Supplemental Material

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

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Supplemental Figure S5. 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 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.

Supplemental references

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

Component	Target trial	Emulation in Swedish Renal Registry
Eligibility	Individuals (both sexes) aged 18 years or older with new-onset CKD G4/5 (defined as an eGFR <30 ml/min/1.73m^2 using the CKD-EPI equation) who were adherent users of RASi and had no history of kidney transplantation or dialysis.	Same as target trial. A medication possession ratio >80% in the 2 years prior to inclusion was used as a proxy for adherence.
Treatment strategies	Stop RASi within 6 months and remain off treatment vs. continue RASi.	In our main analysis, we compared the treatment strategies stopping RASi within 6 months and remaining off treatment after first observed eGFR <30 ml/min/1.73m^2 or continue RASi during the entire follow-up.
Treatment assignment	Eligible individuals are randomly assigned to one of the two strategies and are aware of the treatment strategy they are assigned to (i.e., no blinding).	Randomisation is emulated via cloning of individuals and assigning each replicate to a treatment strategy.
Follow-up	For each individual follow-up starts at the time of assignment to a strategy (i.e., baseline is the moment when eGFR first drops <30 ml/min/1.73m^2) and ends at the occurrence of death, major cardiovascular event, kidney replacement therapy or 5 years, whichever comes first.	Same as target trial.
Primary end point	All-cause mortality. Secondary endpoints include major adverse cardiovascular events and initiation of kidney replacement therapy.	Same as target trial. All-cause mortality is identified from the Swedish Death Registry. Cardiovascular hospitalizations are identified through ICD-10 codes in the National Patient Registry: myocardial infarction: I21, I22; cerebrovascular event: G45, G464, G463, I63, I64, I693, I694, I698. Initiation of KRT is ascertained from the Swedish Renal Registry.
Causal contrast	Intention-to-treat effect. Per protocol effect.	Per protocol effect: effect of adhering to the strategies as specified under "Treatment strategies" during follow-up.
Statistical analysis	Intention-to-treat analysis. Per protocol analysis: Individuals are artificially censored when they deviate from their assigned strategy as follows: *Stop within 6 months and remain off treatment:* Censored at the beginning of the 6th month if not stopped. Censored if RASi treatment	Same as per protocol analysis. We created an expanded dataset including 2 replicates for each included individual and assigned one replicate to each treatment strategy. We adjusted for the following baseline and time-varying variables and assumed that adjustment for these variables was sufficient to adjust for informative censoring: age, sex, calendar year, eGFR, systolic and diastolic blood pressure,

	is restarted after discontinuation at any moment during follow-up. *Continue:* Censored when individual stopped during follow-up. Note that inverse probability weighting is required also in a randomized trial to validly estimate the per-protocol effect. IP weights are estimated as a function of time-fixed variables (age, sex, calendar year) and the following baseline variables and time-varying variables: 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, hyperkalemia hospitalization). Standardized, weighted survival curves under each strategy.	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, hyperkalemia hospitalization). Sensitivity analyses were additionally adjusted for ACR and potassium values.

Supplemental Table S2. Definition of study outcomes and covariates.

Outcomes	**Definition**	
Mortality	Death in the Swedish Causes of Death Registry	
MACE	Composite of death, hospitalization due to myocardial infarction and stroke	
Myocardial infarction	Main hospitalization diagnosis with ICD-10 codes I21, I22	
Stroke	Main hospitalization diagnosis with ICD-10 codes G45, G464, G463, I63, I64, I693, I694, I698	
Kidney replacement therapy	Registration of date of kidney transplantation or initiation of maintenance dialysis in the Swedish Renal Registry	
Cancer diagnosis (negative control outcome)	Diagnosis with ICD-10 codes C00-C26, C30-C34, C37-C41, C43, C45-58, C60-C76, C81-C86, C88, C90-C97	
Medication	**ATC codes**	
Beta blockers	C07	
Calcium-channel blockers	C08, C07FB, C09BB, C09DB, C10BX03	
Diuretics	C03, C02LA01, C07BA02, C07BB, C07CA03, C07DA06, C08GA02, C09BA, C09XA52, S01EC01	
Statins	C10AA	
Potassium binder	V01AE01	
Antiplatelet agents	B01AC	
Comorbidities	**ICD-10 codes**	**ATC codes**
Hypertension	I10-I15	
Myocardial infarction	I21, I22, I25.2	
Ischemic heart disease	I20-I25	
Arrhythmia	I47-I49	
Heart failure	I50, I42, I43, I25.5, K76.1, I11.0, I13.0, I13.2, J81	
Peripheral vascular disease	I70-I73	
Cerebrovascular disease	G45.8, G45.9, I61-I64	
Diabetes mellitus	E10-E14	A10
Chronic pulmonary disease	I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3	R03
Tumor during the previous 2 years except for metastatic solid tumor	C00-C26, C30-C34, C37-C41, C43, C45-58, C60-C76, C81-C86, C88, C90-C97	
Hospitalizations		
Number of hospitalizations during previous year	All hospitalizations recorded in the National Patient Registry in the previous year	
Hyperkalemia hospitalization in previous year as primary cause	E87.5	
AKI hospitalization in previous year as primary cause	N17	

ICD = International Classification of Diseases; ATC = Anatomic Therapeutic Chemical Classification System, NPR = National Patient Registry; AKI = acute kidney injury.

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

Strategy	**Time Point**	**Contribution to Weights**
Stop RASi within 6 mo and remain off treatment	$0 \leq t < 1$ $t \geq 1$	1 1/p
Continue RASi	$0 \leq t < 1$ $t \geq 1$	1 1/p

* *t* is the time in months since first observed eGFR drop <30 ml/min/1.73m^2, and *p* is the probability of remaining uncensored conditional on baseline and time-varying covariates. Replicates were censored if they did not follow their assigned treatment strategy. 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. Weights are set to 1 during the first 5 months for replicates in the stopping arm that have not yet discontinued RASi, as their probability of remaining uncensored is 1. See also the graphical depiction in *Supplemental Figure 1* and the *Supplemental Methods* section.

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

Variable	Coefficient	Standard Error
Intercept	3.132	0.186
Month	0.029	0.003
Month squared	0.000	0.000
Baseline		
Age	-0.008	0.001
Women	0.063	0.031
Hypertension	-0.272	0.086
Myocardial infarction	0.078	0.100
Ischemic heart disease	-0.116	0.091
Arrhythmia	-0.128	0.069
Heart failure	0.012	0.067
Peripheral vascular disease	0.007	0.086
Cerebrovascular disease	0.042	0.099
Diabetes	-0.170	0.113
Cancer	-0.146	0.069
Beta blocker	0.085	0.047
Calcium channel blocker	0.146	0.039
Diuretic	0.133	0.044
Statins	0.246	0.043
eGFR	0.009	0.003
Systolic blood pressure	0.002	0.001
Diastolic blood pressure	-0.003	0.002
Hyperkalemia hospitalization	-0.235	0.107
Chronic obstructive pulmonary disease	-0.109	0.064
Antiplatelet therapy	0.070	0.049
Number of hospitalizations in previous year	-0.122	0.034
AKI hospitalization in previous year	-0.253	0.040
Calendar year 2011-2013	-0.136	0.007
Calendar year 2014-2016	-0.525	0.070
Time-varying		
Hypertension	0.216	0.072
Myocardial infarction	0.004	0.104
Ischemic heart disease	0.040	0.094
Arrhythmia	0.167	0.075
Heart failure	0.039	0.070
Peripheral vascular disease	-0.023	0.094
Cerebrovascular disease	-0.115	0.104
Diabetes	0.204	0.114
Cancer	0.038	0.074
Beta blocker	-0.004	0.046
Calcium channel blocker	-0.019	0.039

Diuretic	0.016	0.045
Statins	-0.068	0.044
eGFR	0.027	0.003
Systolic blood pressure	0.001	0.001
Diastolic blood pressure	0.001	0.002
Hyperkalemia hospitalization	0.215	0.128
Chronic pulmonary disease	-0.021	0.067
Antiplatelet therapy	-0.039	0.050
Number of hospitalizations in previous year	0.020	0.009
AKI hospitalization in previous year	-0.179	0.079

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

Variable	Coefficient	Standard Error
Intercept	18.829	0.317
Month	-4.287	0.048
Month*	397.709	4.522
Month**	-808.030	9.245
Baseline		
Age	0.010	0.002
Women	0.100	0.086
Hypertension	-0.016	0.177
Myocardial infarction	-0.134	0.208
Ischemic heart disease	0.312	0.187
Arrhythmia	0.042	0.149
Heart failure	0.015	0.131
Peripheral vascular disease	0.261	0.186
Cerebrovascular disease	-0.046	0.221
Diabetes	0.378	0.285
Cancer	0.375	0.134
Beta blocker	0.144	0.070
Calcium channel blocker	0.078	0.059
Diuretic	0.141	0.086
Statins	-0.141	0.062
eGFR	0.016	0.005
Systolic blood pressure	-0.002	0.002
Diastolic blood pressure	0.004	0.003
Hyperkalemia hospitalization	-0.274	0.263
Chronic obstructive pulmonary disease	-0.066	0.098
Antiplatelet therapy	-0.208	0.077
Number of hospitalizations in previous year	0.547	0.162
AKI hospitalization in previous year	0.866	0.168
Calendar year 2011-2013	0.126	0.03
Calendar year 2014-2016	0.405	0.135
Time-varying		
Hypertension	0.011	0.168
Myocardial infarction	0.195	0.211
Ischemic heart disease	-0.417	0.189
Arrhythmia	-0.111	0.153
Heart failure	-0.045	0.132
Peripheral vascular disease	-0.237	0.192
Cerebrovascular disease	0.123	0.224
Diabetes	-0.263	0.273
Cancer	-0.197	0.138
Beta blocker	-0.13	0.069

Calcium channel blocker	-0.024	0.058
Diuretic	0.031	0.063
Statins	-0.041	0.062
eGFR	-0.034	0.007
Systolic blood pressure	-0.001	0.002
Diastolic blood pressure	-0.002	0.003
Hyperkalemia hospitalization	0.493	0.276
Chronic pulmonary disease	0.041	0.099
Antiplatelet therapy	0.189	0.077
Number of hospitalizations in previous year	0.014	0.016
AKI hospitalization in previous year	0.279	0.138
Calendar year 2011-2013*eGFR	-0.019	0.007
Calendar year 2014-2016*eGFR	-0.028	0.008
Diabetes*Diuretic	-0.198	0.098
Women*Diuretic	-0.181	0.096
Diuretic*Number of hospitalizations in previous year	-0.045	0.030

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).

	Before weighting			**After weighting**		
	Continue	**Discontinue**	**SMD**	**Continue**	**Discontinue**	**SMD**
Number of individuals	8484*	1311*		9772.4	9820.1	
Median Age (IQR), ***years***	71.0 [62.0, 79.0]	74.0 [67.0, 81.0]	0.23	72.0 [63.0, 79.0]	72.0 [63.0, 79.0]	0.02
Women	3063 (36.1)	463 (35.3)	0.02	3518.0 (36.0)	3662.9 (37.3)	0.03
Median eGFR (IQR)‡, ***ml/min/1.73 m²***	22.8 [17.6, 27.0]	21.2 [15.4, 26.4]	0.17	22.5 [17.3, 26.9]	23.1 [17.3, 27.4]	0.04
Mean SBP (SD), ***mmHg***	138.7 (20.8)	138.7 (21.2)	<0.01	138.8 (20.9)	138.1 (21.0)	0.03
Mean DBP (SD), ***mmHg***	75.8 (11.6)	75.6 (11.8)	0.02	75.7 (11.6)	75.7 (11.9)	<0.01
Comorbidities						
Hypertension	7598 (89.6)	1209 (92.2)	0.09	8779.5 (89.8)	8815.9 (89.8)	<0.01
Myocardial infarction	1817 (21.4)	320 (24.4)	0.07	2145.6 (22.0)	2151.1 (21.9)	<0.01
Ischemic heart disease	2803 (33.0)	470 (35.9)	0.06	3275.7 (33.5)	3337.5 (34.0)	0.01
Arrhythmia	1916 (22.6)	342 (26.1)	0.08	2267.9 (23.2)	2380.6 (24.2)	0.02
Heart failure	2407 (28.4)	423 (32.3)	0.08	2845.9 (29.1)	3036.0 (30.9)	0.04
Peripheral vascular disease	1083 (12.8)	199 (15.2)	0.07	1276.4 (13.1)	1166.1 (11.9)	0.04
Cerebrovascular disease	1333 (15.7)	261 (19.9)	0.11	1589.0 (16.3)	1588.6 (16.2)	<0.01
Diabetes mellitus	4247 (50.1)	619 (47.2)	0.06	4844.2 (49.6)	4885.4 (49.7)	<0.01
Chronic obstructive pulmonary disease	1511 (17.8)	262 (20.0)	0.06	1784.2 (18.3)	1803.9 (18.4)	<0.01
Cancer diagnosis in previous 2 years	824 (9.7)	205 (15.6)	0.18	1037.4 (10.6)	979.8 (10.0)	0.02
Medication						

Beta blockers	5823 (68.6)	894 (68.2)	0.01	6714.1 (68.7)	6640.0 (67.6)	0.02
Calcium channel blockers	5281 (62.2)	774 (59.0)	0.07	6040.2 (61.8)	5862.6 (59.7)	0.04
Diuretics	6825 (80.4)	1023 (78.0)	0.06	7840.3 (80.2)	7835.0 (79.8)	0.01
Statins	5374 (63.3)	718 (54.8)	0.18	6094.9 (62.4)	6091.0 (62.0)	0.01
Antiplatelets	3900 (46.0)	584 (44.5)	0.03	4477.4 (45.8)	4412.9 (44.9)	0.02
Calendar year			0.18			0.02
2007-2010	2950 (34.8)	370 (28.2)		3316.1 (33.9)	3437.2 (35.0)	
2011-2013	2842 (33.5)	421 (32.1)		3269.0 (33.5)	3220.6 (32.8)	
2014-2016	2692 (31.7)	520 (39.7)		3187.3 (32.6)	3162.2 (32.2)	
Hospitalizations						
Mean number of hospitalizations (SD)	1.1 (1.9)	1.8 (2.4)	0.34	1.2 (2.3)	1.2 (1.8)	<0.01
Hyperkalemia Hospitalization, *n (%)*	358 (4.2)	70 (5.3)	0.05	435.0 (4.5)	441.0 (4.5)	<0.01
Mean number of AKI hospitalizations (SD)	0.0 (0.2)	0.1 (0.3)	0.30	0.0 (0.2)	0.0 (0.2)	<0.01

* Numbers do not add up to original sample size (N = 10,254) since characteristics are reported after 6 months of follow-up (end of grace period). Hence, individuals who are administratively censored, switched between treatment strategies (and artificially censored) or died are not included.

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.

	eGFR between 20-30 ml/min/1.73m^2 cohort (*n* = 7277)	**eGFR <20 ml/min/1.73m^2 cohort (*n* = 6907)**
Median Age (IQR)‡, *years*	72 [64, 79]	71 [62, 79]
Age category, *n (%)*		
<50	602 (8.3)	682 (9.9)
50-59	706 (9.7)	804 (11.6)
60-69	1687 (23.2)	1618 (23.4)
70-79	2526 (34.7)	2172 (31.4)
>=80	1756 (24.1)	1631 (23.6)
Women	2506 (34.4)	2490 (36.1)
Median eGFR (IQR)‡, *ml/min/1.73 m^2*	25 [23, 28]	17 [14, 19]
eGFR category, *n (%)*		
<15 ml/min/1.73 m^2, *n (%)*	-	2085 (30.2)
≥15 ml/min/1.73 m^2, *n (%)*	7277 (100)	4822 (69.8)
Primary kidney disease, *n (%)*		
Diabetes	2037 (28.0)	2024 (29.3)
Hypertension	1841 (25.3)	1488 (21.6)
Glomerulonephritis	789 (10.8)	852 (12.3)
Polycystic kidney disease	367 (5.0)	469 (6.8)
Pyelonephritis	120 (1.6)	103 (1.5)
Other	1246 (17.1)	1166 (16.9)
Missing	877 (12.1)	805 (11.7)
Mean SBP (SD), *mmHg*	138 (21)	140 (22)
SBP category, *n (%)*		
<120	1112 (15.3)	854 (12.4)
120-139	2723 (37.4)	2429 (35.2)
140-159	2242 (30.8)	2226 (32.2)
>160	1200 (16.5)	1398 (20.2)
Mean DBP (SD), *mmHg*	75 (12)	76 (12)
DBP category, *n (%)*		
<80	4079 (56.1)	3602 (52.1)
80-89	2289 (31.5)	2237 (32.4)
90-99	683 (9.4)	815 (11.8)
>100	226 (3.1)	253 (3.7)
Median urinary ACR [IQR], *mg/mmol*	26 [5, 120]	75 [12, 224]

ACR category, *n (%)*		
A1 (<3)	723 (9.9)	392 (5.7)
A2 (3-29)	1241 (17.1)	905 (13.1)
A3 (30-69)	517 (7.1)	397 (5.7)
A3 (≥70)	1295 (17.8)	1798 (26.0)
Missing	3501 (48.1)	3415 (49.4)
Mean serum potassium (SD), *mg/mmol**	4.5 (0.5)	4.5 (0.6)
Comorbidities, *n (%)*		
Hypertension	6498 (89.3)	6142 (88.9)
Myocardial infarction	1624 (22.3)	1428 (20.7)
Ischemic heart disease	2480 (34.1)	2195 (31.8)
Arrhythmia	1718 (23.6)	1396 (20.2)
Heart failure	2090 (28.7)	1832 (26.5)
Peripheral vascular disease	928 (12.8)	865 (12.5)
Cerebrovascular disease	1134 (15.6)	1047 (15.2)
Diabetes mellitus	3660 (50.3)	3365 (48.7)
Chronic obstructive pulmonary disease	1317 (18.1)	1202 (17.4)
Cancer diagnosis in previous 2 years	696 (9.6)	681 (9.9)
Medication, *n (%)*		
Beta blockers	4875 (67.0)	4712 (68.2)
Calcium channel blockers	4201 (57.7)	4531 (66.6)
Diuretics	5705 (78.4)	5564 (80.6)
Statins	4499 (61.8)	4309 (62.4)
Antiplatelets	3336 (45.8)	3197 (46.3)
Potassium binder	557 (7.7)	938 (13.6)
Calendar year		
2007-2010	2017 (27.7)	2347 (34.0)
2011-2013	2598 (35.7)	2211 (32.0)
2014-2016	2662 (36.6)	2349 (34.0)
Hospitalizations		
Any hospitalization in previous year, *n (%)*	2905 (39.9)	3028 (43.8)
Hyperkalemia hospitalization, *n (%)*	288 (4.0)	316 (4.6)
AKI hospitalization in previous year, *n (%)*	268 (3.7)	320 (4.6)

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 35% and 33% of individuals, respectively.

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

	Estimated 5-year RD, %
Untruncated	
Mortality	14.1
MACE	14.8
KRT	-14.0
Cancer	-0.5
Main analysis (truncated at 99.5th percentile)	
Mortality	13.6
MACE	11.9
KRT	-8.3
Cancer	-0.4

RD = risk difference.

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.

	Weighted persons, *n*	**Weighted events, *n***	**5-year absolute risk, % (95% CI)**	**5-year risk difference, % (95% CI)**
Main cohort (eGFR <30 ml/min/1.73m^2)				
Continuing RASi	7637	655	8.6 (7.7, 9.6)	Reference
Stopping RASi	7371	602	8.2 (5.1, 12.0)	-0.4 (-3.6, 3.6)
Cohort with eGFR decrease to 20-30 ml/min/1.73m^2				
Continuing RASi	5307	420	7.9 (6.9, 8.9)	Reference
Stopping RASi	5563	399	7.2 (3.6, 12.3)	-0.8 (-4.4, 4.4)
Cohort with eGFR decrease to <20 ml/min/1.73m^2				
Continuing RASi	5085	439	8.6 (7.4, 10.0)	Reference
Stopping RASi	5017	510	10.2 (6.1, 14.9)	1.5 (-2.8, 6.2)

N = number; CI = confidence interval; eGFR = estimated glomerular filtration rate; RASi = renin-angiotensin system inhibitor.

†Analyses 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). 95% confidence intervals were calculated 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. Total sample size after exclusion of individuals with an ongoing cancer (diagnosis within 2 years before inclusion) was 9236 for the main cohort (1018 excluded), 6581 for the cohort with eGFR between 20-30 ml/min/1.73m^2 (696 excluded) and 6226 for the cohort with eGFR <20 ml/min/1.73m^2 (681 excluded).

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.

	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	48.5 (47.4, 49.6)	Reference	38.0 (36.3, 40.6)	Reference
Stopping RASi	43.6 (43.0, 44.1)	-4.9 (-6.1, -3.7)	49.3 (47.1, 52.4)	11.3 (8.1, 14.5)
MACE				
Continuing RASi	45.2 (44.1, 46.4)	Reference	45.1 (43.8, 48.0)	Reference
Stopping RASi	41.2 (40.6, 41.7)	-4.1 (-5.4, -2.8)	53.9 (51.8, 57.5)	8.8 (5.5, 12.5)
KRT				
Continuing RASi	47.8 (46.3, 49.4)	Reference	36.0 (34.9, 38.4)	Reference
Stopping RASi	48.5 (47.9, 49.0)	0.6 (-1.0, 2.3)	28.9 (25.1, 32.8)	-7.1 (-11.8, -3.4)

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

[†]Analyses were adjusted using stabilized inverse probability of treatment and censoring weights 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). 95% confidence intervals were calculated using nonparametric bootstrap based on 500 samples. The mean of the untruncated stabilized weights was 1.0 and ranged from 0.1 to 68.2.

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).

	Weighted persons, *n*	**Weighted events, *n***	**5-year absolute risk, % (95% CI)**	**5-year risk difference, % (95% CI)**
All-cause mortality				
Continuing RASi	2202	876	39.8 (34.9, 43.5)	Reference
Stopping RASi	1957	961	49.1 (37.8, 61.7)	9.3 (-1.1, 23.7)
MACE				
Continuing RASi	2301	1059	46.0 (42.1, 49.6)	Reference
Stopping RASi	2108	1131	53.7 (42.6, 66.6)	7.6 (-3.6, 21.2)
KRT				
Continuing RASi	2418	727	30.1 (26.8, 33.1)	Reference
Stopping RASi	1804	394	21.8 (14.1, 34.7)	-8.2 (-15.8, 5.8)
Cancer (negative control outcome)				
Continuing RASi	2132	200	9.4 (8.0, 11.5)	Reference
Stopping RASi	2410	160	6.6 (2.6, 11.2)	-2.7 (-7.1, 2.0)

n = number; CI = confidence interval; MACE = major adverse cardiovascular events; RASi = renin-angiotensin system inhibitor; KRT = renal replacement therapy.

[†]Analyses 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), ACR and potassium. 95% confidence intervals were calculated 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.

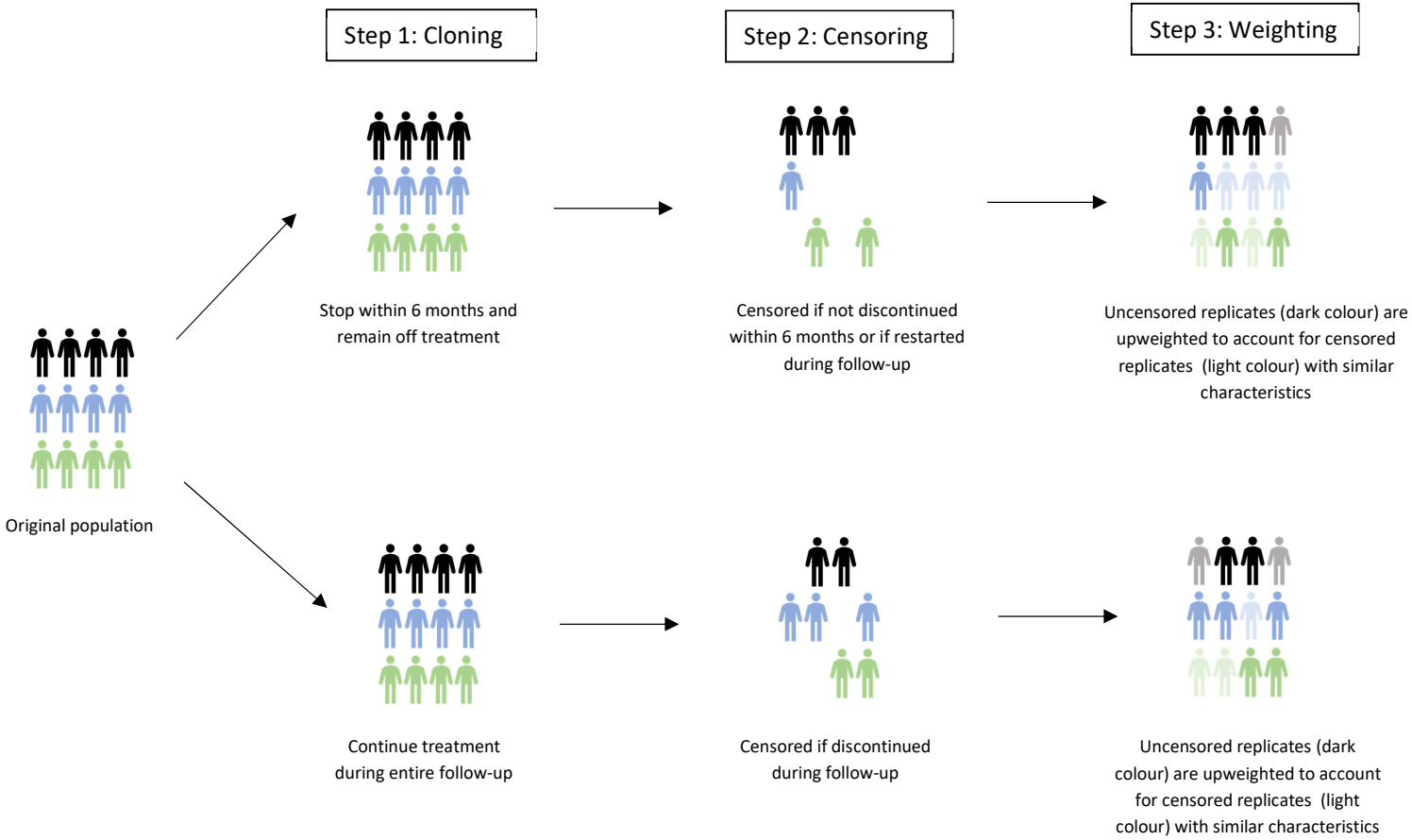
Supplemental Table S12. Sensitivity analysis: 5-year absolute risks and risk differences associated with stopping vs. continuing RASi on the composite outcome of death or KRT.

	Weighted persons, *n*	**Weighted events, *n***	**5-year absolute risk, % (95% CI)**	**5-year risk difference, % (95% CI)**
Main cohort (eGFR <30 ml/min/1.73m^2)				
Continuing RASi	8311	5436	65.4 (63.7, 67.2)	Reference
Stopping RASi	7800	5496	70.5 (65.2, 76.9)	5.1 (-0.2, 11.3)
Cohort with eGFR 20-30 ml/min/1.73m^2				
Continuing RASi	5543	3163	57.1 (55.0, 59.1)	Reference
Stopping RASi	4798	2739	57.1 (48.0, 66.1)	0.0 (-9.5, 9.0)
Cohort with eGFR <20 ml/min/1.73m^2				
Continuing RASi	5897	4703	79.7 (78.1, 81.5)	Reference
Stopping RASi	6230	5462	87.7 (82.7, 92.0)	7.9 (2.5, 12.7)

N = number; CI = confidence interval; RASi = renin-angiotensin system inhibitor.

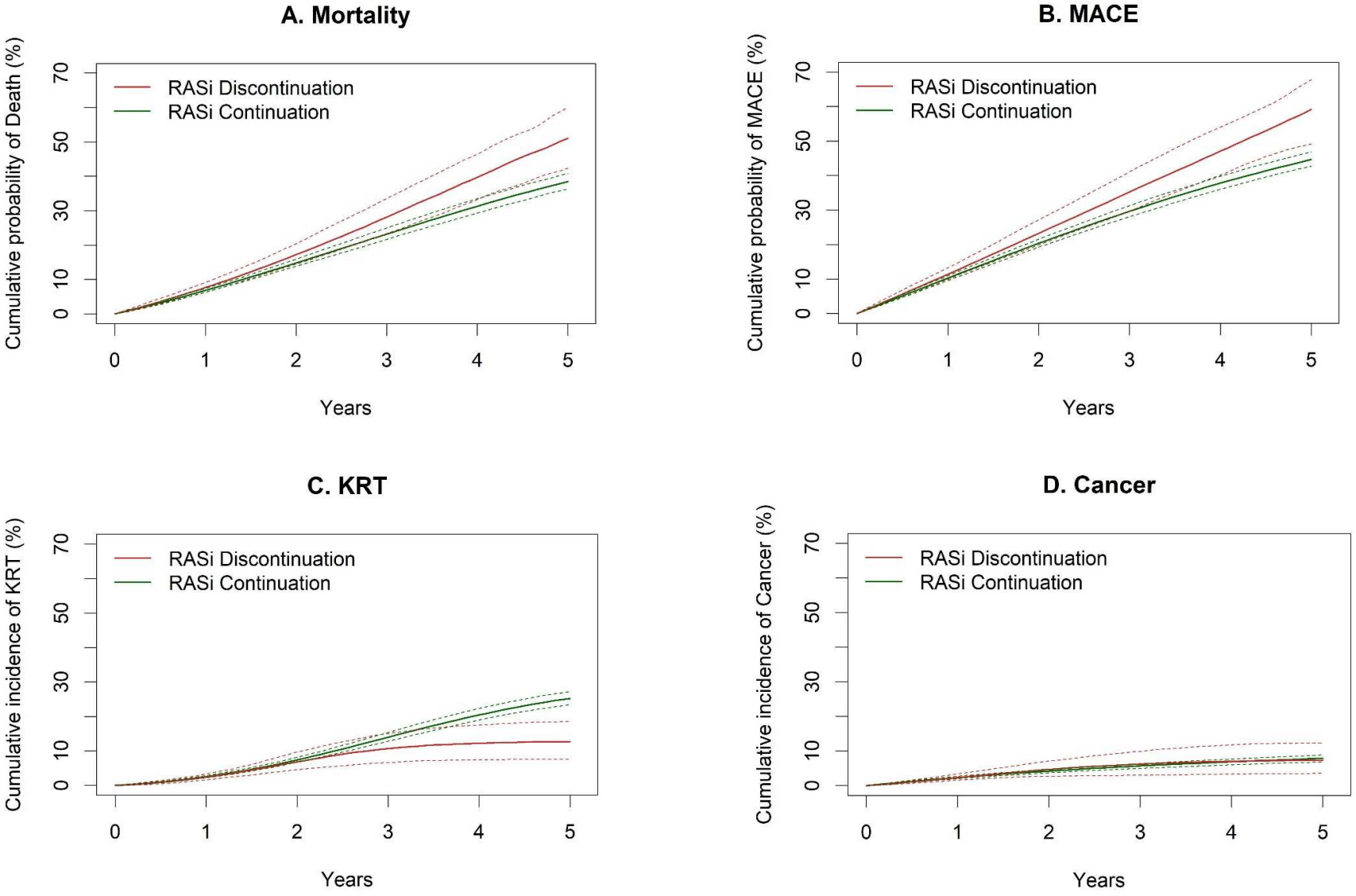
†Analyses were adjusted through inverse probability weighting for age, sex, calendar year, eGFR, systolic and diastolic blood pressure, comorbidities (ischemic heart disease, myocardial infarction, arrhythmia, heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, chronic pulmonary 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). 95% confidence intervals were calculated 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.

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

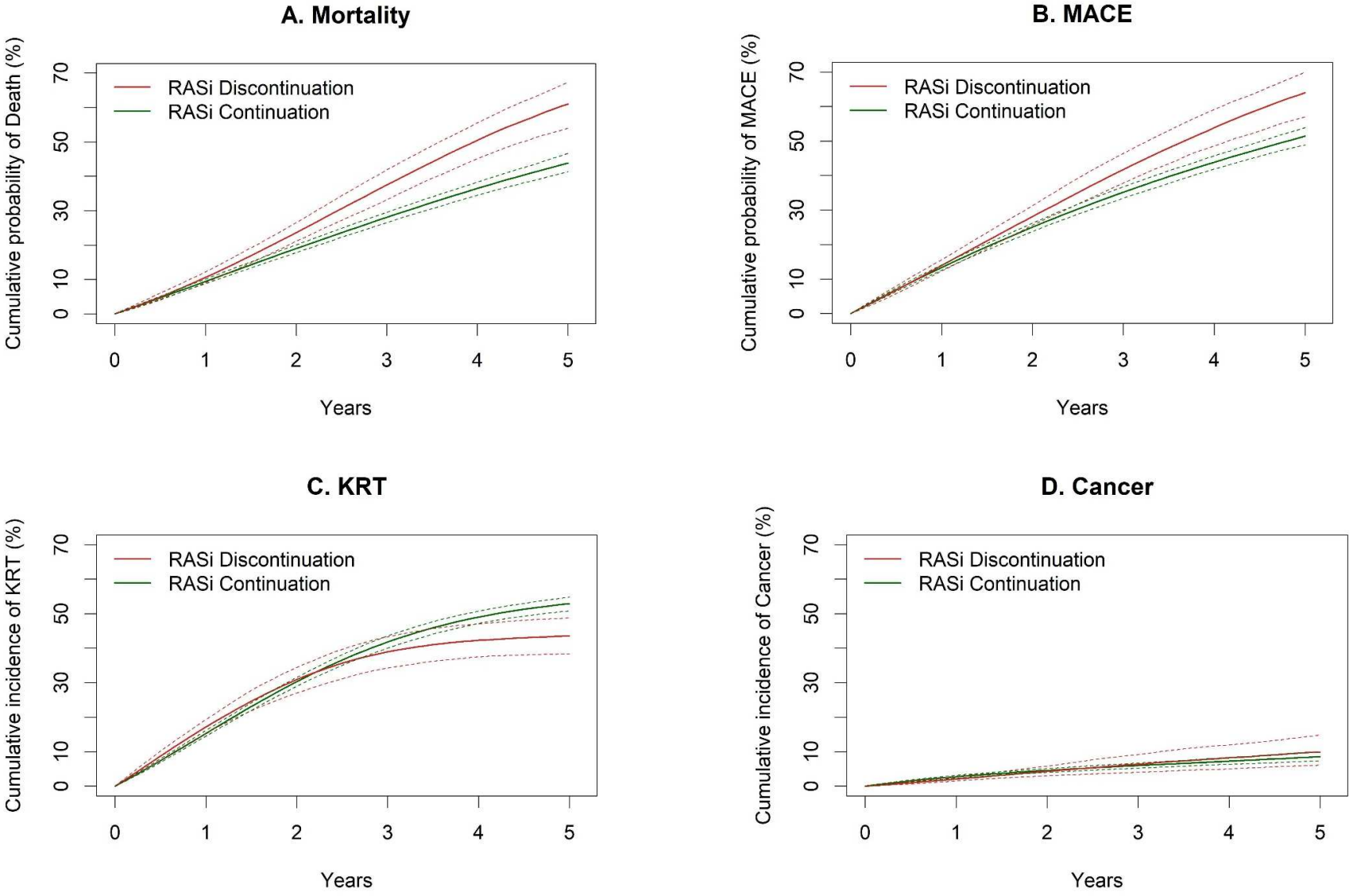


To emulate the target trial we used an analytical approach based on cloning, censoring and weighting. In the first step, each individual in the dataset is duplicated. Each replicate is then assigned to one of two treatment strategies: *discontinue within 6 months and remain off treatment* or *continue treatment during follow-up*. In the second step, we censored replicates if and when they deviated from their assigned strategy. I.e., replicates assigned to the stopping arm were censored if they had not discontinued treatment within 6 months after eGFR drop <30 ml/min/1.73m^2 or if they restarted treatment at any point during follow-up after they discontinued. Replicates assigned to the continuation arm were censored if they discontinued RASi treatment at any point during follow-up. However, such censoring is likely to be informative and will lead to selection bias. In the third step, we therefore used inverse probability weighting to adjust for the informative censoring. The weighting ensures that uncensored replicates who have similar characteristics as the censored replicates will be upweighted. This creates a pseudopopulation in which censoring no longer depends on these characteristics.

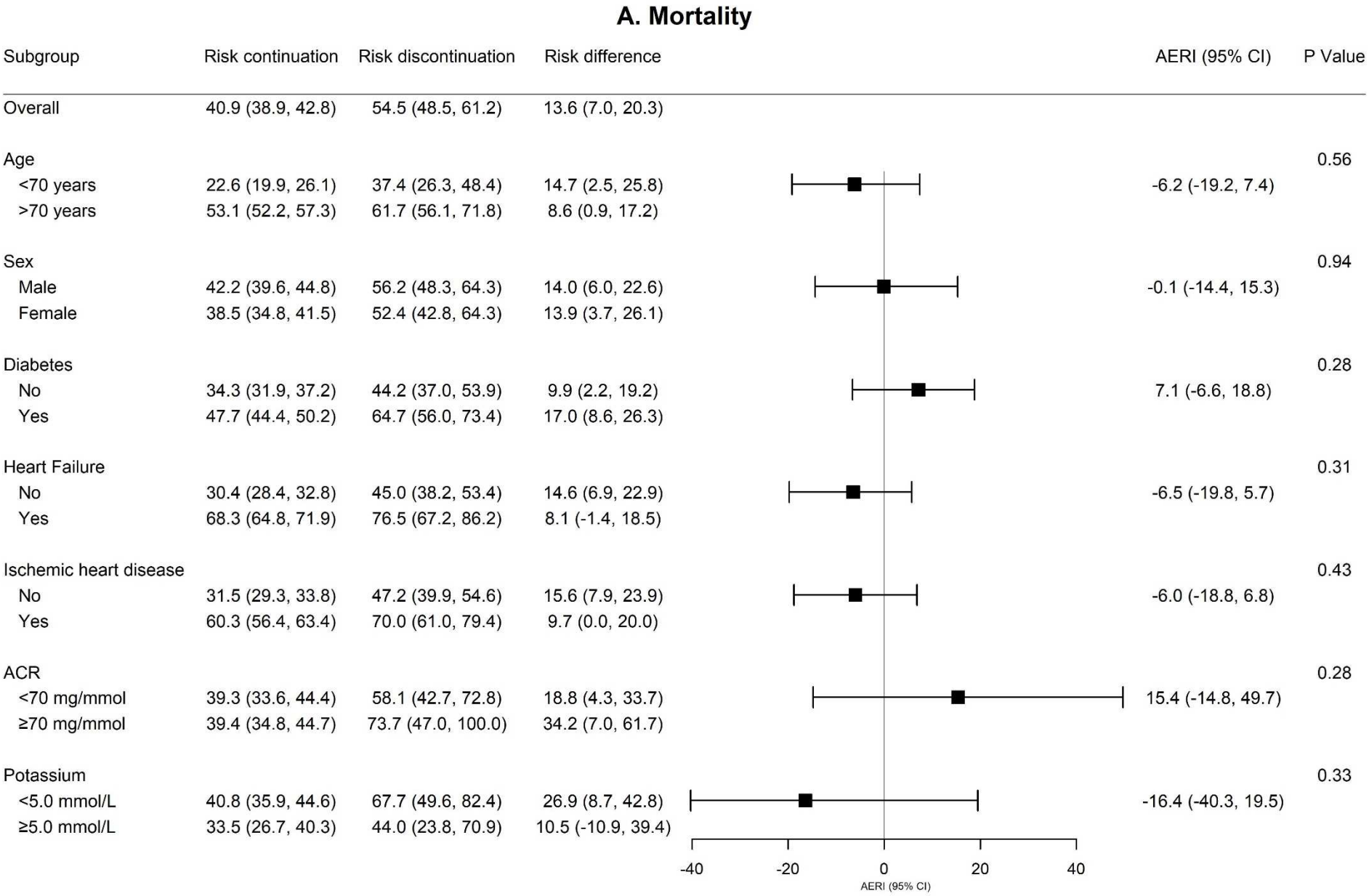
Supplemental Figure S2. Weighted cumulative incidence curves for mortality (A), MACE (B), KRT (C) and cancer (D) stratified by RASi use strategy in the cohort with first detected eGFR drop between 20-30 ml/min/1.73m^2. Thinner dotted lines represent 95% confidence intervals.



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.

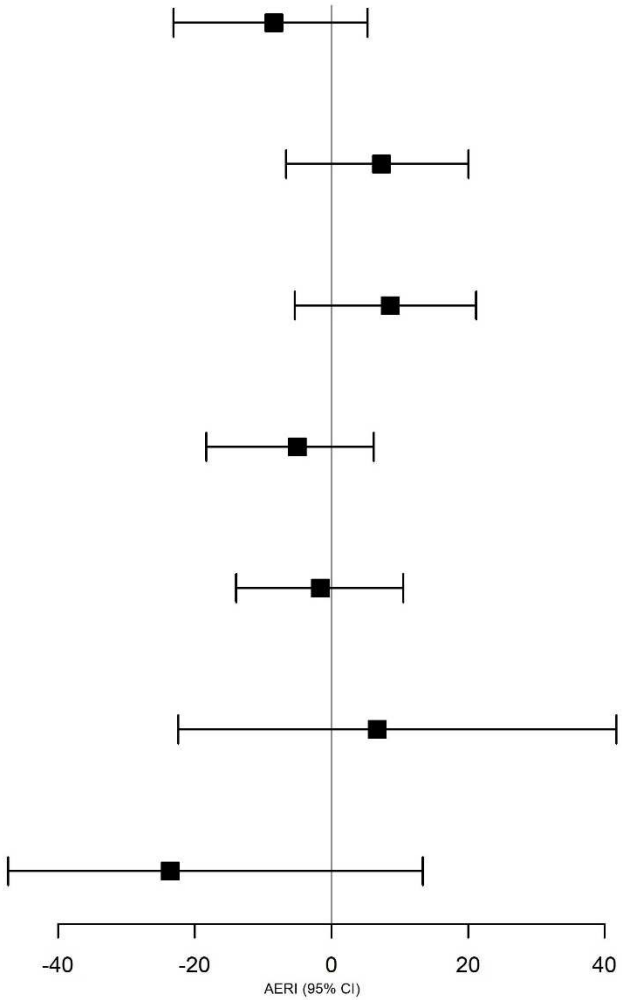


Supplemental Figure S4. Effect of stopping RASi on mortality (A), MACE (B) and KRT (C) across categories of age, sex, diabetes, heart failure, ischemic heart disease, ACR and potassium.



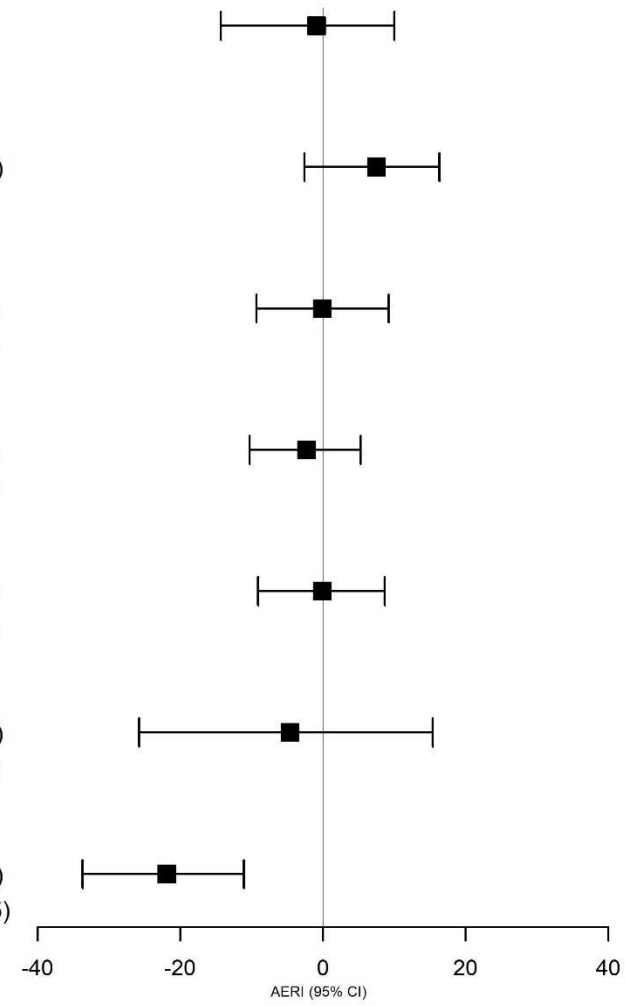
B. MACE

Subgroup	Risk continuation	Risk discontinuation	Risk difference	AERI (95% CI)	P Value
Overall	47.6 (45.9, 49.4)	59.5 (53.8, 66.1)	11.9 (5.7, 18.6)		
Age					0.22
<70 years	29.0 (26.6, 31.7)	44.1 (32.1, 55.0)	15.2 (3.3, 26.2)	-8.4 (-23.1, 5.3)	
>70 years	60.1 (59.4, 64.5)	66.9 (60.0, 75.4)	6.8 (-2.1, 13.4)		
Sex					0.31
Male	48.6 (46.5, 51.1)	58.3 (50.9, 66.6)	9.6 (1.8, 17.8)	7.3 (-6.6, 20.1)	
Female	45.9 (42.6, 49.0)	62.7 (52.8, 73.4)	16.9 (6.1, 27.7)		
Diabetes					0.16
No	40.7 (37.9, 43.5)	48.3 (39.5, 58.1)	7.6 (-1.0, 17.2)	8.6 (-5.3, 21.2)	
Yes	54.8 (52.1, 57.3)	71.1 (62.4, 80.0)	16.2 (7.3, 25.1)		
Heart Failure					0.45
No	37.7 (35.6, 40.0)	50.4 (43.4, 58.1)	12.7 (5.3, 20.5)	-5.0 (-18.3, 6.2)	
Yes	73.4 (70.1, 76.7)	81.0 (72.2, 90.0)	7.7 (-2.3, 16.7)		
Ischemic heart disease					0.83
No	37.5 (35.4, 39.6)	50.3 (42.3, 57.9)	12.8 (5.0, 20.2)	-1.6 (-13.9, 10.5)	
Yes	68.1 (65.0, 71.2)	79.3 (70.1, 87.6)	11.2 (1.5, 19.4)		
ACR					0.57
<70 mg/mmol	44.6 (40.2, 49.1)	63.0 (48.3, 77.0)	18.4 (3.0, 32.5)	6.7 (-22.4, 41.7)	
≥70 mg/mmol	48.5 (44.2, 54.2)	73.6 (48.5, 99.9)	25.1 (-1.2, 51.8)		
Potassium					0.17
<5.0 mmol/L	46.4 (42.8, 49.8)	70.8 (53.3, 85.5)	24.4 (6.2, 39.1)	-23.6 (-47.3, 13.4)	
≥5.0 mmol/L	44.0 (37.1, 51.4)	44.9 (24.5, 72.2)	0.8 (-19.8, 28.7)		



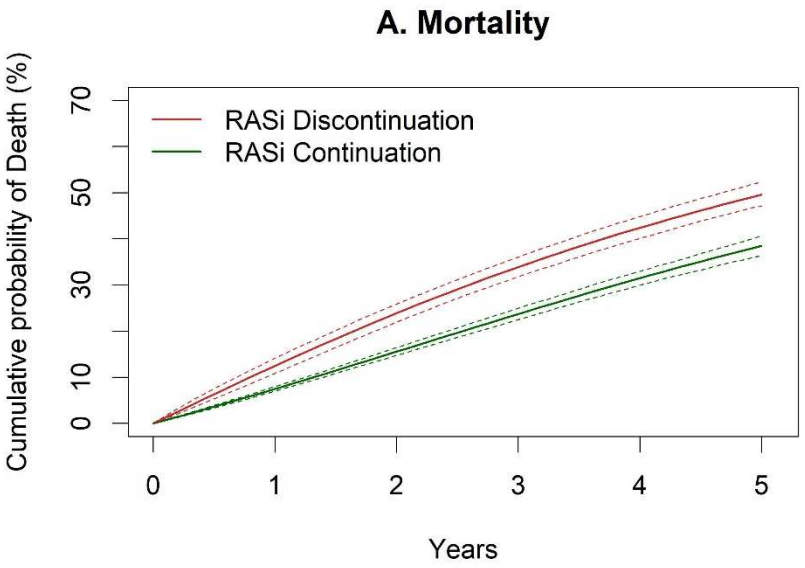
C. Kidney replacement therapy

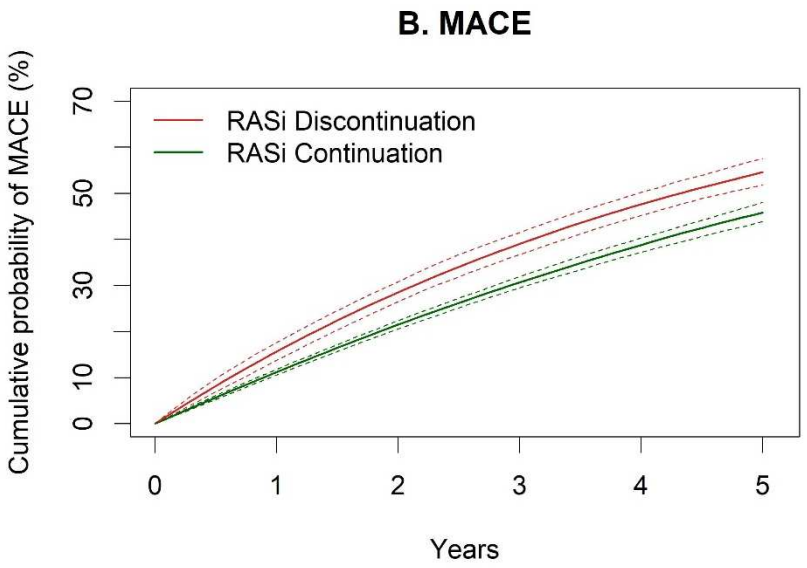
Subgroup	Risk continuation	Risk discontinuation	Risk difference	AERI (95% CI)	P Value
Overall	36.1 (34.7, 37.7)	27.9 (23.5, 32.5)	-8.3 (-12.8, -3.6)		
Age					0.69
<70 years	52.9 (50.3, 55.0)	49.4 (39.8, 61.6)	-3.5 (-12.7, 8.7)	-0.9 (-14.3, 10.0)	
>70 years	22.9 (21.1, 24.7)	18.5 (14.5, 23.6)	-4.4 (-8.6, 0.6)		
Sex					0.17
Male	38.7 (36.8, 40.5)	28.1 (22.9, 33.7)	-10.6 (-16.0, -4.7)	7.5 (-2.6, 16.3)	
Female	31.3 (28.9, 34.0)	28.2 (20.5, 35.2)	-3.1 (-10.8, 4.6)		
Diabetes					0.90
No	36.9 (34.6, 39.3)	29.0 (22.7, 36.1)	-7.9 (-14.3, -1.1)	-0.1 (-9.3, 9.2)	
Yes	35.9 (33.9, 38.0)	27.8 (21.7, 34.9)	-8.1 (-14.6, -0.8)		
Heart Failure					0.58
No	40.8 (39.1, 42.4)	33.4 (27.8, 39.7)	-7.4 (-12.7, -1.1)	-2.3 (-10.3, 5.3)	
Yes	24.0 (21.3, 26.7)	14.3 (10.0, 19.6)	-9.7 (-14.4, -3.5)		
Ischemic heart disease					0.91
No	40.4 (38.7, 42.1)	33.2 (27.7, 39.9)	-7.1 (-12.8, -0.4)	-0.1 (-9.1, 8.7)	
Yes	27.3 (24.7, 29.9)	20.0 (13.9, 25.9)	-7.3 (-13.7, -0.9)		
ACR					0.60
<70 mg/mmol	18.0 (14.9, 21.3)	7.6 (3.5, 13.2)	-10.3 (-15.9, -3.9)	-4.6 (-25.8, 15.4)	
≥70 mg/mmol	53.4 (49.0, 57.4)	38.4 (18.6, 56.2)	-14.9 (-34.3, 4.0)		
Potassium					<0.001
<5.0 mmol/L	29.1 (26.2, 31.8)	17.6 (9.8, 25.9)	-11.4 (-19.5, -2.6)	-21.9 (-33.7, -11.1)	
≥5.0 mmol/L	41.8 (35.4, 49.1)	8.5 (3.1, 14.6)	-33.3 (-41.9, -25.5)		

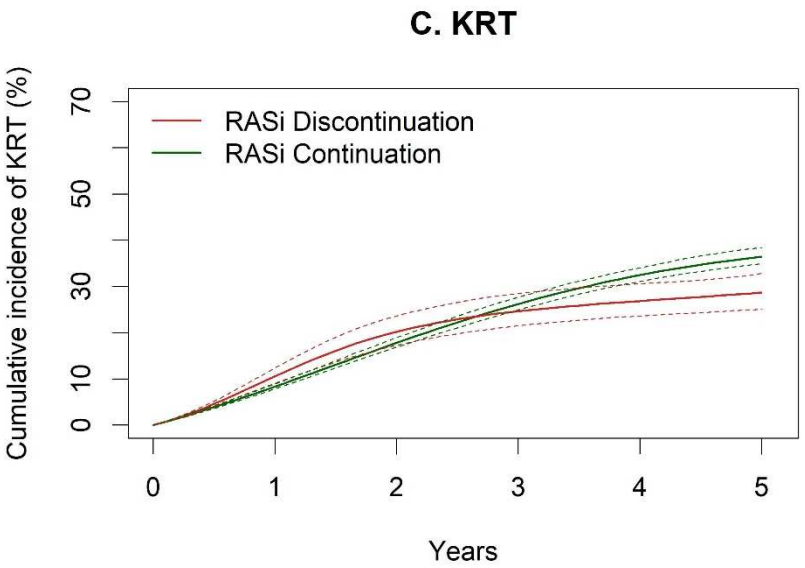


AERI = absolute excess risk due to interaction; CI = confidence interval. Subgroup analyses for ACR and potassium were performed on the subset of individuals with these measurements available.

Supplemental Figure S5. 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 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.