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

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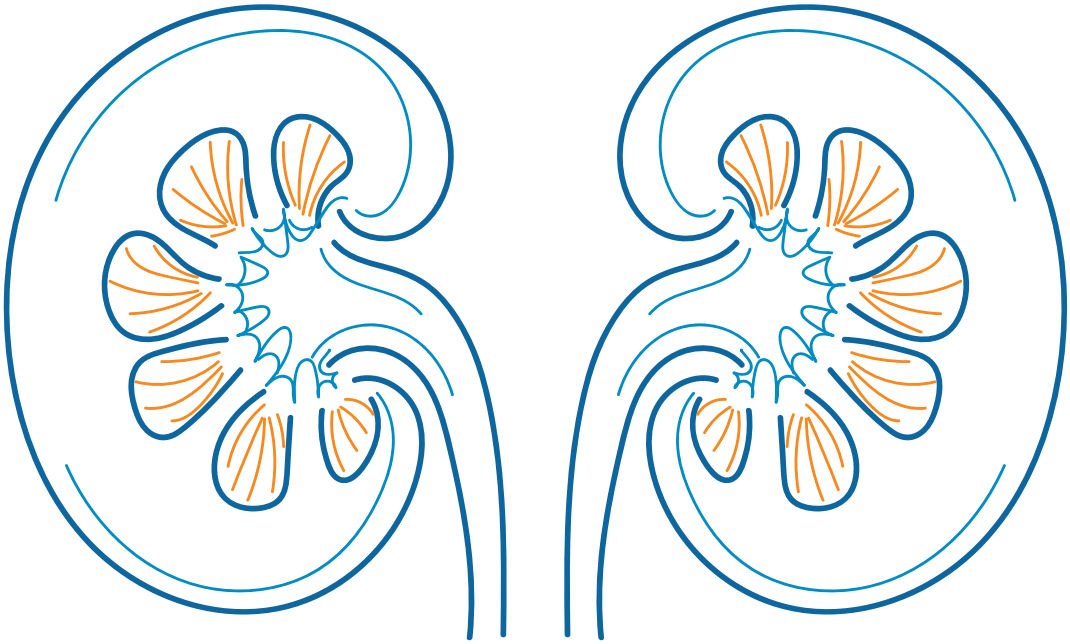

CHAPTER 8

Stopping renin-angiotensin system inhibitors in patients with advanced CKD and risk of adverse outcomes: a nationwide study

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Abstract

Background: It is unknown whether outcomes are affected by stopping renin-angiotensin system inhibitor (RASi) therapy in patients with advanced chronic kidney disease (CKD).

Methods: We studied 10,254 nephrologist-referred patients from the Swedish Renal Registry during 2007-2017 who reached advanced CKD (glomerular filtration rate [eGFR] <30 ml/min/1.73m^2) while on RASi therapy. Target trial emulation techniques based on cloning, censoring and weighting were used to compare the risks of stopping within 6 months and remaining off treatment vs. continuing RASi on subsequent 5-year mortality, major adverse cardiovascular events (MACE) and initiation of kidney replacement therapy (KRT).

Results: Of 10,254 prevalent RASi users with new-onset eGFR <30 ml/min/1.73m^2, 1553 (15%) stopped RASi within 6 months. Median age was 72 years, 36% were women, and median eGFR was 23 mL/min/1.73m^2. Compared with the decision to continue, stopping RASi was associated with a higher absolute 5-year risk of death (40.9% vs. 54.5%) and MACE (47.6% vs. 59.5%), but lower risk of KRT (36.1% vs. 27.9%), corresponding to absolute risk differences of 13.6 (95% CI 7.0, 20.3), 11.9 (5.7, 18.6) and -8.3 (-12.8, -3.6) events per 100 patients, respectively. Results were consistent whether patients stopped at higher or lower eGFR, across pre-specified subgroups, after adjustment and stratification for albuminuria and potassium, and when modelling RASi as a time-dependent exposure using a marginal structural model.

Conclusion: In this nationwide study of people with advanced CKD, stopping RASi was associated with a higher absolute risk of mortality and MACE, but a lower absolute risk of KRT.

Introduction

Renin-angiotensin system inhibitors (RASi), that is, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), are a cornerstone in the treatment of proteinuric chronic kidney disease (CKD), supported by trials showing their effectiveness in delaying the progression of CKD (1-7). However, evidence regarding the efficacy and safety of RASi in individuals with advanced CKD is limited to a small single-center trial (8) and post-hoc analyses of the few patients with advanced CKD who were included in the pivotal RASi trials (9, 10).

A small observational study, showing improved glomerular filtration rate (GFR) after stopping RASi (11), led to the hypothesis that continuing RASi in patients with advanced CKD might accelerate the need for kidney replacement therapy (KRT) (12). This, together with the concern that the persistent hemodynamic effects of RASi, which are manifested by an acute change in GFR at initiation (13, 14), may cause harm by chronically lowering the GFR, has led to frequently stopping RASi among patients with advanced CKD in routine clinical practice (15, 16). However, stopping RASi may also harm patients by increasing cardiovascular risk and mortality (17).

This clinical equipoise is being addressed by an ongoing randomized trial that evaluates the difference in 3-year eGFR change in patients with advanced CKD at baseline, randomized to continue or discontinue RASi, with publication anticipated in 2022 (18, 19). Recently, an observational study from a private healthcare provider in the United States (U.S.) suggested that stopping RASi in patients with advanced CKD was associated with an increased risk of major cardiovascular events (MACE) and death, but not with the risk of KRT (17). While this study has generated considerable attention, confirmation of such findings in independent and geographically diverse health systems is needed to increase generalizabilty and provide the strength of evidence needed to inform clinical practice.

We used routine-care data from patients referred to nephrologist care in Sweden, to compare the outcomes of long-term users of RASi who stopped or continued treatment after developing advanced CKD (eGFR <30 ml/min/1.73m^2). Our primary objective was to evaluate the risks of death, MACE and commencement of KRT by this treatment decision. As a secondary objective, we investigated whether observed risks and benefits differed in individuals who stopped earlier (eGFR 20-30 ml/min/1.73m^2) or later (eGFR <20 ml/min/1.73m^2) in the course of their disease progression.

Methods

Swedish Renal Registry

We used data from the Swedish Renal Registry (SRR), a nationwide registry of patients with CKD G3–5 attending routine nephrologist-specialist care in Sweden (20, 21), during the period 2007-2017. The SRR collects routine information from outpatient nephrologist visits, including CKD aetiology, laboratory tests, blood pressure and other results obtained from routine clinical examination. The registry has a mandatory enrolment policy for patients with an eGFR <30 mL/min/1.73m^2, but the registry also encourages the inclusion of patients earlier in the course of the disease (eGFR<45 mL/min/1.73m^2) provided it is done systematically by the nephrology clinic (i.e., all or none are registered from each specific clinic with eGFR<45 mL/min/1.73m^2). Registrations of subsequent outpatient visits to nephrology care (on average 2-3 per year per patient) are thereafter recorded until death, emigration from the country or start of KRT. Nearly all nephrology clinics in Sweden (96%) report to the SRR-CKD and the estimated national coverage is >75% for nephrologist-referred patients with G4-5 CKD (20).

Via each citizen's unique personal identification number, the SRR was linked to other national registries; the Swedish Prescribed Drug Registry provided complete information on all prescribed drugs dispensed at Swedish pharmacies (22), and this was used to define RASi use and changes in RASi therapy; the Swedish Patient Registry added information on all outpatient specialist consultations and hospitalizations occurring in Swedish healthcare since 1997 until end of follow up, and this was used to obtain information on comorbidities and outcomes (23); the Swedish Death Registry added information on date and causes of death (24). All these registries are run by the Swedish National Board of Welfare, a government institution, and are considered to have no, or minimal, loss to follow up. All patients are informed about their participation in the registry and have the possibility to opt out at any time. We used data linked and de-identified by the Swedish government and were judged not to require informed consent, being approved by the regional ethical review boards and the Swedish National Board of Welfare.

Patient selection and study design

This observational study emulated a pragmatic clinical trial (25) comparing the effect of stopping vs. continuing RASi on cardiovascular and renal outcomes in people with advanced CKD (19). **Supplemental Table S1** outlines the protocol of such trial, which would randomize prevalent RASi users reaching incident CKD G4-5 to either stop RASi within 6 months or to continue with the treatment.

We created a cohort of all adult (≥18 years) patients registered in the SRR after 2007 January 01, who experienced new CKD G4 (ie, whose GFR decreased to <30 ml/min/1.73m^2), and who had taken RASi for more than 80% of the two years before that date. We defined this using a medication possession ratio >80%, the proportion of the number of days of medication dispensed to total number of days of observation. Baseline (T_0) was defined as the day on which the first recorded eGFR <30 ml/min/1.73m^2 was identified. We chose to include only patients apparently adherent to RASi therapy to decrease the possibility of confounding bias due to nonadherence. We excluded patients with a history of kidney transplantation, patients with missing blood pressure measurements at the time of eGFR decrease to <30 ml/min/1.73m^2 or those who stopped RASi before the decrease in eGFR. eGFR was calculated with the CKD-EPI equation (26) from routine plasma creatinine measurements performed by enzymatic or corrected Jaffe methods traceable to isotope dilution mass spectroscopy standards. As information on race is not available in Sweden by law, we did not use the variable for African American ethnicity.

Treatment strategies

We compared the strategies "stop RASi within 6 months and remain off treatment after eGFR decrease <30 ml/min/1.73m^2" vs. "continue RASi for the whole follow-up". We chose to examine the effect of stopping and remaining off treatment because a significant proportion of individuals who discontinued RASi restarted during follow-up (57.1%). Stopping of RASi was defined as absence of a dispensation of RASi within 60 days (lag phase) after the estimated last day of pill supply from the previous dispensation, assuming the most common prescription pattern of one pill per day. When a prescription was filled before the expected end of the previous dispensation, we added the remaining pills onto the next period, for the first occurrence, but did not carry this forward. In the case of hospitalization, we added as many additional pills as days spent in the hospital.

Study outcomes

Each patient was followed until the first of: occurrence of an event, five years after baseline, or administrative censoring (June 1, 2017). The primary outcome was 5-year all-cause mortality. Secondary outcomes included MACE (defined as a composite endpoint of mortality, myocardial infarction and cerebrovascular events) and KRT (defined as undergoing kidney transplantation or initiating maintenance dialysis). ICD-10 codes for ascertainment of cardiovascular outcomes are listed in **Supplemental Table S2**. Information on date of initiation of KRT was obtained from the SRR.

Emulation of the target trial

We used the method of cloning, censoring and weighting (25, 27-29) to emulate a target trial comparing the effects of "stopping RASi within 6 months after eGFR dropped <30 ml/min/1.73m^2 and remaining off treatment" vs. "continuing RASi" (see **Supplemental Methods** and **Supplemental Figure S1** for a detailed discussion on target trial emulation). Briefly, we created a dataset with two copies of each eligible individual (cloning, or replicating) and assigned each of the replicates to one of the treatment strategies at the start of follow-up. Thereafter, we assessed at monthly intervals whether replicates adhered to their assigned treatment strategy; replicates were censored if and when their actual treatment deviated from their assigned treatment strategy, thereby ensuring that replicates followed their assigned strategy. For example, if a replicate was assigned to continuing RASi, but actually stopped RASi treatment on day 90, they would be censored at that point. A replicate that was assigned to the discontinuation arm, and discontinued within 6 months but subsequently restarted treatment would also be censored at the date of treatment restart. To adjust for the potential selection bias induced by this artificial censoring, each individual received a time-varying inverse probability weight (30). Informally, the denominator of the weights was the probability that a replicate remained uncensored (i.e., remained on the assigned treatment strategy) conditional on baseline and time-varying variables (**Supplemental Table S3**). The weights created two pseudopopulations in which treatment was independent of measured prognostic factors. We estimated the time-varying weights by fitting a pooled logistic model for the monthly probability of remaining uncensored, including variables for time and the baseline and time-varying covariates listed in **Table 1**. Models were fitted separately in both treatment arms to allow for treatment-covariate interaction (29). The variables for each model and their regression coefficients are reported in **Supplemental Tables S4-5**. To avoid undue influence of outliers, weights were truncated at the 99.5th percentile (31).

We estimated the effect of stopping RASi on 5-year all-cause mortality, MACE and KRT using weighted pooled logistic regression, including an indicator for treatment strategy, month and its quadratic term, and their interactions to allow for non-proportional hazards. The predicted probabilities from this logistic model were used to estimate the adjusted 5-year predicted probability of mortality, MACE and KRT under each treatment strategy and produce weighted cumulative incidence curves (32, 33). For the KRT curves, the competing risk of death was taken into account. Pointwise 95% confidence intervals were calculated using nonparametric bootstrap based on 500 full samples. In addition to absolute risks and risk differences, we estimated the 5-year restricted mean survival time (RMST) under each treatment strategy and the 5-year RMST difference between both strategies. The RMST is interpreted as the average survival time over a fixed follow-

up period and graphically it corresponds to the area under the survival curve (34, 35). The 5-year RMST *difference* compares the areas under the two survival curves for the intervention and control group. It is interpreted as the mean postponement of the outcome in one group compared with the other. E.g., if the 5-year RMST difference equals 6 months, then on average, patients on one strategy survive 6 months longer compared with patients on another strategy over a 5-year follow-up period. We used nonparametric bootstrapping to obtain 95% confidence intervals using the standard deviation (SD) of the bootstrap estimations as an estimation of the standard error of the RMST (36). We did not calculate hazard ratios since the proportionality of hazards assumption was not met and hazard ratios were thus difficult to interpret (29, 37, 38). R version 3.6.2 was used for all statistical analyses.

Secondary objective: stopping RASi at different eGFRs

In order to evaluate whether observed associations differed in individuals who stopped earlier or later in the course of their disease progression, we created two additional cohorts using the same methodology: we evaluated separately the outcomes associated with stopping vs. continuing RASi in a cohort of individuals on their first detected eGFR decrease to between 20-30 ml/min/1.73m^2 (higher eGFR cohort) and another cohort of individuals on their first detected eGFR below 20 ml/min/1.73m^2 (lower eGFR cohort). Note that there is some overlap of patients in these cohorts as patients progress to a lower eGFR during observation.

Supporting and sensitivity analyses

We pre-specified several analyses to test the robustness and consistency of our main results. First, we compared results when using nontruncated weights. Second, we performed stratified analyses by age (≥70 vs. < 70 years), sex, presence of diabetes, and presence of heart failure, and investigated the interaction of each of these variables with treatment on an additive scale by calculating the absolute excess risk due to interaction. Third, as a negative control analysis, we examined the association between stopping or continuing RASi and the long-term diagnosis of cancer (39). We did not expect stopping RASi to cause or prevent cancer. If we found stopping RASi to be associated with an increased risk of cancer, this would suggest that the observed effect estimate suffers from residual confounding by unmeasured clinical conditions that are associated with stopping RASi, and which are also likely to be associated with the risk of cancer, such as smoking and BMI. For this analysis, patients with a recent cancer diagnosis (within two years from the index date) were excluded from this analysis to minimise the effects of reverse causality, since people may have stopped RASi because they had been diagnosed with cancer. Fourth, we compared results from our trial emulation design with an analysis handling RASi as a time-varying covariate (40). The effect of "always using

RASi" vs. "immediately stopping and not restarting RASi" after eGFR dropped <30 ml/min/1.73m^2 was estimated using inverse probability of treatment and censoring weighted estimation of a marginal structural model (see *Supplemental Methods* for detailed explanation) (30, 41). Fifth, we additionally adjusted our analyses for time-dependent measures of urinary albumin-to-creatinine ratio (ACR) and plasma potassium. This analysis was restricted to the 3049 individuals with this data available, and evaluated consistency across baseline albuminuria (≥70 vs. <70 mg/mmol) and potassium (≥5.0 vs. <5.0 mmol/L) strata. Finally, after reviewing the results of the work above, we conducted a non-prespecified analysis, in which we examined the associations of stopping vs. continuing RASi on the combined outcome of death and KRT, as a surrogate of "net clinical benefit."

Results

Of 30,180 individuals registered in SRR during the study period, 10,254 prevalent RASi users with a medication possession ratio >80% and no history of kidney transplantation were included from the day of their first recorded eGFR below 30 ml/min/1.73m^2.

Figure 1 displays the patient selection flow chart, and **Table 1** describes their baseline characteristics. At baseline, patients had a median (IQR) age of 72 (63-79) years and 35.7% were women. Median eGFR was 23 (18-27) ml/min/1.73m^2, median ACR 35 (6-156) mg/mmol, mean (± SD) systolic blood pressure 139 (SD 22) mmHg and mean diastolic blood pressure 76 (SD 12) mmHg. Hypertension (88.7%), diabetes (49.5%), ischemic heart disease (33.1%) and heart failure (28.0%) were the most common comorbidities. Concurrent use of diuretics (79.3%), beta blockers (67.6%), statins (61.6%) and calcium channel blockers (60.5%) was also prevalent. During the first 6 months of observation 1,553 (15.1%) individuals stopped RASi. Of these, 887 (57.1%) of patients restarted RASi during follow-up.

Figure 1. Selection of study participants.
Abbreviations: RASi = Renin-angiotensin-system inhibitor; eGFR = estimated glomerular filtration rate; MPR = medication possession ratio; KRT = renal replacement therapy.

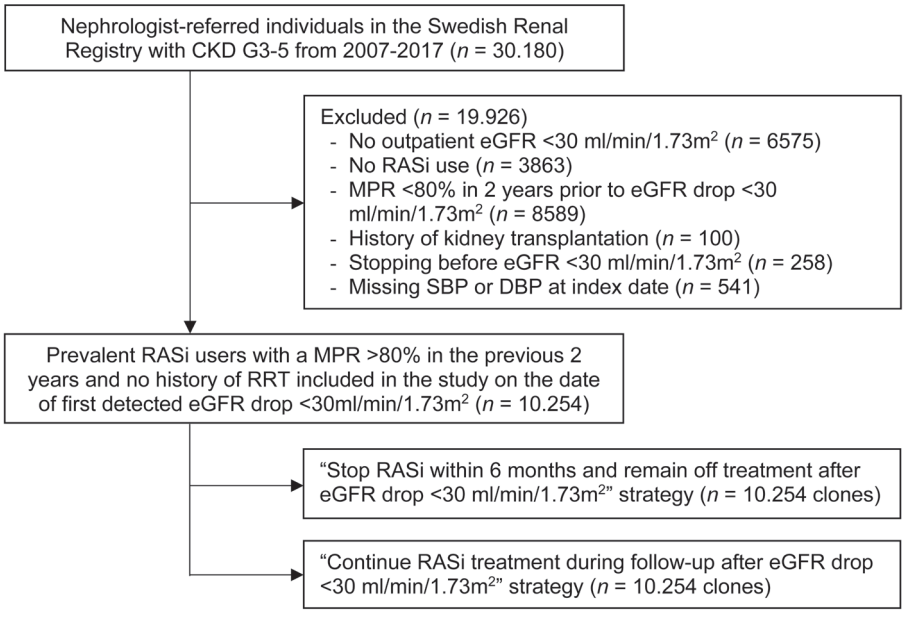

Table 1. Baseline characteristics of prevalent RASi users with eGFR <30 ml/min/1.73m² registered in the Swedish Renal Registry during 2007-2017.

	eGFR <30 ml/min/1.73m² cohort (*n* = 10,254)
Median Age (IQR)[‡], *years*	72 [63, 79]
Age category, *n (%)*	
<50	848 (8.3)
50-59	1046 (10.2)
60-69	2400 (23.4)
70-79	3471 (33.9)
>=80	2489 (24.3)
Women	3662 (35.7)
Median eGFR (IQR)[‡], *ml/min/1.73m²*	23 [18, 27]
eGFR category, *n (%)*	
<15 ml/min/1.73m², *n (%)*	1557 (15.2)
≥15 ml/min/1.73m², *n (%)*	8697 (84.8)
Primary kidney disease, *n* (%)	
Diabetes	2878 (28.1)
Hypertension	2512 (24.5)
Glomerulonephritis	1096 (10.7)
Polycystic kidney disease	574 (5.6)
Pyelonephritis	171 (1.7)
Other	1753 (17.1)
Missing	1270 (12.4)
Mean SBP (SD), *mmHg*	139 (22)
SBP category, *n (%)*	
<120	1430 (13.9)
120-139	3670 (35.8)
140-159	3224 (31.4)
>160	1930 (18.8)
Mean DBP (SD), *mmHg*	76 (12)
DBP category, *n (%)*	
<80	5502 (53.7)
80-89	3340 (32.6)
90-99	1066 (10.4)
>100	346 (3.4)
Median urinary ACR [IQR], *mg/mmol*	35 [6, 156]

	eGFR <30 ml/min/1.73m² cohort (*n* = 10,254)
ACR category, *n (%)*	
A1 (<3)	785 (7.7)
A2 (3-29)	1445 (14.1)
A3 (30-69)	614 (6.0)
A3 (≥70)	1835 (17.9)
Missing	5575 (54.4)
Mean serum potassium (SD), *mg/mmol**	4.5 (0.6)
Comorbidities, *n (%)*	
Hypertension	9099 (88.7)
Myocardial infarction	2212 (21.6)
Ischemic heart disease	3390 (33.1)
Arrhythmia	2302 (22.4)
Heart failure	2868 (28.0)
Peripheral vascular disease	1269 (12.4)
Cerebrovascular disease	1620 (15.8)
Diabetes mellitus	5079 (49.5)
Chronic obstructive pulmonary disease	1811 (17.7)
Cancer diagnosis in previous 2 years	1018 (9.9)
Medication, *n (%)*	
Beta blockers	6928 (67.6)
Calcium channel blockers	6202 (60.5)
Diuretics	8128 (79.3)
Statins	6312 (61.6)
Antiplatelets	4736 (46.2)
Potassium binder	941 (9.2)
Calendar year	
2007-2010	3431 (33.5)
2011-2013	3399 (33.1)
2014-2016	3424 (33.4)
Hospitalizations	
Any hospitalization in previous year, *n (%)*	4325 (42.2)
Hyperkalemia hospitalization, *n (%)*	415 (4.0)
AKI hospitalization in previous year, *n (%)*	481 (4.7)

eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; ACR = albumin-to-creatinine ratio; AKI = acute kidney injury.
* potassium was missing in 37% of individuals.

Stopping RASi and outcomes

After cloning, 10,254 individuals were assigned to each treatment strategy. The mean of the truncated inverse probability weights was 2.2 (maximum 35.0). The characteristics in each treatment arm at the end of the grace period (six months after baseline) before and after weighting are shown in **Supplemental Table S6**. The inverse probability weighting showed a good ability to remove covariate imbalance. The estimated 5-year mortality risk was 40.9% (95% CI 38.9, 42.8) among those who continued RASi, and 54.5% (95% CI 48.5, 61.2) among those who stopped RASi, corresponding to an absolute risk difference of 13.6 (95% CI 7.0, 20.3) deaths per 100 individuals and a 5-year RMST difference of -3.6 months (95% CI -5.4, -1.8) (**Table 2**). The 5-year risk of MACE was 47.6% (95% CI 45.9, 49.4) in the RASi continuation arm and 59.5% (95% CI 53.8, 66.1) percent in the stopping RASi arm, with an estimated 5-year absolute risk difference of 11.9 (95% CI 5.7, 18.6) events per 100 individuals and a 5-year RMST difference of -3.3 months (95% CI -5.3, -1.4) (**Figure 2, Table 2**).

Figure 2. Weighted cumulative probability curves for mortality (A), MACE (B), KRT (C) and cancer (D, negative control outcome) stratified by RASi use strategy. Thinner dotted lines represent 95% confidence intervals.

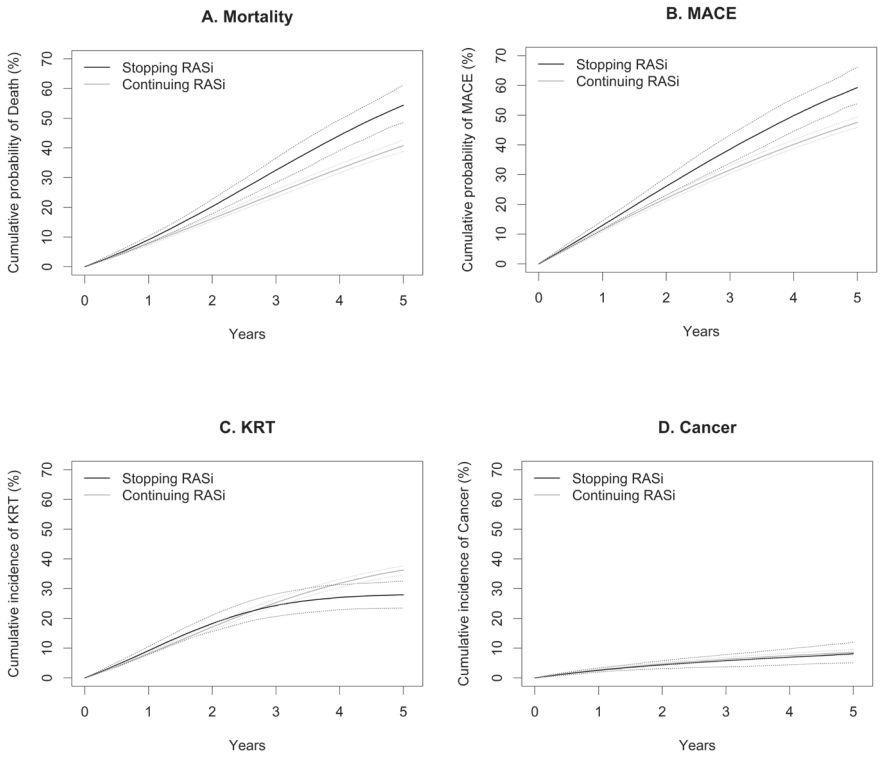

Table 2. 5-year RMST, RMST differences, absolute risks and risk differences associated with stopping RASi and continuation on mortality, MACE and KRT in advanced CKD patients with eGFR <30 ml/min/1.73m^2.

	Weighted persons, *n*	Weighted events, *n*	5-year RMST, months (95% CI)	5-year RMST difference, months (95% CI)	5-year absolute risk, % (95% CI)	5-year risk difference, % (95% CI)
All-cause mortality						
Continuing RASi	7971	3258	47.9 (46.2, 49.7)	Reference	40.9 (38.9, 42.8)	Reference
Stopping RASi	7078	3852	44.3 (43.8, 44.8)	-3.6 (-5.4, -1.8)	54.5 (48.5, 61.2)	13.6 (7.0, 20.3)
MACE						
Continuing RASi	8127	3870	44.7 (42.8, 46.5)	Reference	47.6 (45.9, 49.4)	Reference
Stopping RASi	7623	4543	41.4 (40.8, 41.9)	-3.3 (-5.3, -1.4)	59.5 (53.8, 66.1)	11.9 (5.7, 18.6)
KRT						
Continuing RASi	8329	3007	48.1 (46.5, 49.7)	Reference	36.1 (34.7, 37.7)	Reference
Stopping RASi	8808	2458	48.9 (48.3, 49.5)	0.8 (-0.8, 2.5)	27.9 (23.5, 32.5)	-8.3 (-12.8, -3.6)

N = number; CI = confidence interval; MACE = major adverse cardiovascular events; RASi = renin-angiotensin system inhibitor; KRT = renal replacement therapy; RMST = restricted mean survival time.

ǂAnalyses were adjusted through inverse probability weighting for age, sex, calendar year, eGFR, systolic and diastolic blood pressure, comorbidities (ischemic heart disease, myocardial infarction, arrhythmia, heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, chronic pulmonary disease, cancer), medication use (beta blockers, calcium channel blockers, diuretic, statins, antiplatelet) and hospitalizations (total number of hospitalizations in previous year, AKI hospitalization in previous year, hyperkalaemia hospitalization). Valid 95% confidence intervals were derived using nonparametric bootstrap based on 500 samples to account for the within-subject correlation induced by weighting. Weights were truncated at the 99.5th percentile.

The 5-year estimated risk of KRT was 36.1 (95% CI 34.7, 37.7) for patients that continued with RASi and 27.9 (95% CI 23.5, 32.5) for those who stopped RASi. This corresponds to an absolute risk reduction of -8.3 (95% CI -12.8, -3.6) KRT events per 100 individuals among patients stopping RASi and a 5-year RMST difference of 0.8 months (95% CI -0.8, 2.5). **Figure 2** shows the weighted cumulative incidence curves for study outcomes stratified according to treatment strategy. The curves for mortality and MACE progressively diverged after a few months, whereas the curves for KRT crossed, and diverged after three years.

Stopping RASi and outcomes at different eGFR

The higher eGFR cohort included 7,277 individuals whose first observed eGFR was between 20-30 ml/min/1.73m² (median eGFR 25; IQR 23-28), and the lower eGFR cohort included 6,907 individuals whose first observed eGFR was below 20 ml/min/1.73m² (median eGFR 17; IQR 14-19). Baseline characteristics for both cohorts are displayed in **Supplemental Table S7**. In both cohorts an increased risk for mortality and MACE was observed when RASi was stopped (**Tables 3-4, Supplemental Figures S2-S3**). For instance, in the lower eGFR cohort, stopping RASi was associated with an increased absolute risk for mortality (17.1; 95% CI 9.9, 23.8 per 100 individuals) and MACE (12.6; 95% CI 5.8, 19.3 per 100 individuals). In both cohorts, there also was a lower absolute risk of KRT among patients stopping RASi. For instance, in the low eGFR cohort there was an absolute risk reduction of -9.6 (95% CI -15.0, -3.8) KRT events per 100 individuals among patients stopping RASi. The cumulative incidence curve showed that the risk for KRT was slightly higher in the stopping arm during the first two years of follow-up, crossed at two years, and diverged gradually (**Supplemental Figures S2-S3**).

Table 3. 5-year RMST, RMST differences, absolute risks and risk differences associated with stopping RASi and continuation on mortality, MACE and KRT in advanced CKD patients with eGFR 20-30 ml/min/1.73m².

	Weighted persons, *n*	Weighted events, *n*	5-year RMST, months (95% CI)	5-year RMST difference, months (95% CI)	5-year absolute risk, % (95% CI)	5-year risk difference, % (95% CI)
All-cause mortality						
Continuing RASi	5471	2114	48.7 (46.4, 50.9)	Reference	38.6 (36.3, 40.9)	Reference
Stopping RASi	4594	2340	46.1 (45.4, 46.8)	-2.6 (-4.9, -0.2)	50.9 (42.4, 60.1)	12.3 (3.3, 21.4)
MACE						
Continuing RASi	5634	2525	45.7 (43.3, 48.1)	Reference	44.8 (42.7, 46.9)	Reference
Stopping RASi	5005	2950	42.7 (42.0, 43.4)	-3.0 (-5.5, -0.5)	58.9 (49.2, 67.8)	14.1 (4.6, 23.5)
KRT						
Continuing RASi	5376	1360	53.3 (51.5, 55.0)	Reference	25.3 (23.4, 27.3)	Reference
Stopping RASi	5312	681	55.4 (54.9, 55.9)	2.1 (-0.3, 3.9)	12.8 (7.6, 18.6)	-12.5 (-17.8, -6.6)

N = number; CI = confidence interval; MACE = major adverse cardiovascular events; RASi = renin-angiotensin system inhibitor; KRT = renal replacement therapy; RMST = restricted mean survival time.

ǂAnalyses were adjusted through inverse probability weighting for age, sex, calendar year, eGFR, systolic and diastolic blood pressure, comorbidities (ischemic heart disease, myocardial infarction, arrhythmia, heart

failure, peripheral vascular disease, cerebrovascular disease, diabetes, chronic pulmonary disease, cancer), medication use (beta blockers, calcium channel blockers, diuretic, statins, antiplatelet) and hospitalizations (total number of hospitalizations in previous year, AKI hospitalization in previous year, hyperkalaemia hospitalization). Valid 95% confidence intervals were derived using nonparametric bootstrap based on 500 samples to account for the within-subject correlation induced by weighting. Weights were truncated at the 99.5th percentile.

Table 4. 5-year RMST, RMST differences, absolute risks and risk differences associated with stopping RASi and continuation on mortality, MACE and KRT in advanced CKD patients with eGFR <20 ml/min/1.73m^2.

	Weighted persons, *n*	Weighted events, *n*	5-year RMST, months (95% CI)	5-year RMST difference, months (95% CI)	5-year absolute risk, % (95% CI)	5-year risk difference, % (95% CI)
All-cause mortality						
Continuing RASi	5470	2401	46.4 (44.7, 48.2)	Reference	43.9 (41.3, 46.6)	Reference
Stopping RASi	5423	3309	42.0 (41.3, 42.7)	-4.4 (-6.3, -2.5)	61.0 (54.0, 67.3)	17.1 (9.9, 23.8)
MACE						
Continuing RASi	5547	2845	43.0 (41.2, 44.8)	Reference	51.3 (48.9, 53.9)	Reference
Stopping RASi	5734	3663	39.9 (39.2, 40.7)	-3.1 (-5.0, -1.1)	63.9 (57.0, 70.0)	12.6 (5.8, 19.3)
KRT						
Continuing RASi	5914	3131	40.6 (38.6, 42.6)	Reference	52.9 (50.8, 54.8)	Reference
Stopping RASi	6872	2981	42.0 (41.3, 42.7)	1.4 (-0.7, 3.5)	43.4 (38.3, 48.8)	-9.6 (-15.0, -3.8)

N = number; CI = confidence interval; MACE = major adverse cardiovascular events; RASi = renin-angiotensin system inhibitor; KRT = renal replacement therapy; RMST = restricted mean survival time.

ǂAnalyses were adjusted through inverse probability weighting for age, sex, calendar year, eGFR, systolic and diastolic blood pressure, comorbidities (ischemic heart disease, myocardial infarction, arrhythmia, heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, chronic pulmonary disease, cancer), medication use (beta blockers, calcium channel blockers, diuretic, statins, antiplatelet) and hospitalizations (total number of hospitalizations in previous year, AKI hospitalization in previous year, hyperkalaemia hospitalization). Valid 95% confidence intervals were derived using nonparamtric bootstrap based on 500 samples to account for the within-subject correlation induced by weighting. Weights were truncated at the 99.5th percentile.

Supporting and sensitivity analyses

Using untruncated weights had no major influence on the point estimates (**Supplemental Table S8**). Subgroup analyses within strata of age, sex, diabetes, heart failure and ischemic heart disease showed no suggestion of heterogeneity, with higher risk differences for mortality and MACE and lower risk differences for KRT observed across all subgroups (**Supplemental Figure S4**). We did not observe an association between continuing/stopping RASi and the risk of cancer in any of the studied cohorts (**Supplemental Table S9**). In the sensitivity analysis using RASi as a time-dependent exposure through inverse probability of treatment and censoring weighted estimation of a marginal structural model, immediately stopping and not restarting RASi compared with always using RASi was associated with an 11.3% (95% CI 8.1, 14.5) higher risk for mortality, an 8.8% (95% CI 5.5, 12.5) higher risk for MACE and a -7.1% (95% CI -11.8, -3.4) lower risk for KRT (**Supplemental Table S10, Supplemental Figure S5**). In patients with available measures of ACR and potassium, additional adjustment for these covariates showed results consistent with our main analysis, although with wider confidence intervals: compared with patients continuing RASi, stopping was associated with a 9.3% (95% CI -1.1, 23.7) higher absolute risk for mortality, 7.6% (95% CI -23.6, 21.2) higher risk for MACE but -8.2% (95% CI -15.8, 5.8) lower risk for KRT (**Supplemental Table S11**). Stratified analyses by baseline ACR and potassium categories were largely consistent with the main results (**Supplemental Figure S5**). There was an increase in the magnitude of the association of stopping RASi on KRT events: risk difference of -11.4 (95% CI -19.5, -2.6) KRT events per hundred patients in patients with baseline potassium <5.0 mmol/l and -33.3 (95% CI -41.9, -25.5) in patients with potassium ≥5.0 mmol/l over a 5-year follow-up period (interaction $p < 0.001$). Finally, evaluating the composite outcome of death plus KRT favored the strategy of continuing with RASi vs. stopping, although confidence intervals were wide, with an absolute 5-year risk difference of 5.1% (95% CI -0.2, 11.3) (**Supplemental Table S12** and **Supplemental Figure S6**).

Discussion

Deciding whether and when to stop RASi in patients with advanced CKD is a frequent issue in clinical practice (15, 16). A single-center UK observational study of 52 individuals (mean eGFR of 16 ml/min/1.73m^2) reported that eGFR increased significantly after stopping RASi, leading to the idea that stopping RASi may prolong the time to KRT (11). Stopping RASi, on the other hand, may also potentially harm patients by increasing cardiovascular risk and mortality, based on generalisation from cardiovascular trials largely conducted in people with higher GFR (17). We addressed this problem by modelling the consequences of this decision in a nationwide observational study of over ten thousand individuals with advanced CKD under routine nephrological care. We found that compared with continuing RASi, stopping treatment was associated

with a higher 5-year risk of mortality and MACE, but a lower absolute KRT risk. These results appeared robust in various sensitivity and subgroup analyses, including the evaluation of stopping at a higher or lower eGFR.

Our findings of a higher absolute risk of death and MACE among patients stopping RASi confirm and expand a recent observational study of 3909 persons with advanced CKD from a single healthcare provider in the U.S. (17). Expansion of this evidence to a large, nationwide and geographically diverse cohort of patients receiving universal government-subsidized healthcare increases generalizability. Collectively, this agrees with trial evidence on the cardioprotection that RASi confers to patients with CKD (42), and with observational evidence of lower cardiovascular risk associated with RASi use at all levels of eGFR (43, 44). Our finding of a lower absolute KRT risk among patients stopping RASi differs from the previous U.S. study. Qiao *et al.* (17) observed that continuing RASi was not associated with increased risk of KRT (HR, 1.19; 95% CI, 0.86-1.65) and they summarized this as "KRT harms may not be excessive". Because the assumption of proportional hazards was not met in our study, we reported absolute risk differences, and observed an association of stopping RASi therapy with reduced risk of KRT (8.3 KRT events could have been prevented per 100 patients who continued with RASi therapy over 5 years). The composite outcome of death plus KRT, which could be considered as the overall "net-clinical benefit" of the decision strategy, favored continuing with RASi. However, this analysis assumes that death and dialysis are of equal importance, which is not the case in aggregate; individual patients may attribute different importance to these outcomes and their priorities should also be considered in decision making. Finally, individual patients may respond differently to RASi, and individualization of treatment and drug dosing are other important aspects not considered in our modelling.

We used comparable designs and analytical strategies to those used in the U.S. study (17), with one exception: we censored patients when their initial strategy was changed, in acknowledgement that patients who stopped their therapy were frequently re-started during follow-up, and thus ensuring no crossovers; we think this is a strength of this current work. However, the source and type of data differ: while our cohort is representative of the CKD population under nephrologist care in Sweden, Geisinger is a large, predominantly rural, private healthcare system in Pennsylvania that included both nephrologist-referred and non-referred patients. We believe that our selection of nephrologist-referred patients is a strength for the evaluation of KRT outcomes, because patients receive and stop or continue RASi for reasons and indications that may differ between primary care and specialist nephrology care. Both studies have a similar duration of follow-up, but a larger proportion of patients initiated KRT in our study, 35%, compared with 8% in the U.S. cohort. Between-country differences and differences between nephrologists and primary health care practitioners in clinical practice may additionally explain the divergent findings: e.g., 15% of patients stopped RASi in our study vs. 32% in the U.S. cohort.

Our study is the largest to date investigating the clinical consequences associated with this common clinical issue, whether to continue or stop RASi in patients with GFR < 30 ml/min/1.73m^2. Additional strengths are: i) the application of two complementary state-of-the-art analytic approaches (i.e. target trial emulation and marginal structural modelling) to account for time-dependent confounding of a rich range of confounders; ii) confirmation of results across risk subgroups, including those with albuminuria or elevated potassium which might have explained why drugs were stopped or continued; iii) modelling a negative control outcome to evaluate the impact of reverse-causation and unknown confounding; iv) evaluation of RASi use by pharmacy dispensations, which may be a better indicator for medication intake than prescriptions. Exclusion of patients with long-term use of RASi who did not have a high medication possession ratio reduces the likelihood that medication non-adherence was the cause of drug cessation. We acknowledge a number of limitations. We did not have information on ethnic origin. Results apply to Swedish practice and extrapolation to other populations and countries should be done with caution. Initiation of KRT is itself a treatment decision that varies by practitioner and variations in physician behavior were not captured in our study. Furthermore, the decision to stop RASi is not a random one, but the consequence of complex factors that likely herald worse outcomes. Frail patients where RASi may have been more likely to be stopped may also be more likely to be treated conservatively. Despite our sophisticated analytical design, residual confounding cannot be excluded from any observational analysis, and the precise reasons for stopping RASi remain unknown. Our conclusions remain observational in nature and therefore do not substitute for randomized trials. However, until these trials are conducted they may assist in informing clinical decisions.

To conclude, in this nationwide study, stopping RASi among patients referred to nephrologists with advanced CKD was associated with an increased absolute risk of mortality and MACE, but a lower absolute risk of KRT. To date, there is no trial evidence to inform the decision of stopping RASi therapy in these patients. Until the ongoing STOP-ACEi trial is completed (19), our analyses support current KDIGO recommendations of not routinely stopping RASi in people with advanced CKD (45, 46).

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Supplemental material

Supplemental Methods

Supplemental Table S1. Brief protocol of the pragmatic target trial and its emulation using data from the Swedish Renal Registry 2007-2017.

Supplemental Table S2. Definition of study outcomes and covariates.

Supplemental Table S3. Contribution to the weights at each time point by RASi treatment strategy.

Supplemental Table S4. Model coefficients for remaining uncensored in the continuation arm.

Supplemental Table S5. Model coefficients for remaining uncensored in the discontinuation arm.

Supplemental Table S6. Characteristics at six months after follow-up (end of grace period on the cloned data while accounting, or not, for informative censoring (before and after weighting, respectively).

Supplemental Table S7. Baseline characteristics of RASi users across two sub cohorts defined on their first detected eGFR drop between 20-30 ml/min/1.73m^2 or below 20 ml/min/1.73m^2.

Supplemental Table S8. Influence of weight truncation on the point estimates of risk differences comparing stopping vs. continuing (reference) RASi.

Supplemental Table S9. Sensitivity analysis: 5-year absolute risks and risk differences associated with stopping vs. continuing RASi on the negative control outcome of cancer diagnosis.

Supplemental Table S10. Sensitivity analysis: 5-year absolute risks and risk differences for always using vs. immediately stopping and not restarting RASi. RASi was modelled as a time-dependent exposure using inverse probability of treatment and censoring weighted estimation of a marginal structural model.

Supplemental Table S11. Sensitivity analysis: 5-year absolute risks and risk differences associated with stopping vs. continuing RASi among patients with ACR and potassium available (N = 3049).

Supplemental Table S12. Sensitivity analysis: 5-year absolute risks and risk differences associated with stopping vs. continuing RASi on the composite outcome of death and KRT.

Supplemental Figure S1. Schematic representation of cloning, censoring and weighting algorithm.

Supplemental Figure S2. Weighted cumulative incidence curves for mortality (A), MACE (B), KRT (C) and cancer (D) stratified by RASi use strategy in the cohort with first detected eGFR drop between 20-30 ml/min/1.73m^2. Thinner dotted lines represent 95% confidence intervals.

Supplemental Figure S3. Weighted cumulative incidence curves for mortality (A), MACE (B), KRT (C) and cancer (D) stratified by RASi use strategy in the cohort with first detected eGFR drop <20 ml/min/1.73m^2. Thinner dotted lines represent 95% confidence intervals.

Supplemental Figure S4. Weighted cumulative incidence curves for mortality (A), MACE (B) and KRT (C) standardized to the baseline distribution of confounders using a time-dependent exposure. The effect of always using vs. immediately stopping and not restarting RASi was estimated using inverse probability of treatment and censoring weighted estimation of a marginal structural model.

Supplemental Figure S5. Effect of stopping RASi on mortality (A), MACE (B) and KRT (C) across categories of age, sex, diabetes, heart failure, ischemic heart disease, ACR and potassium. Subgroup analyses for ACR and potassium were performed on the subset of individuals with these measurements available.

Supplemental Figure S6. Weighted cumulative incidence curves for the composite outcome of death or KRT by RASi strategy for the main cohort (A), cohort of individuals with first detected eGFR drop between 20-30 ml/min/1.73m^2 (B), and cohort of individuals with first detected eGFR drop <20 ml/min/1.73m^2 (C). Thinner dotted lines represent 95% confidence intervals.

Supplemental Methods

Target trial emulation using cloning, censoring and weighting

Here we describe in detail our implementation of target trial emulation and the cloning, censoring and weighting procedure. A thorough review of trial emulation can be found elsewhere (1, 2), as well as recent applications of the methodology (3-8).

Specifying details of the target trial

A simple way to structure the study design and analysis of an observational comparative effectiveness study is to use the target trial framework (1). This means that we think about a hypothetical randomized trial we would like to conduct and then use our observational data to explicitly emulate it. Explicitly emulating a randomized trial can prevent unnecessary biases such as immortal time bias and prevalent user bias (10-12), as well as making results from observational analyses more comparable to those from trials (13). Similar to a real trial, we first need to formally define the eligibility criteria of our hypothetical trial, the treatment strategies we would like to compare, how treatment is assigned to each individual, the duration of follow-up, the primary and secondary endpoints, the causal contrast of interest (intention-to-treat or per protocol effect), and the statistical analysis. Details of the target trial we wanted to emulate in our analysis are given in **Supplemental Table S1**.

In our study we were interested in comparing the treatment strategies "stop RASi within 6 months and remain off treatment" vs. "continue RASi during follow-up". We deliberately chose treatment strategies that required patients to be on or off treatment during the whole follow-up period, which ensured no cross-over between treatment arms. For example, in our study 57% of individuals who discontinued RASi within the first six months restarted treatment during follow-up. Comparing strategies such as "stop RASi within 6 months" vs. "continue RASi for 6 months" would therefore suffer from a lot of cross-over and dilution of the treatment effect.

Comparing treatment strategies that are sustained over time (as opposed to point interventions which happen only once, such as surgery or vaccination) requires methods that can appropriately adjust for time-varying confounding, such as the parametric G-formula or cloning, censoring and weighting (1, 14). We now explain in detail our implementation of the latter approach. A graphical depiction of the cloning, censoring and weighting procedure can be found in **Supplemental Figure S1**.

Step 1: Cloning and assigning replicates to the treatment strategies

The first step consists of cloning each individual into two identical replicates, each of whom is assigned to one strategy. The dataset will now be twice as large compared with the original dataset. Since each individual occurs in both strategies, no baseline confounding is present.

Step 2: Censoring replicates if and when they do not adhere to their assigned strategy

Note that there are now clones included in both strategies that do not necessarily always adhere to their assigned strategy. To estimate the effect of a particular treatment strategy, we therefore need to censor clones if and when their observed treatment does not match their assigned strategy anymore.

In our dataset, we therefore determined at each month whether a replicate was adherent to their assigned strategy and artificially censored them if they stopped adhering. Those assigned to the stopping strategy had to stop RASi within 6 months and remain off treatment for the remainder of the follow-up. Therefore, replicates in this treatment arm are censored under the following two conditions: if they had not stopped by month 6, or if they restarted treatment at any moment during follow-up after stopping. Those assigned to continuation were censored if they stopped treatment at any moment during follow-up.

Step 3: Inverse probability weighting to adjust for informative censoring

Because the artificial censoring of replicates is likely to be informative, this will lead to selection bias (collider stratification bias). We therefore need to use inverse probability weighting to adjust for this selection bias, which is the most involved step of the cloning, censoring and weighting procedure. In brief, uncensored replicates receive a weight that is equal to the inverse of the probability of remaining uncensored, conditional on their own covariate history. Intuitively, the weighting will upweight uncensored replicates who have similar characteristics as censored replicates (see also **Supplemental Figure 1**). This creates a pseudopopulation in which censoring does not depend on measured characteristics and is no longer informative.

To estimate the inverse probability of censoring weights, we first fit a pooled logistic model with being uncensored as the outcome and as independent variables an indicator for time (e.g., month and month squared [quadratic term], or more flexible functions of time such as restricted cubic splines), baseline and time-varying confounders. We fit a pooled logistic model for each arm separately for two reasons. First, the censoring pattern is likely different between both treatment strategies and secondly, this will better capture treatment by covariate interaction (2). The regression coefficients from these models are shown in **Supplemental Tables S4-5**.

Next, we used the probabilities estimated by these models to construct the inverse probability of censoring weights as shown in **Supplemental Table S3**. Weights were set to 1 during the first 5 months for replicates in the stopping arm that had not yet discontinued RASi, as their probability to remain uncensored is per definition 1. We truncated the weights at the 99.5th percentile to avoid undue influence of very large weights. Truncating the weights is a trade-off between bias and precision: truncation of large weights will lead to narrower confidence intervals at the expense of introducing some bias. The mean of the truncated weights was 2.2 and the maximum 35.0. Using untruncated weights showed virtually similar results (**Supplemental Table S8**). The weights showed good ability to remove imbalance at the end of the grace period (6 months after baseline) (**Supplemental Table S6**).

Step 4: Primary analysis

Next, we stacked the two datasets (stopping and continuing). We used a weighted pooled logistic model to estimate the per protocol effect of stopping vs. continuing. The pooled logistic model contained indicators for time (month and month squared), an indicator for treatment strategy, and interactions between time and treatment strategy, as well as the weights estimated in step 3. The pooled logistic model was used to calculate weighted cumulative incidence curves. The weighted curves were then used to calculate 5-year absolute risk differences and differences in restricted mean survival time. To account for the weighting we used nonparametric bootstrapping based on 500 samples to obtain valid 95% confidence intervals.

RASi as time-dependent exposure using inverse probability of treatment and censoring weighted estimation of a marginal structural model

We used a marginal structural model to estimate the effect of time-varying RASi use on outcomes. A marginal structural model was used because some of the time-varying confounders may also be affected by treatment itself (i.e., over time the covariate plays both the role of confounder and mediator of the effect of treatment on outcomes). Using a time-dependent regression analysis would therefore lead to biased results due to adjustment in the causal pathway and introducing collider stratification bias (15).

The method described here instead uses inverse probability weighting to appropriately adjust for time-varying confounding and censoring. Inverse probability of treatment weights (IPTW) were used to adjust for time-varying confounding, whereas inverse probability of censoring weights (IPCW) were used to adjust for informative censoring. The IPTW and IPCW were estimated using the same time-fixed and time-varying confounders that were used in the main analysis using the cloning, censoring and weighting design (see **Supplemental Table 1** for variables).

Treatment weights

The IPTW consists of a numerator and a denominator. The denominator is used to adjust for the time-varying confounding, whereas the numerator is used to stabilize the weights so that they do not become excessively large. To estimate the numerator and denominator for the IPTW, we fitted two separate pooled logistic regression models. The pooled logistic regression model for the numerator had discontinuation as the outcome and an indicator for time and all time-fixed confounders as independent variables. The pooled logistic regression model for the denominator additionally included all time-varying confounders as independent variables. Time in both models was modelled using month and month squared as predictors. The predicted values from these pooled logistic models were used to estimate the IPTW.

Censoring weights

In order to estimate the effect of "always" vs. "never" using RASi, we censored patients when they restarted RASi treatment after they had discontinued. This censoring is likely to be informative. We therefore additionally constructed IPCW to adjust for this informative censoring. The IPCW were constructed in a similar manner as the IPTW specified above, with the only difference being that the outcome was "remaining uncensored" instead of "discontinuation". Since patients who had not discontinued (yet) cannot be censored by definition, censoring weights were only calculated for the patients after they discontinued. For the other records, the IPCW were set to 1.

Outcome model

The IPTW and IPCW were multiplied to obtain the final stabilized weights used in the outcome model. We estimated the effect of RASi discontinuation vs. continuation on all-cause mortality, MACE and KRT by fitting a weighted pooled logistic model that included month, month squared, a time-dependent treatment variable, interactions between time and treatment and all baseline covariates. This model was used to estimate adjusted cumulative incidence curves. The cumulative incidence curves were standardized to the distribution of baseline variables in the study population (17). Under the assumptions of exchangeability, positivity, consistency and no model misspecification, this approach estimates the average causal effect of treatment discontinuation on outcomes in the original study population (15).

The stabilized weights had a mean of 1.0, a minimum of 0.095 and a maximum of 69.9. Weights were not truncated; truncation at the 99.5th percentile gave virtually identical results (mean of weights after truncation: 1.0; maximum: 2.4; results not shown). Nonparametric bootstrap with 500 samples was used to compute percentile-based 95% confidence intervals for the absolute estimates.

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