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Elucidating the present and future of individuals with kidney disease: a multifaceted epidemiological approach

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Citation

Janse, R. J. (2026, January 8). *Elucidating the present and future of individuals with kidney disease: a multifaceted epidemiological approach*. Retrieved from <https://hdl.handle.net/1887/4286980>

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



Chapter 04

Stopping versus continuing renin-
angiotensin-system inhibitors after
acute kidney injury and adverse clinical
outcomes: an observational study from
routine care data

Clin Kidney J. 2022 Jan 12;15(6):1109-1119 |  Open access

<https://doi.org/10.1093/ckj/sfac003>

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Abstract

Background. The risk-benefit ratio of continuing with renin-angiotensin-system inhibitors (RASi) after an episode of acute kidney injury (AKI) is unclear. While stopping RASi may prevent recurrent AKI or hyperkalemia, it may deprive patients of the cardiovascular benefits of using RASi.

Methods. We analyzed outcomes of long-term RASi users experiencing AKI (stage 2 or 3, or clinically coded) during hospitalization in Stockholm, Sweden, during 2007–2018. We compared stopping RASi within 3 months after discharge with continuing. The primary study outcome was the composite of all-cause mortality, myocardial infarction and stroke. Recurrent AKI was our secondary outcome, and we considered hyperkalemia as a positive control outcome. Propensity score overlap weighted Cox models were used to estimate hazard ratios, balancing 75 confounders. Weighted absolute risk differences (ARD) were also determined.

Results. We included 10,165 individuals, of whom 4,429 stopped and 5,736 continued RASi, with a median follow-up of 2.3 years. Median age was 78 years, 45% were women, and median kidney function before the index episode of AKI was 55 ml/min/1.73m². After weighting, those who stopped had an increased risk (HR, 95% CI) of the composite of death, myocardial infarction and stroke (1.13, 1.07–1.19; ARD 3.7, 95% CI 2.6, 4.8) compared with those who continued, a similar risk of recurrent AKI (0.94, 0.84–1.05), and a decreased risk of hyperkalemia (0.79, 0.71–0.88).

Discussion. Stopping RASi use among survivors of moderate-to-severe AKI was associated with a similar risk of recurrent AKI, but higher risk of the composite of death, myocardial infarction and stroke.

Background

Acute kidney injury (AKI) is a common complication in hospitalized patients that predicts worse outcomes, including a higher risk of death, cardiovascular events, and chronic kidney disease (CKD) (1-6). Renin-angiotensin-system inhibitors (RASi) are a cornerstone of care in preventing cardiovascular events and progression of proteinuric CKD (7-13) and may also decrease the risk of events post AKI, as found in intensive care settings (14-16). However, RASi have also been associated with the development of AKI (17-19), and there is the belief that in the setting of acute intercurrent illness, RASi can cause recurrent AKI (20). This leaves the risk-benefit ratio of RASi after an episode of AKI unclear.

Recent observational studies have tried to address this issue (20-24), but provided conflicting results of higher (20) and similar (22-24) risks of recurrent AKI. Differing results may be attributed to differences in study designs, as some studies excluded patients with heart failure (23) or focused on veterans, the majority of whom are men (24). Most studies also included participants after KDIGO stage 1 AKI (20, 22, 23). Stage 1 AKI may reflect non-pathological changes in creatinine levels, for example due to surgery, hydration, or drugs, which may not be clinically relevant. Previous studies often included both prevalent and new users of RASi (20, 22, 23), and we argue that stopping vs. continuing RASi is a different scenario than newly initiating vs. never initiating RASi after AKI. Finally, the likelihood of stopping vs. continuing therapy is influenced by whether patients needed RASi in the first place (i.e. whether they had a specific evidence-based indication).

In this study, we tried to overcome the identified limitations and investigated the association of stopping RASi within 3 months after hospital discharge with the risk of adverse clinical outcomes among long-term users of RASi who developed moderate or severe AKI during hospitalization.

Methods

This study was reported according to the REporting of studies Conducted using Observational Routinely collected health Data for PharmacoEpidemiology statement (RECORD-PE) (25). A visual depiction of the study design and analysis is available in **S-Figure 1** (26). Methods employed are elaborated in **Supplemental Methods**.

Data sources

We used data from the Stockholm CREATinine Measurements (SCREAM) project, a health care utilization cohort of all residents in the region of Stockholm who accessed healthcare between the 1st of January 2006 and the 31st of December 2019 (27). The region of Stockholm provided universal healthcare access to approximately 2.9 million citizens during the study period. Laboratory data was linked with other administrative databases to ascertain demographics, diagnoses, drug dispensations, health care use, vital status, and the start of kidney replacement therapy (KRT).

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Study design

We included all patients >18 years who were long-term prevalent users of RASi with a guideline indication for RASi treatment, and who, between January 1st 2007 and December 31st 2018, survived stage 2 or 3 AKI or a clinically recognized AKI.

First we identified all hospital admissions during which an AKI diagnosis was issued or where creatinine changes defining AKI stage 2 or 3 according to creatinine changes were detected (9). Admission creatinine used in KDIGO AKI staging was defined as the mean of all creatinine measurements in the previous year up to 7 days before the index admission date. We then selected those participants who had an indication for RASi use (8-11, 13, 28). For the definition of exposures, covariates and outcomes, see **S-Table 1 and S-Figure 1**. Finally, we selected only those who had at least one dispensation for ACEi or ARB in the year prior to hospitalization.

We excluded patients who did not reside in Stockholm at the time of AKI admission, whose baseline kidney function was <15 ml/min/1.73m², or who had ever undergone dialysis or kidney transplantation. We also excluded those in whom admission creatinine could not be calculated and those who died either during their hospital stay or within 90 days from hospital discharge (**S-Figure 1**).

We applied a landmark design at 3 months to avoid immortal time bias, in which follow-up started at day 91 after hospitalization. Study exposure was determined from day 1 to day 90 after hospitalization (29). The landmark design assumed a fixed exposure and thereby simulated an intention-to-treat effect. Study participants were followed up until the occurrence of death, emigration, five years after the landmark, or administrative censoring (31st of December 2019).

Exposure

Stopping was defined as the absence of a pharmacy dispensation for RASi within the first 3 months after hospital discharge, indicating stopping RASi treatment. Continuing was defined as at least one pharmacy dispensation for RASi at any point during the first 3 months after hospital discharge.

Outcomes

The primary outcome was the composite outcome of stroke, myocardial infarction and all-cause mortality, the secondary outcome was recurrent AKI (by clinical diagnosis). We used only a clinical diagnosis because a first AKI obscures what can be considered 'baseline creatinine' needed to determine AKI based on creatinine changes. For completeness, and because previous studies have reported contradictory results for the risk of heart failure hospitalization (HFF) (20-22) and CKD progression (20, 22), we included these as tertiary outcomes. Finally, the risk of moderate hyperkalemia (potassium ≥ 5.5 mmol/L) was selected as a positive control outcome, this being a recognized adverse event of RASi therapy (**S-Table 1**).

Covariates

Covariates included age at discharge, sex, baseline eGFR (calculated from admission creatinine determined for KDIGO AKI criteria), eGFR at 90 days (calculated as the closest to [but not after] day-90 post-discharge outpatient creatinine measurement), attained education, medical history (including events occurring up to discharge), medication use (between 180 days and 1 day before the index admission), healthcare access in the year prior to hospitalization, cause of, and procedures and conditions during the index hospitalization, and laboratory values (**S-Figure 1; S-Table 1**). eGFR was calculated using the 2009 Chronic Kidney Disease – Epidemiology Collaboration formula without considerations for race (30).

Statistical analyses

Categorical variables are presented as proportions. Depending on the distribution, continuous variables are either presented as the mean with standard deviation (SD) or the median with interquartile range (IQR). Overlap weighted Cox regression with 75 covariates was used to estimate adjusted hazard ratios (HR) (31). Weighted absolute risks and absolute risk differences at 5 years after start of follow-up were also calculated for all outcomes and weighted cumulative incidence curves were computed for all outcomes.

We performed prespecified subgroup analyses stratified by age (<vs>=65 years), heart failure, ischemic heart disease, diabetes, and moderately to severely decreased CKD (<vs>= 45 ml/min/1.73²). P-values for interaction in subgroups were calculated using a Wald test. We performed four sensitivity analyses: we a) re-estimated our HRs with double robust Cox regression; b) additionally adjusted for ACR categories; c) restricted analyses to participants with a diagnostic code N17 during their index AKI; and d) changed the landmark from 3 to 6 months. All statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results*Baseline characteristics*

Between 2007 and 2018, we identified 10,165 prevalent users of RASi with an indication for the therapy and who survived for at least 3 months after discharge following a hospitalization which included a moderate to severe AKI. The frequency of indications overall and between stoppers and continuers is shown in **S-Table 2**. 71 study participants (1%) started maintenance dialysis during the landmark period. Of the 10,165 prevalent RASi users, 4,429 stopped RASi and 5,736 continued (**Figure 1**). The time course of restarting is shown in **S-Figure 2**. The majority of continuers dispensed RASi already before the landmark and among continuers, 608 (13%) discontinued for more than 30 days after the landmark with a median of 0.5 years until discontinuation. The study participants had a median (IQR) age of 78 (69–85) years, with the majority of participants being older than 80 years (**Table 1**), and 45% of participants being women. Median kidney function was 55 ml/min/1.73m². Common comorbidities

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included hypertension (91%), chronic heart failure (54%), and diabetes (45%). The most commonly-used medications in the year prior to hospitalization were anticoagulants (71%), beta blockers (66%), and loop diuretics (52%). After weighting, all baseline characteristics were well-balanced (**Table 1** and **S-Table 3**).

Table 1. Baseline characteristics (before and after weighting) of patients stopping or continuing renin-angiotensin-system inhibitor treatment three months after an AKI. All values represent percentages unless otherwise specified.

	Before weighting				After weighting		
	Overall	Stopped RASi	Continued RASi	SMD*	Stopped RASi	Continued RASi	SMD*
Number of individuals	10,165	4,429	5,736		4,429	5,736	
Median age[†] (IQR) (years)	78 [69, 85]	79 [70, 85]	77 [69, 84]	0.111	78 [69, 85]	78 [70, 85]	<0.001
Age category				0.104			0.025
<50 years	2	2	2	<0.001	2	2	<0.001
50-59 years	5	4	6	0.092	5	5	<0.001
60-69 years	18	18	19	0.026	18	18	<0.001
70-79 years	31	30	32	0.043	30	31	0.022
>80 years	44	46	42	0.081	44	44	<0.001
Women	45	46	45	0.024	46	46	<0.001
Highest level of education achieved[‡]				0.064			0.035
Compulsory school	36	36	36	<0.001	36	36	<0.001
Secondary school	40	39	41	0.041	40	40	<0.001
University	20	22	19	0.074	21	20	0.025
Missing	3	3	3	<0.001	3	3	<0.001
Median admission eGFR[§] (IQR) (mL/min/1.73 m²)	55 [41, 74]	53 [39, 70]	57 [43, 76]	0.193	55 [40, 73]	55 [41, 73]	<0.001
eGFR categories in mL/min/1.73m²				0.191			0.016
≥90	9	7	10	0.108	9	8	0.036
≥60 - <90	32	29	34	0.108	31	31	<0.001
≥45 - <60	27	28	27	0.022	28	28	<0.001
≥30 - <45	22	24	21	0.072	22	23	0.024
≥15 - <30	10	12	8	0.134	10	10	<0.001
Median eGFR 90 days post discharge (IQR) (mL/min/1.73m²)	50.7 [36.0, 69.6]	48.7 [33.9, 67.3]	52.3 [37.7, 71.2]	0.136	50.5 [35.9, 69.4]	50.4 [35.7, 68.7]	0.021
^{†,‡,§}							
Medical history							
Hypertension	91	91	91	0.017	91	91	<0.001
Diabetes mellitus	45	42	47	0.108	45	45	<0.001
Chronic heart failure	54	52	56	0.072	54	54	<0.001
Myocardial infarction	28	27	30	0.064	28	28	<0.001
Arrhythmia	45	45	46	0.018	45	45	<0.001

Stopping RASi after hospitalization for AKI

	Before weighting				After weighting		
	Overall	Stopped RASi	Continued RASi	SMD*	Stopped RASi	Continued RASi	SMD*
Cerebrovascular disease	27	26	28	0.043	27	27	<0.001
Peripheral vascular disease	20	20	20	0.013	20	20	<0.001
Ischemic heart disease	43	41	45	0.082	42	42	<0.001
Extracranial hemorrhage	1	1	1	0.029	1	1	<0.001
Valvular heart disease	12	11	12	0.027	12	12	<0.001
COPD	20	19	20	0.020	20	20	<0.001
Cancer	28	32	26	0.132	29	29	<0.001
Liver disease	5	5	5	0.001	5	5	<0.001
Dyslipidemia	37	35	39	0.090	37	37	<0.001
Hypothyroidism	13	13	13	0.028	13	13	<0.001
Prior medication use							
Beta blockers	66	63	68	0.100	65	65	<0.001
CCBs	33	33	34	0.032	33	33	<0.001
Loop diuretics	52	51	53	0.038	52	52	<0.001
Thiazide diuretics	6	6	6	0.018	6	6	<0.001
Potassium-sparing diuretics	21	20	23	0.083	21	21	<0.001
NSAIDs	13	13	14	0.011	13	13	<0.001
LLAs	49	45	52	0.127	48	48	<0.001
Alpha blockers	8	8	8	0.004	8	8	<0.001
Nitrate	18	17	18	0.051	17	17	<0.001
MRAs	21	19	22	0.084	20	20	<0.001
Hydralazine	0	0	0	0.019	0	0	<0.001
Anti-arrhythmics	1	1	1	0.008	1	1	<0.001
Digoxin	8	7	9	0.061	8	8	<0.001
Anticoagulants	71	69	73	0.089	71	71	<0.001
Diabetes medication	33	30	36	0.119	33	33	<0.001
Opioids	30	31	30	0.006	31	31	<0.001
Characteristics of index hospitalization							
Median LOS [†] (IQR) (days)	8 [4, 17]	10 [5, 18]	8 [4, 16]	0.156	9 [4, 17]	8 [4, 17]	<0.001
AKI as cause of admission, %	19	22	17	0.139	20	20	<0.001
Stage of AKI [‡] , %				0.126			0.045
N17	28	28	28	<0.001	28	27	0.022
Stage 2	49	46	51	0.100	47	49	0.040
Stage 3	24	27	21	0.141	25	23	0.047
Need for acute dialysis, %	2	2	1	0.060	2	2	<0.001
Median of average plasma creatinine [¶] (IQR) (μmol/L)	180 [135, 251]	191 [142, 273]	171 [131, 238]	0.196	184 [138, 255]	179 [134, 253]	<0.001

	Before weighting				After weighting		
	Overall	Stopped RASi	Continued RASi	SMD*	Stopped RASi	Continued RASi	SMD*
Median of peak plasma creatinine [†] (IQR) (μmol/L)	231 [170, 334]	246 [179, 362]	221 [164, 309]	0.178	235 [174, 342]	231 [170, 332]	<0.001
Mean potassium ^{‡,§} (mmol/L)	4.4 (0.7)	4.4 (0.7)	4.3 (0.7)	0.106	4.4 (0.7)	4.3 (0.7)	0.049
Peak potassium ^{‡,§} (mmol/L)	4.9 (1.0)	4.9 (1.0)	4.8 (1.0)	0.119	4.9 (1.0)	4.8 (1.0)	0.054
Missing potassium ^{¶,} , %	1	1	1				

Categorical variables are presented as percentage. Continuous variables are presented as mean (SD) or as median [IQR] if specified.

RASi, renin-angiotensin-system inhibitors; SMD, standardized mean difference; IQR, interquartile range; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CCBs, calcium-channel blockers; NSAID, non-steroidal anti-inflammatory drugs; LLAs, lipid-lowering agents; MRA, mineralocorticoid receptor antagonist; LOS, length of stay; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

* A standardized mean difference >0.1 indicates meaningful imbalance between groups.

[†] Standardized difference for the mean was calculated for age, eGFR at admission, eGFR at day 90 after discharge, healthcare access in the past year, duration of stay, and plasma creatinine during admission.

[‡] Education, eGFR at day 90 after discharge, and potassium were missing in 3%, 17% and 1%, respectively.

[§] Admission eGFR was calculated from the mean of all creatinine measurements a year prior to hospitalization with exclusion of the measurements seven days prior to admission.

^{||} If an individual met criteria for AKI according to serum creatinine changes and had had a diagnostic code defining AKI during the same hospitalisation, the AKI was typed according to serum creatinine changes.

[¶] The median of the average plasma creatinine was calculated as follows: for each individual, the average of all creatinine measurements during their hospitalization was calculated. Then, because the distribution of these average values was non-normal, we calculated the median of the values.

[#] Not adjusted for in analyses.

Association of stopping vs. continuing RASi with the composite of death, myocardial infarction and stroke

During a median (IQR) follow-up of 2.3 (1.0–4.4) years, 3,020 individuals in the continuation group and 2,613 individuals in the stopping group developed our primary study outcome, corresponding with an incidence rate (95% confidence interval [CI]) of 19.8 (19.1–20.5) and 24.6 (23.7–25.6) per 100 person-years, respectively. Of the 5,633 events, 4,489 were deaths, 591 were myocardial infarctions, and 553 were strokes. After weighting, the adjusted hazard ratio (95% CI) was 1.13 (1.07–1.19) for the stopping group compared with the continuation group (**Table 2**). The weighted cumulative incidence curve is shown in **Figure 2A**, and shows a consistent difference in the risk of death, myocardial infarction and stroke over time with a higher risk in the stopping group. Correspondingly, the weighted 5-year absolute risk (95% CI) was 63% (61–64%) in those who continued and 66% (65–68%) in those who stopped: a difference of 3.7% (2.6, 4.8%) higher for the stopping group compared with the continuation

group. Results for the individual components of the composite outcome are reported in **S-Table 4**.

Association of stopping vs. continuing RASi with recurrent AKI

Total 780 individuals in the continuation group and 552 individuals in the stopping group had a recurrent AKI episode, corresponding with incidence rates of (95% CI) of 5.1 (4.8-5.5) and 5.2 (4.8-5.7) per 100 person-years, respectively. The adjusted hazard ratio (95% CI) was 0.94 (0.84-1.05) for the stopping group compared with the continuation group. The weighted cumulative incidence curve shown in **Figure 2B** shows no consistent difference over time in the risk of recurrent AKI between the two groups. Correspondingly, at 5 years, the absolute risk difference (95% CI) was 0.2% (-0.9, 1.4%) lower for the stopping group compared with the continuing group.

Association of stopping vs. continuing RASi with other outcomes

The adjusted HR (95% CI) for the positive control outcome hyperkalemia was 0.79 (0.71-0.88). The adjusted HRs (95% CI) for the association of stopping vs. continuing RASi with tertiary outcomes were 1.01 (0.94-1.07) for HHF and 1.05 (0.96-1.15) for CKD progression. The weighted cumulative incidence curves are shown in **Figure 2C** for hyperkalemia and in **S-Figures 3A-B** for the tertiary outcomes.

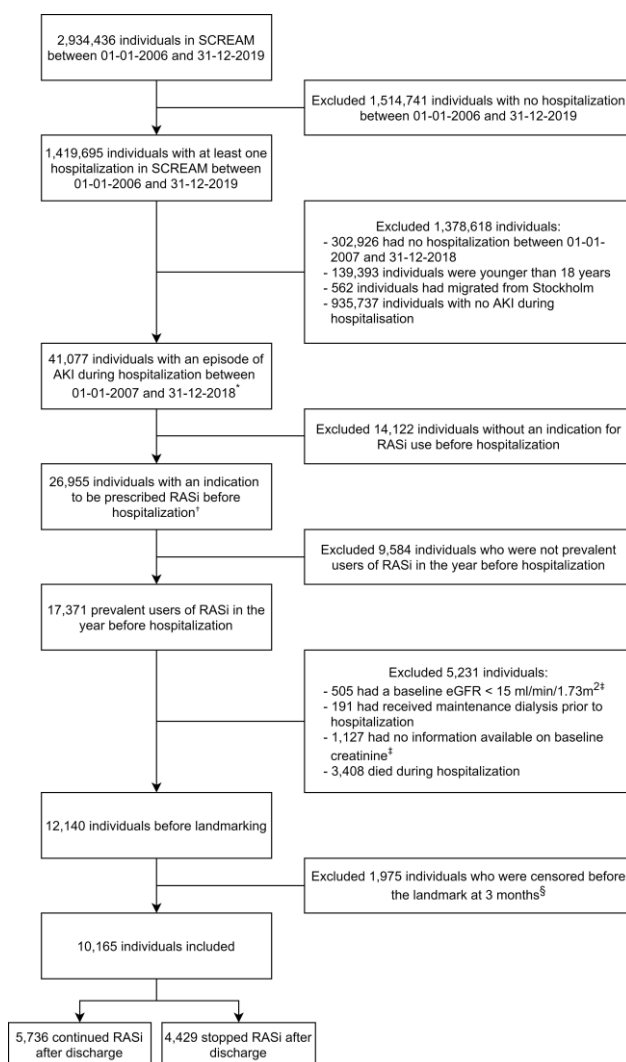
Subgroup analyses

The increased risk of the primary outcome among stoppers was observed among subgroups of age, HHF, ischemic heart disease and diabetes mellitus with p-values for interaction >0.05 (**Figure 3**). For decreased kidney function, there was a statistically significant interaction with the risk being higher among study participants with a higher kidney function. A statistically significant interaction was observed for history of heart failure and stopping vs. continuing for the recurrent AKI outcome (**Figure 4**). No interactions were observed for the outcomes hyperkalemia and HHF. For the outcome CKD progression, there was an interaction between decreased kidney function and stopping vs. continuing (**S-Figures 4-6**).

Sensitivity analyses

When using double robust Cox regression, adjusting for ACR categories, restricting the analysis to individuals with a N17 diagnostic code or moving the landmark from 3 to 6 months provided results consistent in magnitude, direction and significance similar to our main analysis (**S-Figure 2; S-Figures 7-9. S-Tables 5-10**).

Figure 1. Flowchart showing patient selection.



* Acute kidney injury was defined as either acute kidney injury stage 2 or stage 3 using plasma creatinine changes according to KDIGO criteria, or as an ICD-10 code N17 in any diagnostic position during hospitalization.

† An indication for RASi use was defined as: 1) cardiovascular disease (i.e. ischemic heart disease, peripheral vascular disease, or cerebrovascular disease), 2) heart failure, 3) diabetes mellitus with kidney function ≤ 60 mL/min/1.73m², 4) diabetes mellitus with albuminuria ≥ 20 mg/L or with an albumin-creatinine ratio (ACR) ≥ 3 mg/mmol, 5) hypertension with kidney function ≤ 60 mL/min/1.73m², or 6) albuminuria ≥ 200 mg/L or ACR > 30 mg/mmol.

‡ Baseline creatinine was defined as the mean of all creatinine measurements within the 365 to 7 days prior to hospital admission. Baseline eGFR was calculated from baseline creatinine.

§ A landmark design was applied in which at 3 months after the study start (day 90), exposure was determined using the past three months and then fixed, with follow-up starting at day 91.

Stopping RASi after hospitalization for AKI

Figure 2. Weighted cumulative incidence curves showing the risk (line) and confidence interval (band) of outcomes stratified by stopping vs. continuing renin-angiotensin-system inhibitors for the primary outcome of composite death, myocardial infarction (MI), and stroke, the secondary outcome recurrent AKI, and the positive control outcome hyperkalemia. Time 0 refers to start of follow-up (i.e. 90 days post-discharge).

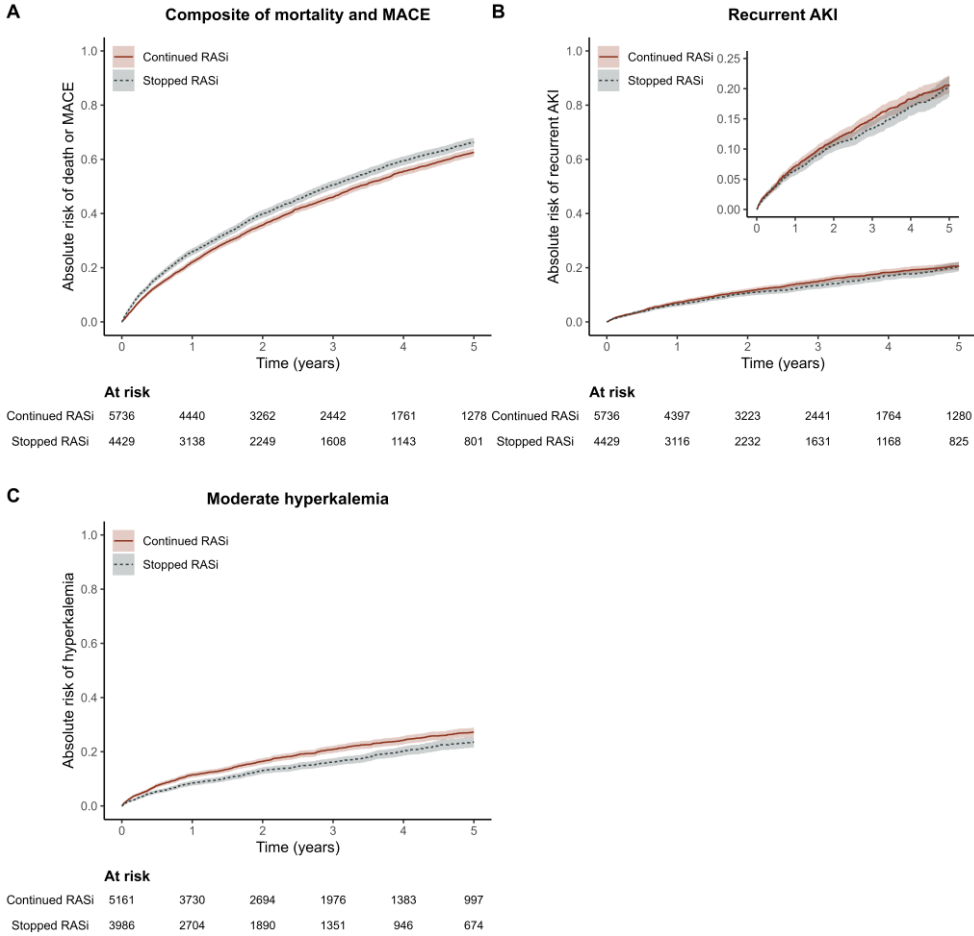
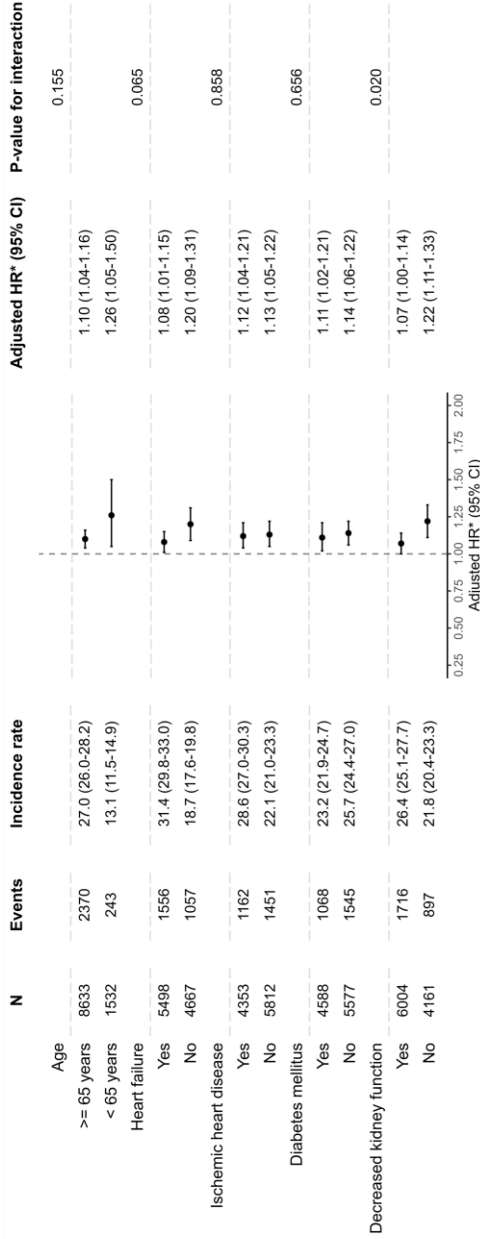
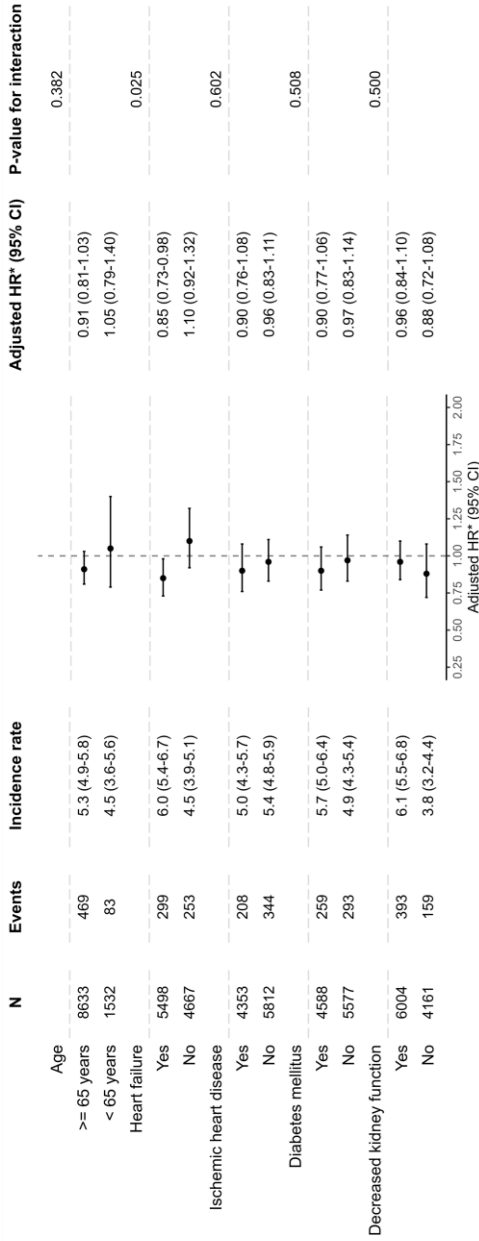


Figure 3. Forest plot showing the association of stopping vs. continuing RASi on the composite outcome of death, myocardial infarction and stroke, stratified by subgroups.



* Adjusted for age, age categories, sex, education, eGFR at admission, eGFR category at admission, medical history of diabetes, hypertension, myocardial infarction, arrhythmia, cerebrovascular disease, peripheral vascular disease, ischemic heart disease, chronic obstructive pulmonary disease, cancer, liver disease, chronic heart failure, dyslipidemia, hypothyroidism, extracranial hemorrhage, and valvular heart disease, use in the year prior to admission of beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, potassium-sparing diuretics, NSAIDs, antilipids, alpha blockers, nitrate, mineralocorticoid receptor antagonists, hydralazine, antiarrhythmics, digoxin, anticoagulants, diabetes medication, and opioids, health care access in the year prior to admission, specialist care context, and hospitalizations, primary cause of admission, complications during admission (i.e. sepsis, cardiac surgery, cardiac catheterization, abdominal aortic aneurysm repair, pneumonia, liver failure, acute myocardial infarction, and non-cardiac surgery), and characteristics of admission including duration of stay, AKI as cause of admission, stage of AKI according to KDIGO, and average and peak creatinine during hospitalization, with exception of the indicator of the subgroup per subgroup (e.g. we did not adjust for diabetes mellitus in the diabetes mellitus subgroup).

Figure 4. Forest plot showing the association of stopping vs. continuing RASi on recurrent AKI.



* Adjusted for age, age categories, sex, education, eGFR at admission, eGFR category at admission, medical history of diabetes, hypertension, myocardial infarction, arrhythmia, cerebrovascular disease, peripheral vascular disease, ischemic heart disease, chronic obstructive pulmonary disease, cancer, liver disease, chronic heart failure, dyslipidemia, hypothyroidism, extracranial hemorrhage, and valvular heart disease, use in the year prior to admission of beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, potassium-sparing diuretics, NSAIDs, antilipids, alpha blockers, nitrate, mineralocorticoid receptor antagonists, hydralazine, antiarrhythmics, digoxin, anticoagulants, diabetes medication, and opioids, health care access in the year prior to admission (i.e. sepsis, cardiac surgery, cardiac catheterization, abdominal hospitalizations, primary cause of admission, complications during admission), and characteristics of admission (aortic aneurysm repair, pneumonia, liver failure, acute myocardial infarction, and non-cardiac surgery), and characteristics of admission including duration of stay, AKI as cause of admission, stage of AKI according to KDIGO, and average and peak creatinine during hospitalization, with exception of the indicator of the subgroup per subgroup (e.g. we did not adjust for diabetes mellitus in the diabetes mellitus subgroup).

Discussion

No randomized trials inform the decision of stopping vs. continuing RASi in patients following AKI, the clinical uncertainty being reflected in the practice variation observed in our study, in which 44% stopped and 56% continued. We explored clinical outcomes associated with stopping versus continuing RASi therapy among 10,165 survivors of a moderate to severe AKI. We observed that compared with continuing RASi, stopping this medication was associated with an increased risk of death, myocardial infarction, and stroke, but with a similar risk of recurrent AKI. We also observed similar risks of HHF or CKD progression. As expected, stopping RASi was associated with a lower risk of hyperkalemia, although, in keeping with other studies, the residual risk of hyperkalemia is high (32). Results supporting the continuation of RASi after AKI were robust across most subgroups, and all sensitivity analyses.

Brar *et al.* evaluated Canadian survivors of AKI during a hospital stay (20), and observed a lower risk (HR, 95% CI) of mortality (0.85, 0.81-0.89), but at a higher risk of recurrent AKI (1.25, 1.08-1.46) for RASi-users compared with non-users. We believe that combining prevalent and new users of RASi in the study of Brar *et al.* combines two different questions in one analysis. Brar *et al.* did however also stratify their treatment groups in a sensitivity analysis, in which they found increased risks for hospitalization for a renal cause for new users (1.32, 1.03-1.69) and continuers (1.34, 1.16-1.55) compared with never users. However, hospitalization for a renal cause as an outcome was defined as a composite of hospitalization for AKI, congestive heart failure, hypervolemia, hyperkalemia, and malignant hypertension, reducing the ability to make inference about AKI alone.

Although use of RASi has been associated with AKI in patients undergoing cardiac surgery (17), surprisingly few studies have explored the risk of AKI associated with RASi. One such study, from UK primary care, reported an increased risk of AKI associated with RASi which was confined to patients who did not have an established indication (33). Neither intervening studies nor the current study observed an increased risk of recurrent AKI among prevalent users with AKI who continued with their RASi. In ASSESS-AKI, a North American prospective cohort study, 769 RASi users with prior AKI were compared with clinically-matched non-users (22); risk of death was decreased (0.62, 0.46-0.84) and risk of recurrent AKI similar (0.88, 0.69-1.13) for RASi users compared with non-users. Siew *et al.* evaluated prevalent users of RASi who developed AKI stage 2-3 during hospitalization in the Veterans Affairs system in the US (24), and reported an increased risk of mortality (1.33, 1.26-1.41) with similar risk of recurrent AKI (0.98, 0.91-1.05) for those who stopped compared with those who continued. Hsu *et al.* selected AKI survivors from another health system in the US, and observed no increased risk of recurrent AKI (0.71, 0.45-1.12) for RASi users compared to non-users (23). Bidulka *et al.* studied stopping vs. continuing RASi in both an English cohort (n=8,566) and a Swedish cohort (n=2,024) (21). Our findings are in accordance with those from

the English cohort, which reported a higher risk (HR, 95% CI) of mortality (1.27, 1.15-1.41) and similar risks of recurrent AKI (0.90, 0.77-1.05). In the Swedish cohort however, no association with mortality (0.94, 0.78-1.13) or with recurrent AKI (0.81, 0.54-1.21) was found at that time. Although the Swedish cohort from Bidulka *et al.* was derived from the same data source as our study, differences in results are likely attributable to differences in population selection. Bidulka *et al.* identified AKI cases solely as an AKI diagnosis coded as the primary cause for hospital admission and limited follow-up to 2 years. In addition, the data collection period was more remote from present day practice (2006-2011). Collectively, we interpret that the majority of observational evidence to date, including this study, supports continued RASi use in this population at high cardiovascular risk, on the basis of consistent associations with decreased cardiovascular events and death, and uncertain, variable effects on recurrent AKI.

Some of the previous studies evaluated risks of heart failure or CKD progression, reaching opposing conclusions. We regarded them as tertiary outcomes for in our understanding the effectiveness of RASi in preventing heart failure has mainly been seen in patients in trials of heart failure patients (34, 35), and the effect of RASi on delaying CKD progression is moderately certain and well known, but unlikely to be the reason for which RASi was initiated in this general population cohort. The increased heart failure risk reported by Brar *et al.* among those who stopped RASi (20), was not seen in our study, nor in previous analyses (21, 22). This is somewhat surprising; however, the evidence that RASi reduces outcomes in patients with heart failure is limited to the study of participants with low ejection fraction, and we do not know what proportion of our participants have low ejection fraction. The lower risk of CKD progression reported by Brar *et al.* among those who stopped (20) was also not seen in our study nor in previous analyses (22). The differences between studies in populations (particularly the selection of both prevalent and incident users in Brar *et al.*) may account for the differences in findings.

Our study has a number of strengths: we focused on evaluating long-term RASi users with moderate to severe AKI, a population in whom this research question is of clinical relevance. We were able to utilize complete healthcare records for a population of a whole region in a country with universal healthcare access; this possibly reduced the risk of healthcare use bias, allowed rich adjustment for confounders and improved the ascertainment of outcomes. Our study also has limitations: it is observational in nature and therefore residual confounding cannot be excluded; recurrent AKI was identified using only diagnostic codes and had a low event rate which reduces precision and power; we used a time-fixed exposure which may result in misclassification, although in a sensitivity analysis we reduced the misclassification and results remained robust; we were unable to identify all indications for RASi use (e.g. hypertension based on blood pressure); and we were unable to adjudicate the cause of the AKI during the index hospitalization, creating possible heterogeneity in the population. Extrapolation to other health

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systems, countries, and periods should be done with caution, but concordance with previous studies suggests that our findings may have generalizability.

To conclude, our study of prevalent users of RASi with a guideline indication for the treatment showed that stopping RASi treatment was associated with an increased risk of death, myocardial infarction and stroke, but with a similar risk of recurrent AKI. These results may inform physicians in their clinical decision making whilst randomized clinical trials remain unavailable.

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Supplemental materials

Supplemental methods

Supplemental tables

Supplemental table 1. Definition of covariates and outcomes.

Supplemental table 2. Proportions of indications overall and between study participants who stopped and who continued renin-angiotensin-system inhibitors. Participants were able to have more than one indication.

Supplemental table 3. Additional baseline characteristics used in the propensity score overlap weighting in addition to those of Table 1, reported overall and stratified by stopping vs. continuing renin-angiotensin-system inhibitors.

Supplemental table 4. Number of events, incidence rates, hazard ratios, and absolute risks at 5 years for the individual components of the composite outcome: death, myocardial infarction, and stroke.

Supplemental table 5. Comparison of weighted hazard ratios (95% CI) from the main analysis with the weighted hazard ratios (95% CI) from the sensitivity analyses.

Supplemental table 6. Association of stopping vs. continuing renin-angiotensin-system inhibitors with adverse outcomes in the sensitivity analysis, which also adjusted for urine albumin-creatinine-ratio categories using a 'missing' category.

Supplemental table 7. Baseline characteristics (before and after weighting) for the sensitivity analyses in which index acute kidney injury was defined using solely by the presence of ICD-10 code N17, stratified by stopping or continuing renin-angiotensin-system inhibitors.

Supplemental table 8. Baseline characteristics (before and after weighting) for the sensitivity analyses in which the landmark was moved from 3 months to 6 months, stratified by stopping or continuing renin-angiotensin-system inhibitors.

Supplemental table 9. Number of events, incidence rates, crude and adjusted hazard ratios, and weighted absolute risks and absolute risk differences for the association between stopping vs. continuing renin-angiotensin-system inhibitors and adverse outcomes in the sensitivity analysis where the index acute kidney injury was determined solely by the presence of an ICD-10 code N17.

Supplemental table 10. Number of events, incidence rates, crude and adjusted hazard ratios, and weighted absolute risks and risk differences for the association between stopping vs. continuing renin-angiotensin-system inhibitors and adverse outcomes in the sensitivity analysis in which the landmark was moved from 3 months to 6 months.

Supplemental figures

Supplemental figure 1. Overview of the study design and analysis steps; from top to bottom equals the order in which the analysis was conducted.

Supplemental figure 2. Reinitiation of renin-angiotensin-system inhibitors after hospital discharge in the main analysis.

Supplemental figure 3. Weighted cumulative incidence curves showing the risk of tertiary outcomes stratified by stopping vs. continuing renin-angiotensin-system inhibitors. Time 0 refers to start of follow-up (i.e. 90 days post-discharge).

Supplemental figure 4. Forest plot showing the association of stopping vs. continuing RASi with moderate hyperkalemia stratified by subgroups.

Supplemental figure 5. Forest plot showing the association of stopping vs. continuing RASi with hospitalization for heart failure stratified by subgroups.

Supplemental figure 6. Forest plot showing the association of stopping vs. continuing RASi with progression of chronic kidney disease by subgroups.

Supplemental figure 7. Flowchart showing inclusion of individuals in the sensitivity analysis in which acute kidney injury during hospitalization was determined solely by the presence of ICD-10 code N17.

Supplemental figure 8. Flowchart showing inclusion of individuals in the sensitivity analysis in which the landmark was set at 6 months instead of 3 months.

Supplemental figure 9. Reinitiation of renin-angiotensin-system inhibitors after hospital discharge in the sensitivity analysis in which acute kidney injury during hospitalization was determined solely by the presence of ICD-10 code N17.

The full supplemental file (32 pages) can be found online at <https://doi.org/10.1093/ckj/sfac003>. The digital manuscript and supplemental file also contain colourblind-accessible figures. All codes underlying the analyses are available at <https://github.com/rjjanse/janse-2022-ckj>.