Optimal cardiovascular treatment strategies in kidney disease: casual inference from observational data

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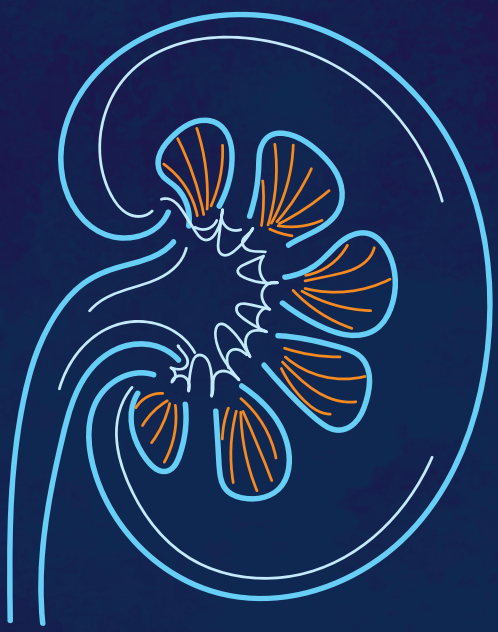
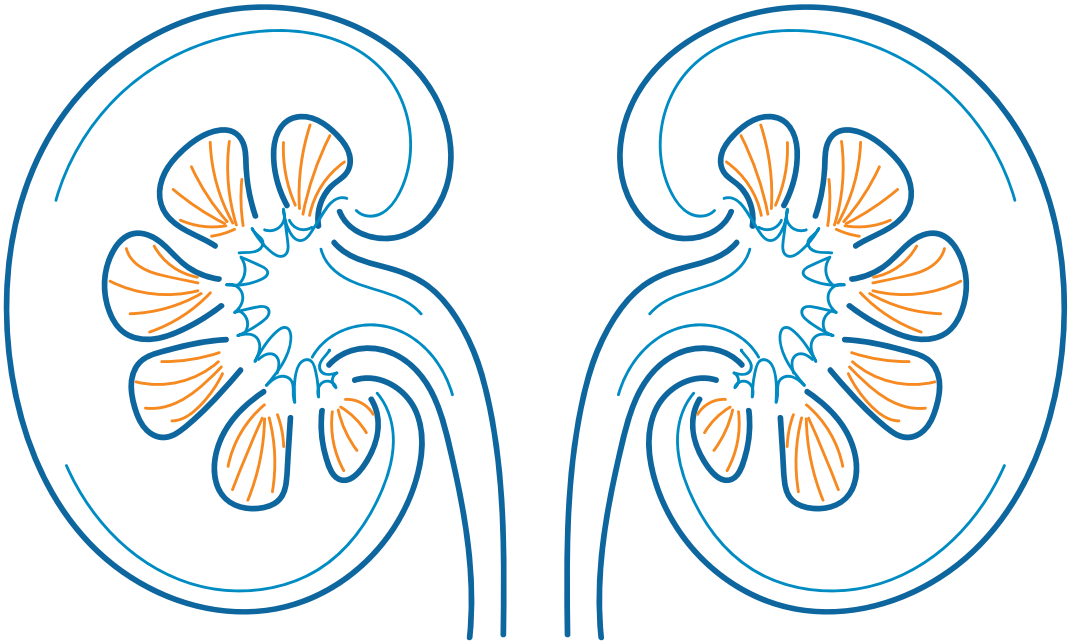
PART II

Clinical applications in kidney disease





CHAPTER 5

Association of acute increases in plasma creatinine after renin-angiotensin blockade with subsequent outcomes

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Abstract

Background and objectives. Data from observational and interventional studies provide discordant results regarding the relationship between creatinine increase following renin-angiotensin system inhibition (RASi) and adverse outcomes. We compared health outcomes among patients with different categories of increase in creatinine upon initiation of RASi in a large population-based cohort.

Design, setting, participants, and measurements. We performed a retrospective analysis of the Stockholm CREAtinine Measurements database, which contains complete information on diagnoses, medication dispensation claims, and laboratory test results for all Stockholm citizens accessing healthcare. Included were 31 951 adults initiating RASi during 2007-2011 with available pre- and post-initiation creatinine monitoring. Multivariable Cox regression was used to compare mortality, cardiovascular and end-stage kidney disease (ESKD) events among individuals with different ranges of creatinine increases within 2 months after starting treatment.

Results. In a median follow-up of 3.5 years, acute increases in creatinine were associated with mortality (3202 events) in a graded manner: compared with creatinine increases <10%, a 10-19% increase showed an adjusted HR of 1.15 (95% CI 1.05-1.27); HR 1.22 (1.07-1.40) for 20-29%; HR 1.55 (1.36-1.77) for ≥30%. Similar graded associations were present for heart failure (2275 events, p for trend <0.001) and ESKD (52 events; p for trend <0.001), and, less consistently, myocardial infarction (842 events, p for trend 0.25). Results were robust across subgroups, among continuing users, when patients with decreases in creatinine were excluded from the reference group, and after accounting for death as a competing risk.

Conclusions. Among real-world monitored adults, increases in creatinine (>10%) following initiation of RASi are associated with worse health outcomes. These results do not address the issue of discontinuation of RASi when plasma creatinine increases but do suggest that patients with increases in creatinine have higher subsequent risk of cardiovascular and kidney outcomes.

Introduction

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), known collectively as renin-angiotensin inhibitors (RASi), are widely prescribed drugs that are cornerstones in the treatment of hypertension, heart failure and proteinuric kidney disease (1, 2). Acute increases in creatinine are often observed after initiation of RASi, but the clinical significance of such increases is controversial (3-10). Current clinical guidelines recommend monitoring of creatinine during the first weeks of RASi, and discontinuing if creatinine increases exceed 30% (1, 2, 11). The rationale for the 30% threshold is unclear (12, 13).

One previous healthcare-based study, and reanalysis of 5 trials, have attempted to identify the threshold of increase in creatinine associated with increased risk of patient-important outcomes (14-17). While two reports found no outcome association for acute decrease of >20% (14) or >15% (15) in estimated glomerular filtration rate (eGFR), two other analyses suggested that increases of plasma creatinine as small as 10% were associated with worse kidney and cardiovascular outcomes (16, 17). Lack of power, limited healthcare coverage and the use of variable time windows to define the increase in creatinine may explain these differences. A report from the U.S. National Kidney Foundation recently emphasized the need to clarify this conflicting and limited evidence (13).

We used a large healthcare-based Swedish population cohort to investigate the frequency of plasma creatinine increases following RASi and whether such increases are associated with adverse health outcomes.

Material and Methods

Data sources

We used data from the Stockholm CREAtinine Measurements (SCREAM) project, a healthcare utilization cohort including all adult residents in Stockholm in whom a creatinine level was measured between 2006 and 2011 (18). SCREAM includes data from about 1.3 million adults, corresponding to 68% of the population of the region for that period (18). Laboratory results were linked to other administrative databases with complete information on demographic data, healthcare use, diagnoses, vital status, validated kidney replacement therapy endpoints, and dispensed prescriptions at Swedish pharmacies. The study utilized only de-identified data and thus was deemed not to require informed consent. It was approved by the regional ethical review boards and the Swedish National Board of Welfare.

Study design

We included all adult (>18 years old) community-dwelling patients newly initiating RASi irrespective of indication, with a creatinine measured on or within 3 months before the dispensation date, and a post-initiation creatinine within two months after. This strict window of pre- and post-initiation monitoring was chosen to align with guideline recommendations as well as previous studies (12, 13, 15, 16). We defined new users as individuals receiving a new RASi dispensation, with no dispensation of a RASi in the preceding 12 months, to ensure that the dispensation was not a continuation of an existing prescription. Additional exclusion criteria were missing age or sex, eGFR <30 ml/min/1.73m^2 or undergoing kidney replacement therapy at RASi dispensation.

Exposure

The study exposure was an increase in creatinine within the first two months of RASi, calculated as the difference between the baseline and first follow-up measurement. We only used creatinine measurements from the ambulatory setting. Creatinine tests from inpatient care, emergency room visits and taken within 24 hours before or after hospital admission were excluded. The date of the follow-up creatinine measurement was the index date of the study; the main analysis was by intention to treat. We categorized the relative increase in creatinine as follows: <10% (reference), 10-19%, 20-29% and ≥30%. In Stockholm healthcare, all laboratory tests are measured by one of three laboratories (Aleris, Unilabs and Karolinska), all of which are captured in SCREAM. Creatinine was measured in plasma, with either an enzymatic or corrected Jaffe method (alkaline picrate reaction), both methods being traceable to isotope dilution mass spectroscopy standards. Creatinine values <25 or >1500 μmol/L were considered outliers and discarded.

Time on RASi

Using information on all subsequent RASi dispensations, we defined continuous use as a refilling of prescription within the prescribed pill supply, adding 45 days to account for stockpiling and events that occur shortly after stopping drug. We quantified the proportion of patients who discontinued RASi within 14 days of the follow-up creatinine, and performed sensitivity analyses using an "as-treated" design, censoring at discontinuation.

Outcomes

Study outcomes were ascertained via linkage with the government-run National Population Registry, which registers all deaths without loss to follow up, and

the National Patient Register with codes diagnoses for essentially all (>99%) hospitalizations. The primary outcome was all-cause mortality. Secondary outcomes were hospitalization or death due to heart failure (*international classification of disease (ICD)-10* code I50); myocardial infarction (I21-I22) and end-stage kidney disease (ESKD, defined as the composite of N18.5-N18.6 codes, kidney replacement therapy initiation recorded in the validated Swedish Renal Registry, or a clinically encountered outpatient eGFR <15 ml/min/1.73m^2, whichever occurred first).

Covariates

Study covariates included age, sex, eGFR, comorbidities (hypertension, diabetes mellitus, myocardial infarction, heart failure, arrhythmia, peripheral vascular disease, cerebrovascular disease, ischemic heart disease) and medications (beta blocker, calcium channel blocker, thiazide diuretic, loop diuretic, potassium-sparing diuretic, non-steroidal anti-inflammatory drug, statin) (definitions in **Table S1**). Comorbidities identified in this study used established algorithms with an 85-95% sensitivity or positive predictive value (19). Drug dispensation data were obtained from the Dispensed Drug Registry, a nationwide register with complete information on all prescribed drugs dispensed at Swedish pharmacies. The coverage of this register is considered virtually complete, as outpatient drugs prescriptions and dispensations in Sweden are linked to the citizen's unique personal identification number. eGFR was calculated using the CKD-EPI formula (20). We defined chronic kidney disease (CKD) as eGFR below 60 ml/min/1.73m^2 on the first creatinine measurement, and categorized patients according to KDIGO criteria: category G3a (eGFR 45-59 ml/min/1.73m^2) and G3b (eGFR 30-44 ml/min/1.73m^2) (21, 22).

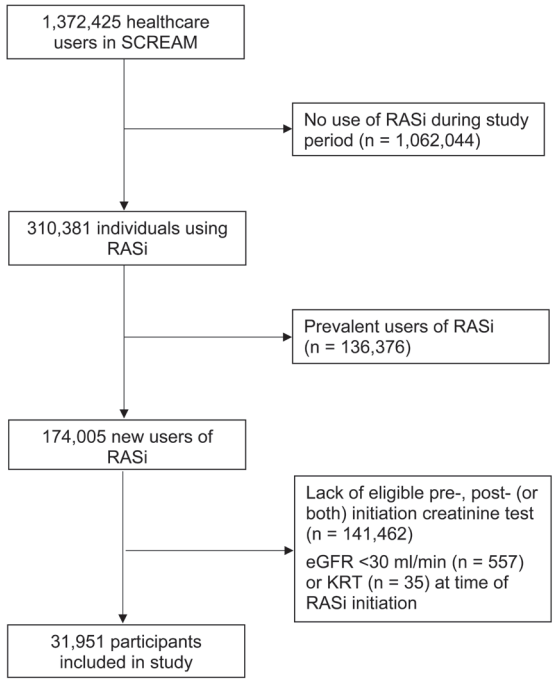
Statistical analyses

Continuous variables are presented as mean with standard deviation or median with interquartile range (IQR), depending on the distribution, and categorical variables as number and percentages. Patients were followed from dispensation of RASi until the occurrence of an event, emigration from Stockholm region or end of follow-up (2012 December 31), whichever occurred first. Cumulative incidence functions were calculated and plotted to account for the competing event mortality. Incidence rates per 1000 person years with 95% confidence intervals were calculated for each outcome. Multivariable Cox proportional hazards regression was used to calculate hazard ratios associated with creatinine increases as earlier defined. The proportional hazards assumption was checked using log-minus-log plots. Our primary analysis followed an intention-to-treat approach, assuming that RASi continued until occurrence of the first event or censoring (emigration or end of follow up). Next, we performed subgroup analyses for *a priori* defined strata: sex, comorbidities (diabetes, myocardial infarction, heart failure, hypertension, chronic

kidney disease) and treatment (ACEi, ARB or both). Finally, creatinine increase was also modelled as a continuous exposure using penalized smoothing splines. In order to elucidate short-term vs long-term risk associations, we performed time-varying Cox regression analysis splitting follow up in two intervals: <1 year and ≥1 year from baseline (23).

Sensitivity analyses included the following approaches: First, we followed an as-treated design censoring at RASi discontinuation. Second, we performed a competing risk analysis to calculate subdistribution hazards for the secondary study outcomes accounting for death as a competing risk. Third, we repeated the main analyses after excluding patients whose creatinine decreased by more than 10%. Fourth, we excluded all patients who developed hyperkalemia within the first three months of RASi (defined as an outpatient plasma potassium > 5.5 mmol/L). Lastly, we excluded patients who were hospitalized for heart failure or a myocardial infarction in the time window between the creatinine measurements. Missing data were rare, and no imputations were made. Statistical analyses were performed using R version 3.4.1 (24).

Figure 1. Flow chart of patient inclusion in the study. SCREAM = Stockholm CREAtinine Measurements project; RASi = renin-angiotensin system inhibition; eGFR = estimated glomerular filtration rate; KRT = kidney replacement therapy.



Results

A total of 174 005 new users of RASi were identified in Stockholm during 2007-2011 (**Figure 1**). Of these, 141 462 patients were excluded due to lack of an eligible pre- or post-initiation creatinine test (or both): 42 713 (30%) had a pre-initiation test, and 29 574 (21%) a post-initiation test. Of patients with chronic kidney disease (CKD; n=8273) on their pre-initiation test, 4852 (59%) had a post initiation test. An additional 592 patients were excluded for baseline eGFR <30 ml/min/1.73m^2 or kidney replacement therapy at time of RASi dispensation. The final study cohort consisted of 31 951 patients (18% of all identified new-users). For these patients, the median (interquartile range; IQR) number of days between the first creatinine measurement and start of RASi treatment was 14 (5-36), whereas median time between start of treatment and the second creatinine measurement was 19 (11-31) days.

Table 1. Baseline characteristics of new users of renin-angiotensin system inhibitors in the Stockholm CREAtinine Measurements project, overall and by increase in plasma creatinine (Cr) following drug initiation.

	Overall (n = 31 951)	**Cr increase <10% (n = 24 671)**	**Cr increase 10-19% (n = 4515)**	**Cr increase 20-29% (n = 1655)**	**Cr increase >=30% (n = 1110)**
Mean age (SD), *y*	65 (14)	64 (14)	66 (14)	66 (14)	69 (15)
Age category, *n (%)*					
<50	4344 (14)	3473 (14)	565 (13)	197 (12)	109 (10)
50-59	6353 (20)	5010 (20)	871 (19)	308 (19)	164 (15)
60-69	9101 (29)	7163 (29)	1222 (27)	456 (28)	260 (23)
70-79	7119 (22)	5429 (22)	1070 (24)	358 (22)	262 (24)
>=80	5034 (16)	3596 (15)	787 (17)	336 (20)	315 (28)
Women, *n (%)*	15768 (49)	12110 (49)	2195 (49)	845 (51)	618 (56)
Mean eGFR (SD), *ml/min/1.73m^2*	82 (19)	81 (18)	85 (19)	86 (20)	84 (22)
eGFR category, *ml/min/1.73m^2*					
30-44	1276 (4)	974 (4)	159 (4)	80 (5)	63 (6)
45-59	3017 (9)	2381 (10)	362 (8)	138 (8)	136 (12)
>=60	27658 (87)	21316 (87)	3994 (89)	1437 (87)	911 (82)
Comorbidities, *n (%)*					
Diabetes mellitus	6101 (19)	4693 (19)	854 (19)	315 (19)	239 (21)
Myocardial infarction	2140 (7)	1514 (6)	347 (8)	149 (9)	130 (12)
Heart failure	3969 (12)	2670 (11)	622 (14)	305 (18)	372 (34)
Hypertension	23374 (73)	18192 (74)	3268 (72)	1169 (71)	745 (67)

	Overall (n = 31 951)	Cr increase <10% (n = 24 671)	Cr increase 10-19% (n = 4515)	Cr increase 20-29% (n = 1655)	Cr increase >=30% (n = 1110)
Arrhythmia	4807 (15)	3500 (14)	689 (15)	315 (19)	303 (27)
Peripheral vascular disease	1362 (4)	969 (4)	214 (5)	93 (6)	86 (8)
Cerebrovascular disease	2136 (7)	1587 (6)	325 (7)	116 (7)	108 (10)
Ischemic heart disease	4587 (14)	3376 (14)	708 (16)	271 (16)	232 (21)
Chronic obstructive pulmonary disease	1826 (6)	1277 (5)	288 (6)	142 (9)	119 (11)
Medication, *n (%)*					
Beta blockers	12691 (40)	9487 (39)	1852 (41)	749 (45)	603 (54)
Calcium channel blockers	7265 (23)	5504 (22)	1053 (23)	406 (25)	302 (27)
Thiazides	2568 (8)	1965 (8)	353 (8)	153 (9)	97 (9)
Loop diuretics	4983 (16)	3305 (13)	822 (18)	400 (24)	456 (41)
Potassium-sparing diuretics	1507 (5)	976 (4)	228 (5)	108 (7)	195 (18)
NSAIDs	5951 (19)	4533 (18)	874 (19)	314 (19)	230 (21)
Statins	9666 (30)	7420 (30)	1422 (32)	484 (29)	340 (33)

eGFR = estimated glomerular filtration rate; SD = standard deviation; NSAIDs = non-steroidal anti-inflammatory drugs.

The characteristics of included patients are described in **Table 1**, overall and by increase in creatinine. Patients had a mean age of 65 years, 49% were women and 13% had CKD. Hypertension (73%), diabetes mellitus (19%), arrhythmias (15%) and ischemic heart disease (14%) were the most common comorbidities. Concurrent use of beta blockers (40%), statins (30%) and calcium-channel blockers (23%) was also common. Creatinine increases of 10-19% occurred in 4515 patients (14%), of 20-39% in 1655 (5%) and ≥30% in 1110 (4%). Patients with higher creatinine increases were on average older, had more comorbidities and a higher proportion were taking additional medications. Excluded patients (i.e., those with missing baseline or follow-up creatinine measurement) differed from those included in several ways, being in general younger, with higher GFR and lower prevalence of comorbidities (**Table S2**).

Association between creatinine increase and study outcomes

During a median follow up of 3.5 (IQR 2.1-4.7) years, there were 3202 deaths, 2275 heart failure hospitalizations, 842 myocardial infarctions and 52 ESKD events; incidence rates (95% CI) were 29.4 (28.4-30.4), 21.7 (20.8-22.6), 7.8 (7.3-8.4) and 0.5 (0.4-0.6) per 1000 person years, respectively.

Table 2. Crude and adjusted hazard ratios for the association between plasma creatinine increase category and death, cardiovascular or end-stage kidney disease outcomes.

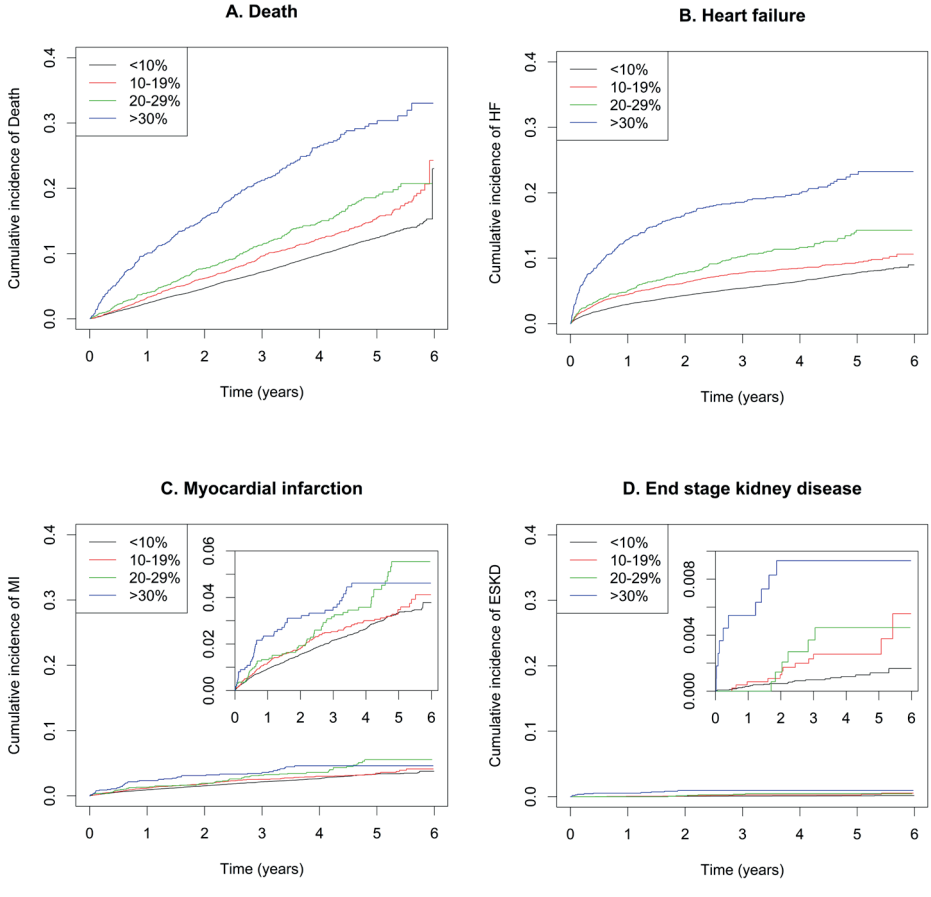
	n	Number of events	Person Years	IR per 1000PY (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	P value for trend
Death							
Overall	31951	3202	108897	29.4 (28.4-30.4)			
<10%	24671	2183	84247	25.9 (24.8-27.0)	1	1	<0.001
10-19%	4515	522	15533	33.6 (30.8-36.6)	1.30 (1.18-1.43)	1.15 (1.05-1.27)	
20-29%	1655	231	5660	40.8 (35.7-46.4)	1.58 (1.38-1.80)	1.22 (1.07-1.40)	
>30%	1110	266	3457	76.9 (68.0-86.8)	2.98 (2.62-3.38)	1.55 (1.36-1.77)	
Heart failure							
Overall	31951	2275	104859	21.7 (20.8-22.6)			
<10%	24671	1505	81627	18.4 (17.5-19.4)	1	1	<0.001
10-19%	4515	367	14830	24.7 (22.3-27.4)	1.34 (1.20-1.51)	1.14 (1.02-1.28)	
20-29%	1655	184	5327	34.5 (29.7-39.9)	1.87 (1.60-2.18)	1.23 (1.05-1.43)	
>30%	1110	219	3075	71.2 (62.1-81.3)	3.73 (3.24-4.30)	1.41 (1.21-1.63)	
Myocardial infarction							
Overall	31951	842	107357	7.8 (7.3-8.4)			
<10%	24671	608	83126	7.3 (6.7-7.9)	1	1	0.25
10-19%	4515	127	15287	8.3 (6.9-9.9)	1.14 (0.94-1.38)	1.05 (0.86-1.27)	
20-29%	1655	62	5559	11.2 (8.6-14.3)	1.53 (1.18-1.98)	1.32 (1.02-1.72)	
>30%	1110	45	3385	13.3 (9.7-17.8)	1.80 (1.33-2.44)	1.29 (0.94-1.76)	
End-stage kidney disease							
Overall	31951	52	108815	0.5 (0.4-0.6)			
<10%	24671	24	84218	0.3 (0.2-0.4)	1	1	<0.001
10-19%	4515	12	15517	0.8 (0.4-1.4)	2.72 (1.36-5.44)	3.25 (1.61-6.53)	
20-29%	1655	6	5644	1.1 (0.4-2.3)	3.73 (1.53-9.13)	2.65 (1.05-6.72)	
>30%	1110	10	3435	2.9 (1.4-5.4)	10.13 (4.84-21.18)	8.31 (3.87-17.83)	

CI = confidence interval; IR = incidence rate; PY = person years; HR = hazard ratio.

[a] Analyses are adjusted for age, sex, diabetes mellitus, myocardial infarction, heart failure, hypertension, arrhythmia, peripheral vascular disease, eGFR, cerebrovascular disease, ischemic heart disease, use of beta blockers, calcium channel blockers, thiazide diuretics, loop diuretics, potassium-sparing diuretics, NSAIDs and statins.

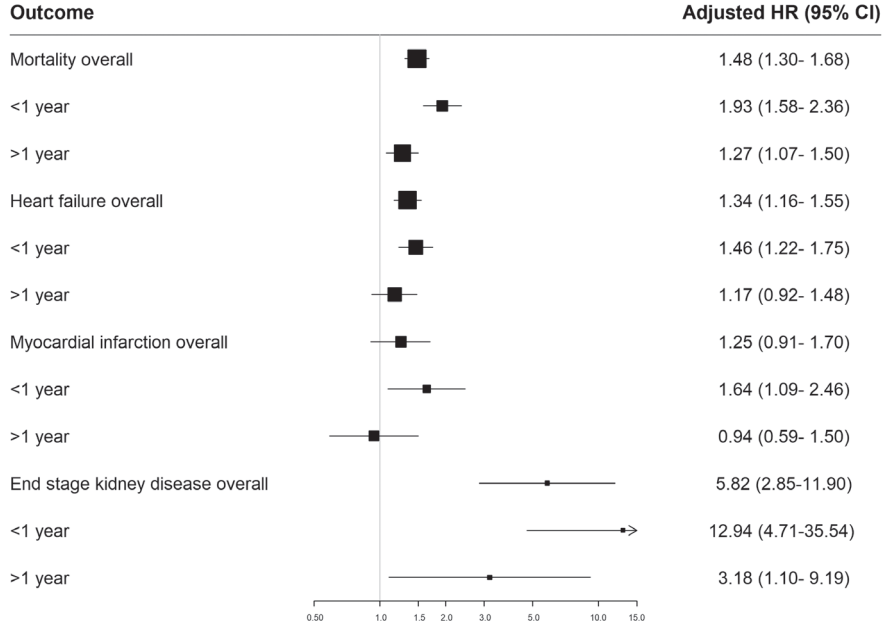
Figure 2 and **Table 2** show that in both crude and multivariable-adjusted models, there was a gradually increased risk of events with larger creatinine increases. For instance, the risk of death, HR (95% CI), was 1.15 (1.05-1.27), 1.22 (1.07-1.40) and 1.55 (1.36-1.77) times higher for increases of 10-19%, 20-29% and ≥30% respectively, compared with patients with creatinine increase <10% (p for trend < 0.001). Similar trends were observed for the outcomes heart failure and ESKD (p values for trend <0.001). The association was less robust for the outcome myocardial infarction (p for trend 0.25), but creatinine increases of 20-29% and ≥30% were associated with tendencies toward increased risk in multivariable analysis. Stratified analyses showed similar associations and tendencies, with wider confidence intervals (**Table S3**).

Figure 2. Cumulative incidence plots for death, cardiovascular and end-stage kidney disease outcomes by ranges of plasma creatinine increase during the first 2 months after RASi treatment initiation. The cumulative incidence plots for heart failure, myocardial infarction and end-stage kidney disease account for the competing risk of death.



For comparison with preceding literature and current guideline recommendations, we compared mortality, kidney and cardiovascular risks associated with increases ≥30% versus <30%. Patients with increases ≥30% were older, had more comorbidities and used more medications (**Table S4**). Creatinine increases ≥30% were associated with an increased risk for all studied outcomes, overall (**Figure 3**; **Table S5**) and across different subgroups (**Figure S1**). In restricted follow-up analyses, the associations were apparent during both short- and long-term follow up, but with consistent tendencies towards higher risk magnitude during the first year of observation (**Figure 3**).

Figure 3. Adjusted hazard ratios for the association between creatinine increase ≥30%, compared with <30%, and death, cardiovascular or end-stage kidney disease outcomes, overall, and within or beyond the first year of follow-up. HR = hazard ratio. The hazard ratio beyond the first year of follow-up is calculated conditional on surviving the first year.



When modelling creatinine change as a continuous exposure through spline curves, we observed an asymmetrical U-shaped association, with the lowest risk at decreases in creatinine of 5 to 20%, for the outcomes death and myocardial infarction. In contrast, for risk of heart failure and ESKD the association was linear (**Figure S2**). The inclusion of patients whose creatinine acutely decreased in the

reference group might alter the effect size associated with increases in creatinine. We therefore tested whether redefining the reference category by excluding patients with creatinine decreases ≥10% would modify our observations; we observed no major deviation from our main results (**Table S6**).

The median length of RASi treatment was 18 (IQR 8-33) months. In the as-treated sensitivity analysis, censoring at RASi discontinuation, effects were similar to the intention-to-treat main analysis (**Table S7**). Of note, 239 (22%) patients with creatinine increase ≥30% discontinued treatment immediately after, compared with 5477 (18%) in those with creatinine increase of <30% (crude relative risk 1.19; 95% CI 1.06-1.33). Potassium was measured at least once within the first 3 months of RASi in 29 152 patients (91%), and there were 241 patients with hyperkalemia (> 5.5 mmol/L). Hyperkalemia was more common among patients with creatinine increases ≥ 30% (5% of patients) than in those with creatinine increases <30% (0.6% of patients, relative risk of hyperkalemia 8.02; 95% CI 5.96-10.80), **Table S8**). Exclusion of patients with concurrent hyperkalemia did not modify our main observations (**Table S9**). Competing risk models accounting for death showed also similar associations regarding the risk of cardiovascular and ESKD events (**Table S10**). Finally, we compared study outcomes in included versus excluded (i.e., unmonitored) patients. Patients who were included in our analysis had a higher risk of death, but no increased risk for hospitalization for heart failure, myocardial infarction or ESKD compared with patients in whom creatinine was not monitored (**Table S11**). Exclusion of patients that were hospitalized in the time window between the creatinine measurements did also not modify the results (**Table S12**).

Discussion

In this large healthcare-based observational study, we found that i) 18% of adults initiating RASi underwent pre- and post-initiation creatinine monitoring according to current guideline recommendations; ii) creatinine increases of 10-29% within the first 2 months of RASi were common among monitored individuals, occurring in 19% of patients, and increases of 30% or more occurred in 4%; iii) acute increases in creatinine of any magnitude above 10%, relative to baseline, were consistently associated, in a graded manner, with increased subsequent risk of death, cardiovascular events and ESKD.

Clinical guidelines recommend monitoring creatinine and considering discontinuation or dose reduction of RASi if creatinine increases by 30% or more (1, 11). We found that 18% of all new users of RASi in our region underwent guideline-recommended creatinine monitoring. This is in keeping with most observations from other countries and healthcare systems (25-32), for example,

in a UK primary health care cohort, 14% of patients were monitored before and after (31). However, in a US health maintenance organization 70% of patients were monitored (33). Comparing monitoring practices between studies is problematic because of differing definitions, data collection periods, database quality and coverage. In Stockholm healthcare, laboratory tests are centrally measured by three different laboratories, all of which contribute to SCREAM, which ensures that our cohort includes all creatinine measurements. Though the proportion of patients monitored in many of these observational studies might be thought low, it is worth considering, in this context, that the recommendation for monitoring is not based on direct evidence of benefit from monitoring, but rather on extrapolation from clinical trials in which monitoring occurred. In these trials, the response to monitoring was not protocolized, and many patients with increases in creatinine likely stayed on drug (15, 17, 34). In our study, monitored patients were older, and had a higher comorbidity burden. The presence of monitoring, in adjusted analysis, was associated with outcomes that were worse than (death) or similar to (heart failure, myocardial infarction, ESKD) those in unmonitored patients, suggesting, to some extent, that its use is selective and directed at patients at higher risk.

Among those who were monitored, acute increases in creatinine were associated in a graded manner with increased subsequent mortality, kidney and cardiovascular events. Our results expand the findings of the UK primary health care cohort (16), but contrast with some analyses from other clinical trials: first, a post hoc evaluation from ONTARGET and TRANSCEND (n=9340) did not find decreases in eGFR of >= 15% to be associated with kidney or cardiovascular events, with an adjusted HR (95% CI) of 1.14 (0.93-1.39) for new micro-albuminuria and 1.17 (0.99-1.38) for the primary cardiovascular composite (15). Second, in analyses from AASK and MDRD (n=1660), acute eGFR decreases between 5-20% in the setting of intensive blood pressure control were not associated with the risk of ESKD, with an adjusted HR (95% CI) of 1.19 (0.84-1.68) for AASK and 1.08 (0.84-1.40) for the MDRD trial (14). In ADVANCE, increase in creatinine was associated with the composite outcome of mortality, major cardiovascular events, and new or worsening nephropathy, in a graded way: HR's were 1.1 (95% CI 1.0-1.3), 1.3 (1.1-1.7) and 1.4 (1.2-1.8) for increases in creatinine of 10-19%, 20-29%, and >=30% respectively, all compared with the referent category of increase <10%, with P for trend < 0.001 (17). However, it is noteworthy that half the patients contributing to these cohort analyses of ADVANCE were randomized to placebo after the active run in phase. Taken together, the tendencies and effects in these studies are in the direction of the effects that we observed, and the differences in statistical significance may reflect the greater power in the observational data sets.

Our finding that associations were stronger during the first year of follow up is a new observation. By demonstrating the asymmetry of the relationships across increase and decrease in creatinine, we have excluded the possibility that the results are

caused solely by variability itself as an adverse prognostic marker, though we recognize that variability may contribute to the magnitude of the observed effects (35, 36). We have also demonstrated that results are largely unchanged after the exclusion of patients whose creatinine significantly decreased, using patients with changes of ±10% as reference. Additional strengths include our use of a stricter definition for pre-initiation testing (a 3-month window), following criticisms that follow up after a 12-month window (13, 16) could reflect long-term progression of CKD rather than acute decreases in GFR. We based our exposure on pharmacy dispensations rather than prescriptions written, which offers better ascertainment, although we cannot ensure that the medication has been taken. We excluded patients with CKD G4-5, as the use of RASi is subject to other considerations in this patient group, and their inclusion might have driven kidney outcomes. Our work illustrates how healthcare-based analyses and clinical trials provide complementary information on benefits and harms of therapy (37).

RASi by ACEi/ARBs leads to the loss of glomerular efferent arteriolar vasoconstriction, which reduces intraglomerular pressure, resulting in an acute decrease in GFR (38, 39); mitigation of maladaptive hyperfiltration by this mechanism is thought to contribute to the kidney benefit of RASi. Studies of intensive blood pressure reduction suggest that decreases in GFR in this context reflect hemodynamic changes rather than intrinsic injury (40, 41), and after long-term empagliflozin, which is also thought to acutely decrease GFR through a hemodynamic mechanism, discontinuation of empagliflozin is followed by an acute increase in GFR (42). Acute hemodynamic change in GFR may therefore carry a different implication and prognosis than change secondary to progression.

The origin of the guideline recommendation to discontinue RASi after acute increases in creatinine >= 30% is unclear (13). It appears to have originated with an influential narrative review of 12 small trials (1102 participants), which concluded that creatinine increases of less than this magnitude were associated with more stable subsequent GFR in patients with CKD; methods and effect size for this conclusion were not shown, so it is difficult to make a direct comparison between these data and our own (12). In our larger, observational dataset, there is increased power to detect outcomes associated with more modest changes, and perhaps explains why we found that acute increases in creatinine of 10% or more were also associated with subsequent adverse events. The most significant limitation of our finding is that one cannot establish causality from this observational evidence: our results do not mean that RASi should be discontinued in any group. Instead, they are part of an emerging network of evidence that informs the decision to monitor and how to respond to monitoring, in the context of robust randomized evidence demonstrating reduction in patient-important kidney and cardiovascular outcomes with RASi (43-48). Because reanalyses of TRANSCEND and ADVANCE found no

evidence for modification of the benefit of RASi by level of creatinine increase (15, 17), we speculate that creatinine increases may therefore be a risk marker of disease rather than directly leading to adverse outcomes (49). We were unable to adjust for blood pressure and proteinuria, because blood pressure is not included in any linked database, and proteinuria data had a high degree of missingness that was unlikely to be random. In previous work, initial blood pressure is not associated with change in GFR, and for albuminuria the effect size is not strong (OR 1.2, 95% CI: 1.0-1.5) (15), so we believe they are unlikely to be important confounders. It is a limitation of our data that we were unable to comment on the persistence of the change: however, in ONTARGET and TRANSCEND, 50% of those with a decrease of GFR of ≥16 15% at 2 weeks did not have a difference of that magnitude at 8 weeks (15). For patients who are monitored and who experience an increase of 30% or more, repeating the value may therefore be helpful. Whether routinely discontinuing versus continuing RASi after a relevant creatinine increase would result in improved outcomes is outside the scope of our analysis because of the complexity of time-dependent confounding. We note that this is precisely the aim of an ongoing trial of patients with CKD G4-5 (50).

To conclude, acute increases in creatinine following initiation of RASi of 10% or more were robustly associated with increased risk of death, cardiovascular events (myocardial infarction, heart failure) and development of ESKD in an observational clinical setting. Monitoring creatinine before and after initiation of RASi identifies patients at high risk.

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Supplementary material

Supplementary Table S1. Definition of medications and comorbidities.

Supplementary Table S2. Characteristics of unmonitored and monitored patients.

Supplementary Table S3. Adjusted hazard ratios for the association between plasma creatinine increase and death, cardiovascular or end-stage kidney disease outcomes in different subgroups.

Supplementary Table S4. Characteristics at initiation of RASi, overall and according to plasma creatinine increase of < or ≥30% within the first 2 months of RASi.

Supplementary Table S5. Crude and adjusted hazard ratios for the association between plasma creatinine increases ≥30% and death, cardiovascular or end-stage kidney disease outcomes.

Supplementary Table S6. Sensitivity analysis: adjusted hazard ratios for the association between plasma creatinine increase and death, cardiovascular or end-stage kidney disease outcomes after exclusion of patients with creatinine decreases >10% following RASi.

Supplementary Table S7. Sensitivity analysis: adjusted hazard ratios for the association between plasma creatinine increase and death, cardiovascular or end-stage kidney disease outcomes censoring at time of RASi discontinuation.

Supplementary Table S8. Risk of hyperkalemia within the first 3 months of RASi overall and according to plasma creatinine increase categories.

Supplementary Table S9. Sensitivity analysis: adjusted hazard ratios for the association between plasma creatinine increase and death, cardiovascular or end-stage kidney disease outcomes after excluding patients developing hyperkalemia (plasma K^+ > 5.5 mmol/L) within the first 3 months of RASi (n = 241).

Supplementary Table S10. Sensitivity analysis: Fine and Gray competing risk analysis showing crude and adjusted subdistributional hazard ratios (sHR) for the association between plasma creatinine increase and cardiovascular or end-stage kidney disease outcomes outcomes with death (by other causes) as competing risk.

Supplementary Table S11. Crude and adjusted hazard ratios for adverse outcomes among monitored and unmonitored patients.

Supplementary Table S12. Sensitivity analysis: adjusted hazard ratios for the association between plasma creatinine increase and death, cardiovascular or end-stage kidney disease outcomes excluding patients with hospitalization between creatinine measurements.

Supplementary Figure S1. Adjusted hazard ratios for the association between plasma creatinine increase ≥30% vs. <30% in different subgroups for (**A)** mortality; (**B)** heart failure; (**C**) myocardial infarction; (**D**) end-stage kidney disease.

Supplementary Figure S2. Penalized smoothing spline curve associated with plasma creatinine increases (continuous variable) for (**A)** mortality; (**B)** heart failure; (**C**) myocardial infarction; (**D**) end-stage kidney disease.