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

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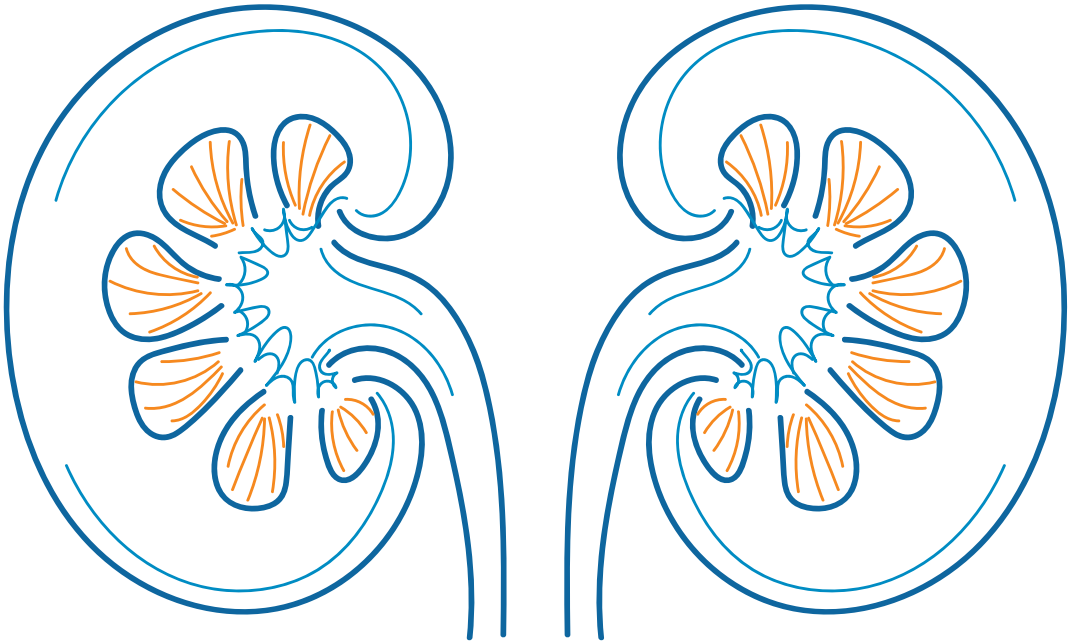

CHAPTER 6

Comparative effectiveness of renin-angiotensin system inhibitors and calcium channel blockers in individuals with advanced CKD: a nationwide observational cohort study

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Abstract

Rationale & Objective. It is unknown whether initiating a renin-angiotensin system inhibitor (RASi) in patients with advanced chronic kidney disease (CKD) is superior to alternative antihypertensive agents such as calcium channel blockers (CCB). We compared the risks of kidney replacement therapy (KRT), mortality and major adverse cardiovascular events (MACE) in patients with advanced CKD in routine nephrology practice who were initiating either RASi or CCB therapy.

Study Design. Observational study in the Swedish Renal Registry, 2007 to 2017.

Settings & Participants. 2458 new users of RASi and 2345 CCB users with estimated glomerular filtration rates (eGFR) <30 ml/min/1.73m^2 (CKD G4-5 without KRT) who were being followed up by a nephrologist. As a positive control cohort, new users of the same drugs in patients with CKD G3 (eGFR 30-60 ml/min/1.73m^2) were evaluated.

Exposures. RASi vs. CCB therapy initiation.

Outcome. Initiation of KRT (maintenance dialysis or transplantation), all-cause mortality and MACE (composite of cardiovascular death, myocardial infarction or stroke).

Analytical approach. Hazard ratios (HRs) with 95% CIs were estimated using propensity score-weighted Cox proportional hazards regression adjusting for demographic, clinical and laboratory covariates.

Results. Median age was 74 years, 38% were women and median follow-up was 4.1 years. After propensity score weighting, there was significantly lower risk of KRT after new use of RASi compared with new use of CCBs (adjusted HR 0.79; 95% CI 0.69-0.89), but similar risks of mortality (adjusted HR 0.97; 95% CI 0.88-1.07) and MACE (adjusted HR 1.00; 95% CI 0.88-1.15). Results were consistent across subgroups and in as-treated analyses. The positive control cohort of patients with CKD G3 showed similar KRT risk reduction (0.67; 0.56-0.80) with RASi therapy compared with CCBs.

Limitations. Potential confounding by indication.

Conclusions. Our findings provide evidence from routine care that initiation of RASi therapy compared with CCBs may confer kidney benefits among patients with advanced CKD, with similar cardiovascular protection.

Introduction

Randomized trials of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), collectively renin-angiotensin system inhibitors (RASi), have shown that these drugs are more effective in delaying the progression of CKD than placebo or alternative agents, such as diuretics, beta-blockers or calcium channel blockers (CCB) (1-6). Clinical guidelines recommend RASi as the first-line pharmacologic antihypertensive treatment strategy in patients with CKD G1-3 and proteinuria, with or without diabetes (7-9). There is, however, less evidence on the benefits of RASi in patients with CKD G4-5, a population that was under-represented in pivotal trials (3, 10-15). A small randomized trial (16) and various observational studies (17-20) suggest that RASi confer reno-protection compared with placebo or no use, but no data exist to inform the choice of RASi over alternative antihypertensive agents. This, together with concerns about the persistent hemodynamic effects of RASi (21, 22), may lead to underutilization of these medications in advanced CKD (23, 24). Indeed, recent studies indicate that a significant proportion of individuals with CKD G3-5 do not receive RASi therapy (23-25). A recent NKF-KDOQI controversies report (14) identified the lack of comparative effectiveness data as a critical knowledge gap, and emphasized the need of further studies to inform practice.

CCBs are also frequently prescribed to treat hypertension, especially to patients with CKD (26-28). Although CCBs were used as an active comparator to RASi in trials such as AASK or IDNT (4, 11), these trials included very few patients with advanced CKD to allow for stratification. In the absence of trial evidence, observational studies in patients cared for in routine clinical practice can provide insights into the relative efficacy of medications. To fill this knowledge gap we studied kidney and cardiovascular outcomes in patients with advanced CKD who initiated RASi or CCB therapy.

Methods

Data sources

We conducted an observational cohort study using data from the Swedish Renal Registry (SRR), a nationwide registry including patients with CKD G3–5 under nephrologist care (29, 30). The SRR includes information on outpatient visits, including laboratory tests and results from clinical examination. According to the guidelines of the registry, patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 should be enrolled. Registrations of subsequent outpatient visits to nephrology care are thereafter performed until death, emigration from the country or start of kidney replacement therapy (KRT). Nearly all nephrology clinics in Sweden (96%) report to the SRR-CKD and the estimated national coverage is 75-90% of nephrologist-referred patients with recognized CKD G4-5 (31).

Using each citizen's unique personal identification number, the SRR-CKD was linked to other national registries. The Swedish Prescribed Drug Register provided complete information on all prescribed drugs dispensed at Swedish pharmacies (32); the Swedish Patient Register added information on all outpatient specialist consultations and hospitalizations occurring in Swedish healthcare, and was used to obtain information on comorbidities and outcomes (33); the Swedish Cause of Death Register added information on date and causes of death (34). All these registers are run by the Swedish National Board of Welfare and are considered to have no or minimal loss to follow up. We used de-identified data, the study was approved by the regional ethical review boards and the Swedish National Board of Welfare, and was judged not to require informed consent.

Patient selection and study design

We created a cohort of all adult patients in the SRR-CKD (≥ 18 years) newly initiating a RASi or CCB between 1 January 2007 and 1 June 2017. New users were defined as individuals receiving a RASi or CCB without dispensation of either drug in the previous six months. Prevalent users of these drugs were excluded to prevent prevalent user bias (35). We further excluded all individuals with a history of kidney transplantation, an eGFR > 30 ml/min/1.73m^2, or those initiating both drugs simultaneously.

The date of initiation was defined as the index date of the study and start of follow-up. Patients were followed from index date to the first occurrence of a study outcome or end of follow-up (1 June 2017). eGFR was calculated with the CKD-EPI equation from routine plasma creatinine measurements performed by enzymatic or corrected Jaffe methods traceable to isotope dilution mass spectroscopy standards. Information on race is not available in Sweden by law; we assumed that all patients were Caucasian.

Study exposure and covariates

The exposure of interest was RASi initiation compared with initiation of a CCB. Baseline covariates included age, sex, eGFR, comorbidities (diabetes mellitus, myocardial infarction, heart failure, arrhythmia, peripheral vascular disease, cerebrovascular disease, ischemic heart disease), medications (β-blocker, thiazide diuretic, loop diuretic, potassium-sparing diuretic, potassium binder, non-steroidal anti-inflammatory drug, statin), systolic blood pressure, diastolic blood pressure, urinary albumin-to-creatinine ratio (ACR), potassium. In addition, we considered other covariates in an attempt to evaluate reasons that led to the use of either medication: the rate of kidney function decline prior to therapy initiation, the occurrence of a cardiovascular-related hospitalization in the preceding six months, the number of overall hospitalizations in the year prior and a history of hyperkalemia or AKI. Covariate definitions are detailed in **Supplemental Table S1**.

Study outcomes

The primary study outcome was initiation of KRT, defined as the date of start of maintenance dialysis or kidney transplantation, as registered in the SRR. Secondary outcomes were all-cause mortality and major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death (ICD-10 code of the I family as main cause of death), hospitalization due to stroke (I63) or myocardial infarction (I21-I23). For the analysis of mortality and MACE, KRT was not considered a censoring event. In addition, we reported information about hospitalizations for hyperkalemia and acute kidney injury (AKI) after medication initiation.

Statistical analysis

We used doubly robust methods, i.e., combining outcome regression with inverse probability of treatment weighting (IPTW), to control for confounding (36). A multivariable logistic regression model was used to calculate the probability of receiving RASi (versus CCB) as a function of baseline covariates. Weighting was considered appropriate if the standardized mean difference (SMD) between treatment groups was <0.1. Weights were stabilized to increase precision by adding the marginal probability of treatment to the numerator of the weights. Robust variance estimation was used to calculate confidence intervals after weighting. We assessed the association between RASi use compared with CCB use on outcomes using multivariable cause-specific Cox proportional hazards regression in the inverse probability weighted sample, additionally adjusting for all baseline covariates. In addition, we estimated adjusted cumulative incidence curves standardized to the distribution of the baseline variables in the study population. To do so, we fitted a weighted pooled logistic model including an indicator for treatment, month and its quadratic term, all baseline confounders, and interactions between treatment and time (37). Interaction terms were included to allow for nonproportional hazards (38). The predicted probabilities from this logistic model were used to estimate the adjusted absolute risks of KRT, mortality and MACE which were then standardized to the baseline distribution of confounders. For the calculation of the cumulative incidence of KRT and MACE, we took into account the competing risk of (non-cardiovascular) death (39-41). Pointwise 95% confidence intervals for the cumulative incidence curves were calculated using nonparametric bootstrap based on 500 full samples. In primary analyses, we adopted an intention-to-treat (ITT) approach and analyzed patients according to their initially assigned treatment group irrespective of discontinuation or treatment switch. Next, we examined whether there was an interaction between treatment effect and the following variables, according to a priori defined strata: age (≥70 vs <70 years), sex, diabetes, myocardial infarction, heart failure, systolic blood pressure (≥140 vs <140 mmHg), eGFR (≥15 vs <15 mL/min/1.73m^2) and ACR (≥70 vs <70 mg/mmol). To calculate the subgroup hazard

ratios, we separately estimated the propensity score model and Cox model in each subgroup (42). Multiplicative interaction was tested by including interaction terms between treatment and the variable of interest to the Cox model.

Multiple imputation by chained equations was used to impute missing data on systolic and diastolic blood pressure (missing for 2.3% of patients). Treatment, confounding variables, outcomes and interaction terms between treatment and confounders were used in the imputation model to derive 50 imputed datasets (43). eGFR was non-normally distributed and was log-transformed before imputation. Multiple imputation was combined with IPTW using the *within* method (44). In the within method, effect estimates are obtained separately in each imputation using the propensity score, which are then combined to an overall estimate. The within method has been shown to produce unbiased estimates with appropriate confidence intervals compared with the *across* approach (44).

We performed several sensitivity analyses to test the robustness of our results. First, we additionally adjusted our analyses for plasma potassium and ACR. These variables were missing for a large proportion of patients (32% and 41%, respectively) because it was not mandatory to report these measures. Those with missing ACR measurements had similar characteristics as those without missing ACR measurements and we assumed data to be missing at random (**Supplemental Table S2**). We used multiple imputation with chained equations, a technique well suited to impute data that are missing at random. Second, we redefined new users as those not using RASi and CCB for at least 12 months. Third, we replicated our analyses in a positive control cohort of patients with CKD G3, for which we expected a reduction in kidney replacement therapy consistent with previously conducted randomized trials (3, 45-47). Fourth, we performed an as-treated analysis in which patients were censored at the time of therapy discontinuation (no dispensation for the index drug within 60 days after the estimated last day of pill supply from the previous drug dispensation), treatment switch (on the day RASi was added to CCB or vice versa) or at the end of the study period. To account for potential informative censoring due to discontinuation or treatment switch, inverse probability of censoring weighting (IPCW) was applied (see **Supplemental methods** for details). Fifth, we used incident cancer diagnosis as a negative control outcome to study the influence of potential unmeasured confounders (such as smoking and alcohol use) on our effect estimates. While unmeasured confounders may predict the risk of cancer, we did not expect initiation of RASi or CCB to cause or prevent cancer (48). For this analysis, we excluded patients with a recent cancer diagnosis (within two years from index date). Lastly, we repeated our analysis adding heart failure related hospitalization (I50) as an outcome in the composite of MACE. All analyses were performed using R version 3.6.2.

Results

Cohort characteristics

We identified 21,065 patients under nephrologist care with eGFR <30 ml/min/1.73m^2 and no history of KRT. Of these, 13 896 (66%) were prevalent users of RASi or CCB and were excluded. We further excluded 1913 patients who received neither of these drugs during observation and 453 patients who were prescribed both medications simultaneously. The final study cohort consisted of 4803 patients: 2458 (51%) who initiated RASi and 2345 (49%) who initiated CCB (**Supplemental Figure S1**). Of patients initiating RASi, the majority initiated enalapril (37.2%), candesartan (23.4%), losartan (21.4%) or ramipril (9.6%). In total, 249 of 2458 (10.1%) individuals initiating RASi had a cardiovascular hospitalization in the 6 months prior to initiation, of which 129 (5.2%) due to heart failure and 37 (1.5%) due to myocardial infarction. Five people initiated dual RAS blockade with an ACEi and ARB. The majority of patients initiating a CCB used a dihydropyridine CCB (97.7%), mainly amlodipine (55.4% of total CCB initiators) or felodipine (36.9%). In total, 231 of 2345 (9.9%) individuals initiating CCB had a cardiovascular hospitalization in the 6 months prior to initiation, of which 49 (2.1%) due to heart failure and 32 (1.4%) due to myocardial infarction.

Overall, study participants had a median (IQR) age of 74 (64-81) years and 38% were women. Median eGFR was 20 (15-21) ml/min/1.73m^2, median ACR 28 (7-108) mg/mmol, median systolic blood pressure 140 (125-153) mmHg and median diastolic blood pressure 80 (70-85) mmHg. The most common comorbidities were diabetes (34%), ischemic heart disease (26%) and heart failure (19%). Concurrent use of β-blockers (63%), loop diuretics (63%) and statins (50%) was prevalent. At baseline, patients who initiated RASi, compared with those initiating CCB, had a higher eGFR, a lower systolic blood pressure and ACR, and a higher prevalence of comorbidities such as diabetes, heart failure and arrhythmia. After weighting, all baseline covariates appeared well balanced between treatment groups (standardized differences <0.1) (**Table 1**).

Table 1. Baseline characteristics of patients with advanced CKD by RASi or CCB treatment, before and after inverse probability weighting.

	Unweighted			Weighted*		
	RASi (N = 2458)	**CCB (N = 2345)**	**Std Diff‡**	**RASi (N = 2473)**	**CCB (N = 2330)**	**Std Diff‡**
Median age (IQR)‡, *years*	73 [62, 80]	74 [66, 81]	0.22	74 [64, 80]	73 [64, 80]	0.00
Age category, *n (%)*						
<50	303 (12.3)	159 (6.8)	0.19	238 (9.6)	210 (9.0)	0.02
50-59	226 (9.2)	189 (8.1)	0.04	195 (7.9)	217 (9.3)	0.05
60-69	461 (18.8)	443 (18.9)	0.00	477 (19.3)	454 (19.5)	0.01
70-79	826 (33.6)	805 (34.3)	0.01	871 (35.2)	800 (34.4)	0.02
>=80	642 (26.1)	749 (31.9)	0.13	692 (28.0)	649 (27.8)	0.00
Women	909 (37.0)	906 (38.6)	0.03	950 (38.4)	898 (38.5)	0.00
Median eGFR (IQR)‡, *ml/min/1.73m²*	22 [17, 26]	18 [13, 24]	0.41	20 [15, 25]	20 [15, 25]	0.00
eGFR category, *n (%)*						
<15 ml/min/1.73m², *n (%)*	399 (16.2)	727 (31.0)	0.35	657 (25.4)	678 (27.0)	0.04
15-30 ml/min/1.73m², *n (%)*	2059 (83.8)	1614 (68.8)	0.36	1816 (74.6)	1652 (73.0)	0.04
Median SBP (IQR)‡, *mmHg*	133 [120, 146]	144 [130, 160]	0.51	140 [125, 155]	140 (125, 154)	0.00
SBP category, *n (%)*						
<120	486 (19.8)	161 (6.9)	0.39	333 (13.5)	304 (13.0)	0.02
120-139	934 (38.0)	689 (29.4)	0.18	842 (34.1)	801 (34.4)	0.01
140-159	661 (26.9)	804 (34.3)	0.16	774 (31.3)	740 (31.8)	0.01
>160	323 (13.1)	633 (27.0)	0.35	524 (21.2)	485 (20.8)	0.01
Missing	54 (2.2)	58 (2.5)	0.02	-	-	-
Median DBP (IQR)‡, *mmHg*	78 [70, 84]	80 [70, 89]	0.28	80 [70, 85]	80 [70, 85]	0.00
DBP category, *n (%)*						
<80	1264 (51.4)	942 (40.2)	0.23	1156 (46.7)	1077 (46.2)	0.01
80-89	776 (31.6)	783 (33.4)	0.04	847 (34.3)	772 (33.1)	0.03
90-99	260 (10.6)	380 (16.2)	0.16	323 (13.1)	330 (14.2)	0.03
>100	104 (4.2)	182 (7.8)	0.15	147 (6.0)	151 (6.5)	0.02
Missing	54 (2.2)	58 (2.5)	0.02	-	-	-
Median ACR (IQR)‡, *mg/mmol*	24 [5, 95]	33 [9, 116]	0.12	29 [7, 111]	29 [7, 113]	0.00
ACR category, *n (%)*						
A1 (<3)	276 (11.2)	150 (6.4)	0.17	373 (15.1)	342 (14.7)	0.01
A2 (3-29)	542 (22.1)	483 (20.6)	0.04	880 (35.6)	829 (35.6)	0.00
A3 (30-69)	240 (9.8)	204 (8.7)	0.04	400 (16.2)	383 (16.4)	0.01

	Unweighted			Weighted*		
	RASi (N = 2458)	CCB (N = 2345)	Std Diff‡	RASi (N = 2473)	CCB (N = 2330)	Std Diff‡
A3 (≥70)	461 (18.8)	472 (20.1)	0.03	820 (33.2)	776 (33.3)	0.00
Missing	939 (38.2)	1036 (44.2)	0.12	-	-	-
Median potassium (IQR)‡, *mmol/L**	4.4 [4.1, 4.8]	4.3 [4.0, 4.7]	0.15	4.4 [4.0, 4.7]	4.4 [4.0, 4.7]	0.00
Comorbidities, *n (%)*						
Diabetes mellitus	916 (37.3)	734 (31.3)	0.13	851 (34.4)	833 (35.8)	0.03
Myocardial infarction	423 (17.2)	353 (15.1)	0.06	398 (16.1)	361 (15.5)	0.02
Heart failure	580 (23.6)	320 (13.6)	0.26	457 (18.5)	420 (18.0)	0.01
Arrhythmia	469 (19.1)	316 (13.5)	0.15	416 (16.8)	395 (17.0)	0.00
Peripheral vascular disease	313 (12.7)	312 (13.3)	0.02	330 (13.3)	313 (13.5)	0.00
Cerebrovascular disease	294 (12.0)	327 (13.9)	0.06	321 (13.0)	311 (13.3)	0.01
Ischemic heart disease	691 (28.1)	574 (24.5)	0.08	657 (26.6)	617 (26.5)	0.00
Medication, *n (%)*						
β-blockers	1443 (58.7)	1586 (67.6)	0.19	1563 (63.2)	1486 (63.8)	0.01
Thiazides	79 (3.2)	66 (2.8)	0.02	71 (2.9)	70 (3.0)	0.01
Loop diuretics	1613 (65.6)	1395 (59.5)	0.13	1551 (62.7)	1463 (62.8)	0.00
Potassium-sparing diuretics	167 (6.8)	114 (4.9)	0.08	136 (5.5)	121 (5.2)	0.01
Potassium binders	242 (9.8)	240 (10.2)	0.01	254 (10.2)	216 (9.3)	0.03
NSAIDs	103 (4.2)	90 (3.8)	0.02	101 (4.1)	92 (4.0)	0.01
Statins	1270 (51.7)	1121 (47.8)	0.08	1232 (49.8)	1167 (50.1)	0.01
Hospitalizations, *n (%)*						
Any hospitalization in previous year	1084 (44.1)	1254 (53.5)	0.19	1210 (48.9)	1138 (48.8)	0.00
Cardiovascular hospitalization in previous 6 months	249 (10.1)	231 (9.9)	0.01	251 (10.1)	229 (9.8)	0.01
Hyperkalemia hospitalization	35 (1.4)	39 (1.7)	0.02	38 (1.5)	37 (1.6)	0.00
AKI hospitalization	125 (5.1)	213 (9.1)	0.16	187 (7.6)	169 (7.2)	0.01
Previous eGFR decline, *ml/min/1.73m² (SE)* §	-2.03 (0.08)	-1.98 (0.08)	0.02	-	-	-

* Inverse probability weighting was performed after imputation. Baseline characteristics are shown after imputation and weighting (marked with *).

‡ A standardized difference >0.1 indicates meaningful imbalance between groups.

‡ Standardized difference for the mean was calculated for age, eGFR, blood pressure, ACR and potassium.

§ Calculated in the overall population on all previous eGFR measurements with a linear mixed model containing fixed effects for time, treatment and time/treatment interaction and random intercept and slope.

Comparative effectiveness of RASi vs. CCB initiation

Median follow-up was 4.1 (95% CI 3.9-4.2) years, maximum follow-up was 10.4 years, and the total follow-up time of the cohort was 14 682 person years. During follow-up 1416 individuals initiated KRT. The absolute 5-year risk of KRT was 39.0% among CCB users and 34.8% among RASi users, with a 5-year absolute risk difference of -4.3% (-8.0 to -0.6). The KRT risk was consistently lower in RASi users compared with CCB users during the entire follow-up period. For instance, risk differences were -3.3% (-4.9 to -1.6) at 1 year and -4.4% (-7.4 to -1.6) at 3 years (**Figure 1** and **Supplemental Table S3**). For patients initiating RASi, compared with those initiating CCB, we observed a weighted hazard ratio of 0.79 (0.69-0.89), in favor of RASi initiation (**Table 2**).

Table 2. Number of events, incidence rates as well as crude and adjusted hazard ratios for the association between RASi vs. CCB initiation and all-cause mortality, MACE and kidney replacement therapy.

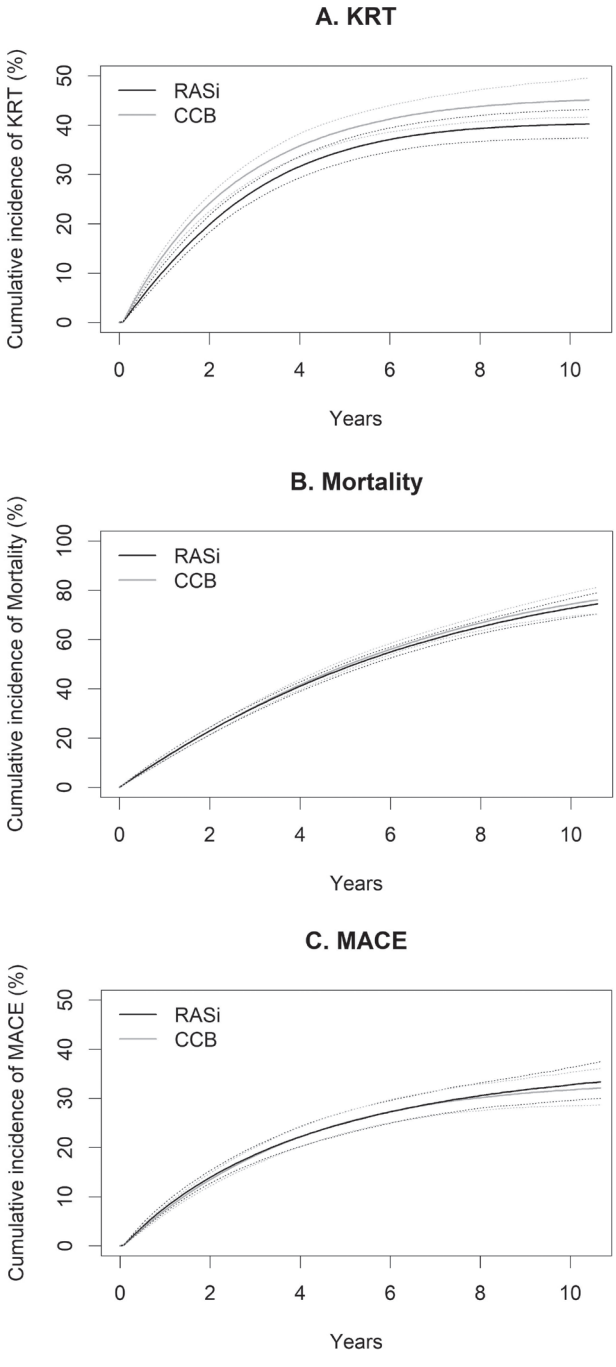
	Number of events*	Person years*	IR per 100PY (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)ǂ
KRT					
Overall	1416	11044	12.8 (12.2-13.5)		
CCB	753	4872	15.5 (14.4-16.6)	1 (reference)	1
RASi	663	6172	10.7 (9.9-11.6)	0.70 (0.63- 0.78)	0.79 (0.69-0.89)
All-cause mortality					
Overall	1974	14682	13.4 (12.9-14.1)		
CCB	991	6769	14.6 (13.7-15.6)	1	1
RASi	983	7912	12.4 (11.7-13.2)	0.85 (0.78- 0.93)	0.97 (0.88-1.07)
MACE					
Overall	1043	13814	7.6 (7.1-8.0)		
CCB	510	6311	8.1 (7.4-8.8)	1	1
RASi	533	7503	7.1 (6.5-7.7)	0.90 (0.80- 1.02)	1.00 (0.88-1.15)

IR = incidence rate; PY = person years; HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular events; RASi = renin-angiotensin system inhibitor; CCB = calcium channel blocker; KRT = kidney replacement therapy.

* Number of events, person years and incidence rates were calculated in the unweighted population.

ǂ Analyses were adjusted for age, sex, eGFR, heart failure, arrhythmia, peripheral vascular disease, cerebrovascular disease, ischemic heart disease, diabetes mellitus, systolic blood pressure, diastolic blood pressure, use of β-blocker, thiazide diuretic, potassium-sparing diuretic and statin, total number of hospitalizations in previous year, hospitalization in previous year (yes/no), history of hyperkalemia hospitalization and history of AKI hospitalization using inverse probability of treatment weighting.

Figure 1. Weighted standardized survival curves for KRT (panel A), mortality (panel B) and major adverse cardiovascular events (MACE, panel C) stratified by RASi or CCB use.

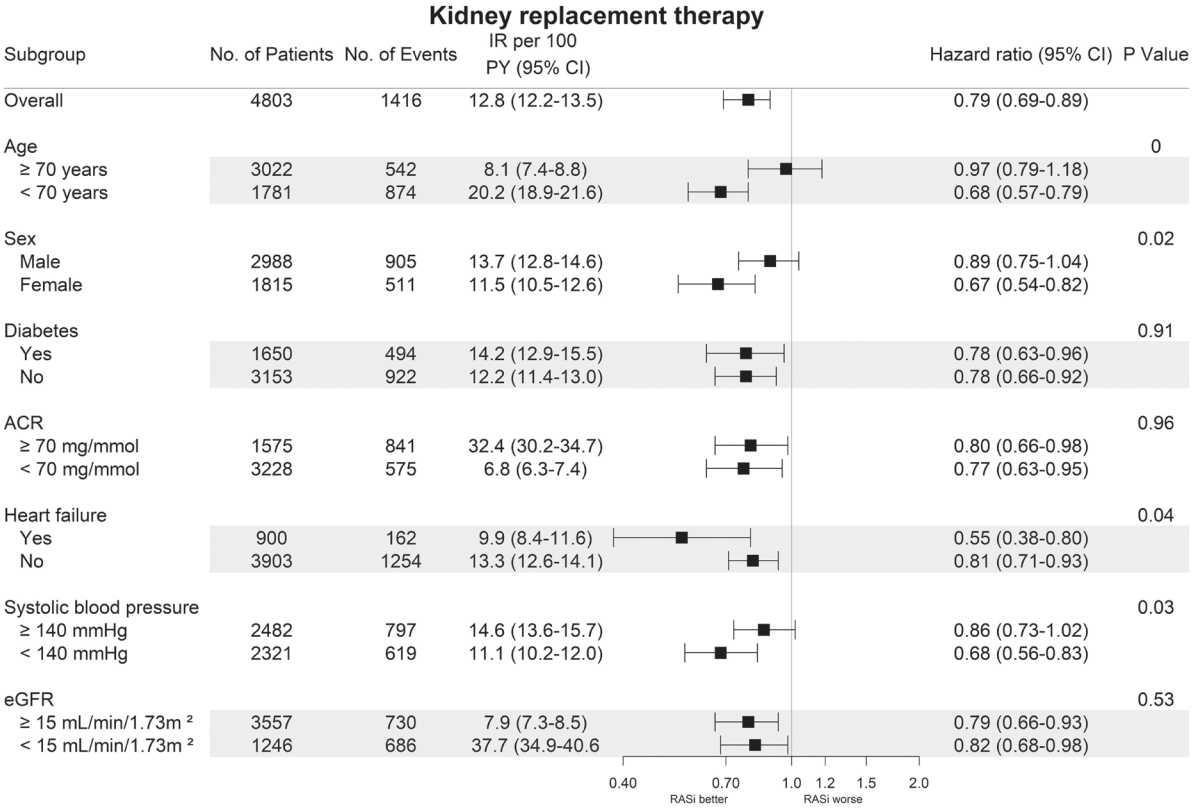


In total, 1974 individuals died, with an absolute 5-year mortality risk of 49.5% among CCB users and 48.3% among RASi users. The absolute risk difference at 5 years was -1.2% (-4.1 to 1.7), with a weighted mortality hazard ratio of 0.97 (95% CI 0.88-1.07). During follow-up, 1043 individuals experienced a MACE, with a weighted hazard ratio of 1.00 (0.88-1.15). The absolute 5-year risk of MACE was 25.1% among CCB users and 25.0% among RASi users, with a 5-year risk difference of -0.1% (-3.4 to 3.0). Among individuals initiating RASi, 18 (0.7%) experienced a hospitalization for hyperkalemia and 83 (3.4%) a hospitalization for AKI. Among those initiating CCB, 18 (0.8%) experienced a hospitalization for hyperkalemia and 72 (3.1%) individuals experienced a hospitalization for AKI.

Subgroup and sensitivity analyses

Results were robust in most subgroup analyses (**Figure 2**, **Supplemental Figures S2-S3**, **Supplemental Table S4**). A lower risk of KRT for RASi users compared with CCB was observed across strata of sex, diabetes, ACR, eGFR, heart failure and systolic blood pressure, but a significant interaction was observed for age, with benefit for initiating RASi in younger but not older patients ($p < 0.01$). An increased risk of mortality and MACE (interaction $p < 0.01$) was observed for patients with baseline heart failure and CKD G4-5 initiating RASi, compared with CCB, as well as a significant interaction for MACE according to sex ($p < 0.01$). Other than this, risks of mortality and MACE did not differ by prespecified subgroups (all interaction $p > 0.12$).

Figure 2. Number of events, incidence rates and adjusted hazard ratios for kidney replacement therapy following RASi vs. CCB initiation, according to subgroups of age, sex, diabetes, ACR, heart failure, systolic blood pressure and eGFR.



The positive control cohort included 2608 nephrologist-referred patients with CKD G3 of whom 1663 started RASi and 945 started CCB (baseline characteristics in **Supplemental Table S5**). After IPTW, the adjusted hazard ratio for RASi compared with CCB was 0.68 (0.48-0.98) for KRT, 0.97 (0.81-1.17) for mortality and 1.09 (0.85-1.40) for MACE (**Supplemental Table S6**).

In the as-treated analysis, a hazard ratio of 0.67 (0.56-0.80) was observed for KRT for RASi initiation compared with CCB initiation. The adjusted hazard ratios for mortality and MACE were 1.05 (0.87-1.26) and 1.03 (0.83-1.26), respectively (**Supplemental Table S7**). Additional adjustment for ACR and potassium or redefining new users as no recorded dispensation of either RASi or CCB for at least 12 months, produced hazard ratios consistent with the results of our main analysis (**Supplemental Table S7**). Individuals who initiated RASi had similar risks of cancer compared with CCB initiators, with a weighted HR of 1.03 (0.87-1.22). Adding heart failure-related hospitalization to the MACE outcome did not alter our results (adjusted HR 1.00; 95% CI 0.89-1.13) (**Supplemental Table S8**).

Discussion

Current clinical guidelines recommend the use of ACEi or ARBs as first-line therapy in patients with CKD and proteinuria, with or without diabetes (7-9, 49), but provide no guidance regarding eGFR thresholds for which these recommendations are valid (14, 15). In our study of a large, nationwide cohort of nephrologist-referred patients with advanced CKD, initiation of RASi compared with CCB was associated with a reduced risk of KRT, but similar risk of mortality and MACE. These findings were robust across subgroups of patients and following an as-treated design.

Our study does not evaluate the health benefits of RASi versus no use in patients with CKD G4 and 5. This has been investigated previously (17, 18, 24), including the randomized trial by Hou *et al.* (16) or the post-hoc analysis of the REIN (Ramipril Efficacy in Nephropathy) trial (10). Our goal was to inform on the choice of antihypertensive agents in the advanced CKD population by comparing outcomes associated with initiating RASi or CCB as the two most commonly used antihypertensive agents in clinical practice (28). A considerable proportion of patients reach CKD stage 4-5 without these medications. In our register this equaled to 34% of the population, a figure which agrees with other contemporary reports: in the CRIC cohort, ~30% of patients CKD G4 and about 73% of patients CKD G5 did not receive RASi, and similar proportions of non-use were reported for CCB in CKD G4 (50% not using CCB) and G5 (40% not using CCB) (24). Recent data from CKDOPPS indicates that this pattern is followed globally: for instance, only 52% of DOPPS patients in the United States and 66% in Brazil were receiving RASi (25).

We observed that RASi may be superior to CCB in delaying KRT in advanced CKD. This is consistent with a recent network meta-analysis of patients with CKD G3 showed that ACEi reduced the odds of KRT by 35% (OR 0.65; 95% credibility interval 0.51-0.80), and ARBs reduced the odds of kidney failure by 25% (0.75; 0.54-0.97), compared with other antihypertensive drugs, which included CCBs, diuretics and beta-blockers (13). Our positive control cohort of individuals with CKD G3 showed a reduction in KRT risk (HR 0.68; 95% CI 0.48-0.98) of magnitude similar to that meta-analysis, which lends reassurance to our observations. We note that 98% of our patients used dihydropyridine CCB, and the comparative effectiveness and safety of non-dihydropyridine CCB cannot be informed by our study.

We observed no differences in the risk of MACE between both therapies in persons with advanced CKD, a finding we believe is novel (7, 14) and in a magnitude similar to our control population of patients with CKD G3. Again this agrees and expands two large meta-analyses of randomized trials comparing antihypertensive agents in patients with CKD G3 (13, 50). Compared with placebo, blood-pressure-lowering regimens significantly reduced the risk of MACE in individuals with CKD G3 (HR 0.83; 95% CI 0.76-0.90), but results were similar whether the regimen was based on ACEi, CCB, diuretics or beta-blockers (50). Another Bayesian network meta-analysis found odds ratios of 0.94 (95% credibility interval 0.75-1.12) for ACEi and 0.86 (95% credibility interval 0.70-1.03) for ARB versus active controls (either CCB, diuretics or beta-blockers) on cardiovascular events (13). Collectively these findings may suggest that there is little evidence to support a particular drug class for the prevention of cardiovascular outcomes in the general population with CKD.

Finally, few studies have compared the mortality risk of RASi versus alternative antihypertensive agents in advanced CKD. In the meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration, both ACEi vs. placebo and CCB vs. placebo were associated with similar reductions in all-cause mortality for CKD patients (predominantly CKD G3a), with HR (95% CI) of 0.86 (0.76-0.97) and 0.83 (0.56-1.24), respectively (50). Head-to-head comparisons of RASi vs. CCB in patients with CKD yielded a hazard ratio of 1.00 (0.89-1.13) (50), which is again similar to what we observed in patients with CKD G4-5ND (0.97; 0.88-1.07) and our control cohort of patients with CKD G3 (0.97; 0.81-1.17).

We studied a unique nationwide inception cohort design of patients referred to a nephrologist in a country with universal healthcare access, with long-term follow-up data of over 10 years, assessment of multiple relevant endpoints, virtually no loss to follow-up and low likelihood of misclassification for the outcomes KRT and mortality. Furthermore, results were robust in multiple subgroup and sensitivity analyses. Our positive control analysis of persons with CKD G3 aligned with findings from two meta-analyses of trials and the patients included are representative of

routine clinical practice. In addition, the negative control analysis with cancer did not indicate that the observed associations were due to different health status. However, we recognize limitations. Despite adjustment for a wide range of potential confounders, selection of patients referred to nephrologists, and the use of an active comparator (CCB initiation), residual confounding-by-indication bias cannot be excluded in observational designs, and the reasons for the initiation of these drugs in the patients of our study remain unknown. Because only around 10% of individuals starting RASi or CCB in our study had a cardiovascular hospitalization in the 6 months prior to therapy start, we speculate that medications may have been initiated for renoprotection or as antihypertensive agents. Data were missing for ACR and potassium, but our results were similar whether these variables were included using multiple imputation or not, and those with missing measurements had similar characteristics to those without missing measurements. We recognize that it may be unusual to start RASi or CCB this late in the course of disease, and that there may be special indications for it. While we acknowledge that we do not have the precise reasons that prompted the use of these therapies, we went through a great deal of efforts to identify and control for these potential indications. Our results are likely generalizable to Swedish clinical practice during the period 2007-2017. However, extrapolations to other ethnicities, countries or periods should be done with caution. Finally, our conclusions remain observational in nature and do not substitute for randomized trials. However, until these trials are conducted they may assist in informing clinical decisions.

In conclusion, in patients with CKD G4-5ND, RASi initiation, compared with CCB initiation, was associated with a lower risk of KRT, but similar risks of MACE or mortality. These results suggest that use of RASi may confer additional renal benefits compared with CCB in patients with CKD G4-5ND. This evidence may potentially inform clinical decisions on the choice of antihypertensive therapy for this patient group, minimally included in pivotal trials.

References

1. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet. 1997;349(9069):1857-63.
2. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9.
3. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135(2):73-87.
4. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-60.
5. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet. 1998;352(9136):1252-6.
6. Kent DM, Jafar TH, Hayward RA, Tighiouart H, Landa M, de Jong P, et al. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. J Am Soc Nephrol. 2007;18(6):1959-65.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney inter, Suppl. 2012;2:337-414.
8. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127-e248.
9. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104.
10. Ruggenenti P, Perna A, Remuzzi G, Gruppo Italiano di Studi Epidemiologici in N. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results. Ramipril Efficacy in Nephropathy. J Am Soc Nephrol. 2001;12(12):2832-7.
11. Wright JT, Jr., Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288(19):2421-31.
12. Wu HY, Huang JW, Lin HJ, Liao WC, Peng YS, Hung KY, et al. Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ. 2013;347:f6008.
13. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. Am J Kidney Dis. 2016;67(5):728-41.

14. Weir MR, Lakkis JI, Jaar B, Rocco MV, Choi MJ, Kramer HJ, et al. Use of Renin-Angiotensin System Blockade in Advanced CKD: An NKF-KDOQI Controversies Report. Am J Kidney Dis. 2018;72(6):873-84.
15. Eckardt KU, Bansal N, Coresh J, Evans M, Grams ME, Herzog CA, et al. Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2018;93(6):1281-92.
16. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006;354(2):131-40.
17. Hsu TW, Liu JS, Hung SC, Kuo KL, Chang YK, Chen YC, et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. JAMA Intern Med. 2014;174(3):347-54.
18. Voskamp PWM, Dekker FW, van Diepen M, Hoogeveen EK, Group P-S. Effect of dual compared to no or single renin-angiotensin system blockade on risk of renal replacement therapy or death in predialysis patients: PREPARE-2 study. J Am Soc Hypertens. 2017;11(10):635-43.
19. Oh YJ, Kim SM, Shin BC, Kim HL, Chung JH, Kim AJ, et al. The Impact of Renin-Angiotensin System Blockade on Renal Outcomes and Mortality in Pre-Dialysis Patients with Advanced Chronic Kidney Disease. PLoS One. 2017;12(1):e0170874.
20. Suissa S, Hutchinson T, Brophy JM, Kezouh A. ACE-inhibitor use and the long-term risk of renal failure in diabetes. Kidney Int. 2006;69(5):913-9.
21. Fu EL, Trevisan M, Clase CM, Evans M, Lindholm B, Rotmans JI, et al. Association of Acute Increases in Plasma Creatinine after Renin-Angiotensin Blockade with Subsequent Outcomes. Clin J Am Soc Nephrol. 2019;14(9):1336-45.
22. Tomlinson LA, Abel GA, Chaudhry AN, Tomson CR, Wilkinson IB, Roland MO, et al. ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. PLoS One. 2013;8(11):e78465.
23. Arora N, Katz R, Bansal N. ACE Inhibitor/Angiotensin Receptor Blocker Use Patterns in Advanced CKD and Risk of Kidney Failure and Death. Kidney Med. 2020;2(3):248-57.
24. Ku E, McCulloch CE, Vittinghoff E, Lin F, Johansen KL. Use of Antihypertensive Agents and Association With Risk of Adverse Outcomes in Chronic Kidney Disease: Focus on Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. J Am Heart Assoc. 2018;7(19):e009992.
25. Pecoits-Filho R, Fliser D, Tu C, Zee J, Bieber B, Wong MMY, et al. Prescription of renin-angiotensin-aldosterone system inhibitors (RAASi) and its determinants in patients with advanced CKD under nephrologist care. J Clin Hypertens (Greenwich). 2019;21(7):991-1001.
26. Pugh D, Gallacher PJ, Dhaun N. Management of Hypertension in Chronic Kidney Disease. Drugs. 2019;79(4):365-79.
27. Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core Curriculum 2019. Am J Kidney Dis. 2019;74(1):120-31.
28. Sinha AD, Agarwal R. Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD. Clin J Am Soc Nephrol. 2019;14(5):757-64.
29. Evans M, Suttorp MM, Bellocco R, Hoekstra T, Qureshi AR, Dekker FW, et al. Trends in haemoglobin, erythropoietin-stimulating agents and iron use in Swedish chronic kidney disease patients between 2008 and 2013. Nephrol Dial Transplant. 2016;31(4):628-35.

30. Evans M, Carrero JJ, Bellocco R, Barany P, Qureshi AR, Seeberger A, et al. Initiation of erythropoiesis-stimulating agents and outcomes: a nationwide observational cohort study in anaemic chronic kidney disease patients. Nephrol Dial Transplant. 2017;32(11):1892-901.
31. Swedish Renal Registry: Annual report 2018. www.snronline.se (2 April 2019, date last accessed).
32. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.
33. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
34. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.
35. Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. Am J Epidemiol. 2012;175(4):250-62.
36. Fu EL, Groenwold RHH, Zoccali C, Jager KJ, van Diepen M, Dekker FW. Merits and caveats of propensity scores to adjust for confounding. Nephrol Dial Transplant. 2019;34(10):1629-35.
37. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med. 1990;9(12):1501-15.
38. Danaei G, Garcia Rodriguez LA, Cantero OF, Logan RW, Hernan MA. Electronic medical records can be used to emulate target trials of sustained treatment strategies. J Clin Epidemiol. 2018;96:12-22.
39. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28(11):2670-7.
40. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009;170(2):244-56.
41. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016;133(6):601-9.
42. Izem R, Liao J, Hu M, Wei Y, Akhtar S, Wernecke M, et al. Comparison of propensity score methods for pre-specified subgroup analysis with survival data. J Biopharm Stat. 2020;30(4):734-51.
43. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
44. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. Stat Med. 2019;38(26):5120-32.
45. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet. 2005;366(9502):2026-33.
46. Maione A, Navaneethan SD, Graziano G, Mitchell R, Johnson D, Mann JF, et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrol Dial Transplant. 2011;26(9):2827-47.

47. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, et al. Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2012;156(8):570-81.

48. Grimaldi-Bensouda L, Klungel O, Kurz X, de Groot MC, Maciel Afonso AS, de Bruin ML, et al. Calcium channel blockers and cancer: a risk analysis using the UK Clinical Practice Research Datalink (CPRD). BMJ Open. 2016;6(1):e009147.

49. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter, Suppl. 2013;3:1-150.

50. Blood Pressure Lowering Treatment Trialists C, Ninomiya T, Perkovic V, Turnbull F, Neal B, Barzi F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ. 2013;347:f5680.

Supplementary Material

Supplemental methods.

Supplemental Table S1. Definition of medications and comorbidities.

Supplemental Table S2. Comparison of baseline characteristics for individuals with and without baseline ACR measurements.

Supplemental Table S3. Absolute risks and risk differences for KRT, mortality and MACE after 1, 2, 3, 5 and 10 years of follow-up.

Supplemental Table S4. Subgroup analyses for systolic blood pressure using 130 mmHg as cutpoint.

Supplemental Table S5. Baseline characteristics of patients in the positive control cohort with CKD G3 by RASi or CCB treatment, before and after inverse probability weighting.

Supplemental Table S6. Number of events, incidence rates and crude and adjusted hazard ratios for the association between RASi vs. CCB initiation and all-cause mortality, MACE and KRT in the positive control cohort of patients with CKD G3.

Supplemental Table S7. Adjusted hazard ratios for the sensitivity analyses.

Supplemental Table S8. Number of events, incidence rates as well as crude and adjusted hazard ratios for the association between RASi vs. CCB initiation and MACE plus (composite of cardiovascular death, hospitalization due to stroke, myocardial infarction or heart failure).

Supplemental Figure S1. Flow diagram depicting the assembly of the study cohort.

Supplemental Figure S2. Number of events, incidence rates and adjusted hazard ratios for mortality following RASi vs. CCB initiation, according to subgroups of age, sex, diabetes, ACR, heart failure, systolic blood pressure and eGFR.

Supplemental Figure S3. Number of events, incidence rates and adjusted hazard ratios for MACE following RASi vs. CCB initiation, according to subgroups of age, sex, diabetes, ACR, heart failure, systolic blood pressure and eGFR.

Supplemental Methods

For the as-treated analysis, we censored individuals when they either discontinued therapy (no dispensation for the index drug within 60 days after the estimated last day of supply), or switched treatment (on the day of a prescription of the drug different from the index drug). To adjust for the time-varying selection bias that is introduced when censoring individuals if they deviate from the initiated medication at cohort entry, we used inverse probability of censoring weighting (IPCW). We constructed our dataset into monthly intervals and updated all comorbidities and medication use at each month. For each subject we estimated a weight that was, informally defined, proportional to the inverse of the probability of observing one's censoring history. The stabilized censoring weight at month t was calculated as

$$swC_t = \prod_{k=0}^{t} \frac{\Pr(C_{k+1} = 0 \mid \bar{C}_k = \bar{0}, \bar{A}_k, V)}{\Pr(C_{k+1} = 0 \mid \bar{C}_k = \bar{0}, \bar{A}_k, V, \bar{L}_k)}$$

where C_t indicates censoring status, A_t treatment history, V is a vector of time-fixed covariates at baseline and L_t represents the time-varying covariates. The denominator of swC_t adjusts for the informative censoring and is the probability of being uncensored in month k, conditional on past censoring history, treatment history, time-fixed covariates (measured at baseline), and time-varying covariates. The numerator of swC_t is not required for censoring adjustment but is used to stabilize the weights and improve statistical efficiency. The numerator represents the probability of remaining uncensored in month k, conditional on censoring history, treatment history, and time-fixed covariates. To estimate the weights, two separate pooled logistic models were fitted for the numerator and denominator respectively:

$$\text{logit}\,[\Pr(C_t = 0 \mid Y_t = C_{t-1} = 0, A, X, V)] = \eta_0 + \eta_1 t + \eta_2 t^2 + \eta_3 A + \eta_4 V + \eta_4 X$$
$$\text{logit}\,[\Pr(C_t = 0 \mid Y_t = C_{t-1} = 0, A, X, V)] = \eta_0 + \eta_1 t + \eta_2 t^2 + \eta_3 A + \eta_4 V + \eta_4 X + \eta_5 L_t$$

As time-fixed covariates we used age and sex, and as time-varying covariates we used all comorbidities, medications and hospitalizations listed in **Supplemental Table S1** as well as eGFR, systolic and diastolic blood pressure. The stabilized censoring weights had a mean of 1.00 and ranged from 0.30 to 5.65, indicating no violation of the positivity assumption. A weighted Cox model was then used to calculate adjusted hazard ratios for mortality, MACE and kidney replacement therapy for the as-treated analysis, using the estimated stabilized censoring weights, and additionally adjusting for all baseline covariates. Robust variance estimation was used to derive conservative 95% confidence intervals. A similar procedure was used for the competing risk analysis.