 5. Subgroup analysis for the incidence of hyperkalemia. HR for the incidence of hyperkalemia in the Restart group versus the non-Restart group were analyzed according to the prespecified subgroups. Bars represent 95% CI.

found that those with a rapid eGFR decline and AKI before RASi discontinuation benefited less for kidney outcomes and mortality. Although it is difficult to accurately diagnose AKI based on real-world data, we used the National Health Service's AKI algorithm, a validated methodology to detect AKI from electronic healthcare records.^{33,34} Although some patients may have discontinued RASi because of a missed scheduled visit, such a case would be rare in the sensitivity analysis where RASi discontinuation was defined as an absence of prescription for ≥ 90 days since patients generally visited the outpatient department at least every 90 days. We were unable to specify RASi discontinuation because of pregnancy, although most of our patients were older, with an average age of 66 years. The causes of death were not available. The reporting of out-of-hospital deaths might be subject to underreporting. However, it is unlikely that reporting of out-of-hospital deaths depended on whether RASi were restarted or not. Because our patients generally initiated dialysis therapy in their study hospitals, the results are unlikely to be affected by nonobservability due to transfers to other hospitals. RASi discontinuation and restart were determined based on prescription data, which may lead to misclassification, although this bias would dilute the observed association toward the null. We confirmed the high accuracy of the prescription data through direct inspection of the EMR. The favorable risk-benefit ratio

observed in restarting RASi may be attributable to the close care and supervision by nephrology specialists in Japan. Therefore, our findings may not generalize to other countries and clinical settings. Nevertheless, the restart rate of RASi in our study (37%) was similar to that in previous studies of advanced CKD.^{9,11} Thus, our practice pattern regarding RASi restarting may not be so distinctive but relatively comparable with different populations. Further research in diverse clinical settings is essential to validate our observations.

In conclusion, our target trial emulation study revealed that restarting RASi within a year after discontinuation was associated with a lower risk of kidney failure and all-cause mortality among patients with CKD, although this association was attenuated among those who had rapid eGFR declines before discontinuation. The risk of hyperkalemia was not elevated after RASi restart. Our findings should be confirmed by future studies. While discontinuation of RASi frequently occurs during the course of CKD, our study provides valuable insights into the risk-benefit balance of restarting RASi, supporting a proactive approach to restarting RASi among patients with CKD.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/JASN/E747>.

Funding

None.

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Partial restrictions to the data and/or materials apply. The analytical datasets and STATA programs used in this study are available on request to the corresponding author.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/JASN/E746>.

[Supplemental Methods.](#)

[Supplemental Table 1.](#) Brief protocol of the target trial and its emulation using the OCKR database.

[Supplemental Table 2.](#) Inverse probability of censoring weights in intention-to-treat and per-protocol analyses.

[Supplemental Table 3.](#) Per-protocol analyses for the composite kidney outcome.

[Supplemental Table 4.](#) Per-protocol analyses for all-cause death and hyperkalemia.

[Supplemental Table 5.](#) Sensitivity analysis: intention-to-treat analyses with the length of RASi discontinuation of ≥ 90 days.

[Supplemental Table 6.](#) Sensitivity analysis: intention-to-treat analyses with the grace period of 6 months.

[Supplemental Table 7.](#) Sensitivity analysis: intention-to-treat analyses with the grace period of 2 years.

[Supplemental Table 8.](#) Sensitivity analysis: redefining the index date as the 30th day after RASi discontinuation.

[Supplemental Table 9.](#) Sensitivity analysis: redefining the baseline eGFR as the value recorded 90 days after the index date.

[Supplemental Table 10.](#) Sensitivity analysis: multivariable analysis after further adjustment for serum albumin level and C-reactive protein.

[Supplemental Table 11.](#) Sensitivity analysis with an alternate definition of hyperkalemia (serum potassium levels of ≥ 6.0 mEq/L).

[Supplemental Table 12.](#) Sensitivity analysis: intention-to-treat analyses with further adjustment for facilities.

[Supplemental Figure 1.](#) Schematic illustration of RASi prescription, discontinuation, and restart.

[Supplemental Figure 2.](#) Process of the cloning, censoring, and weighting method for the intention-to-treat analysis.

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