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It is unknown whether initiating diuretics on top of renin-angiotensin system inhibitors (RASi) is superior to alternative antihypertensive agents such as calcium channel blockers (CCBs) in patients with chronic kidney disease (CKD). For this purpose, we emulated a target trial in the Swedish Renal Registry 2007-2022 that included nephrologist-referred patients with moderate-advanced CKD and treated with RASi, who initiated diuretics or CCB. Using propensity score-weighted cause-specific Cox regression, we compared risks of major adverse kidney events (MAKE; composite of kidney replacement therapy [KRT], experiencing over a 40% eGFR decline from baseline, or an eGFR under 15 ml/min per 1.73m^2), major cardiovascular events (MACE; composite of cardiovascular death, myocardial infarction or stroke), and all-cause mortality. We identified 5875 patients (median age 71 years, 64% men, median eGFR 26 ml/min per 1.73m^2), of whom 3165 started a diuretic and 2710 a CCB. After a median follow-up of 6.3 years, 2558 MAKE, 1178 MACE and 2299 deaths occurred. Compared to CCB, diuretic use was associated with a lower risk of MAKE (weighted hazard ratio 0.87 [95% confidence interval: 0.77-0.97]), consistent across single components (KRT: 0.77 [0.66-0.88], over 40% eGFR decline: 0.80 [0.71-0.91] and eGFR under 15ml/min/1.73m^2: 0.84 [0.74-0.96]). The risks of MACE (1.14 [0.96-1.36]) and all-cause mortality (1.07 [0.94-1.23]) did not differ between therapies. Results were consistent when modeling the total time drug exposure, across sub-groups and a broad range of sensitivity analyses. Thus, our observational study suggests that in patients with advanced CKD, using a diuretic rather than a CCB on top of RASi may improve kidney outcomes without compromising cardioprotection.

Lay Summary

In patients with chronic kidney disease, it is unknown whether initiating a diuretic on top of renin-angiotensin system inhibitors is superior to other alternative antihypertensive agents such as calcium channel blockers. We emulated a target trial in the Swedish Renal Registry 2007 to 2022 including patients with chronic kidney disease stages G3–G5 and hypertension who had good adherence to renin-angiotensin system inhibitors and further initiated either a diuretic ($n = 3165$) or a calcium channel blocker ($n = 2710$). Compared with patients initiating a calcium channel blocker, those initiating a diuretic had a significantly lower risk of chronic kidney disease progression and a similar risk of cardiovascular events and all-cause mortality. Our study suggests that in patients with moderate to advanced chronic kidney disease, antihypertensive therapy with diuretics may be associated with further kidney benefits and similar cardioprotection compared with calcium channel blockers.

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As chronic kidney disease (CKD) progresses to advanced stages, impaired kidney sodium and water excretion often results in fluid overload and salt-sensitive hypertension, which are independently associated

with resistant hypertension,[1] need of kidney replacement therapy (KRT), cardiovascular events, and mortality.[2–7] Targeting optimal extracellular fluid volume status is thus critical to the clinical management of these patients and may be achieved by adjusting diuretic therapy and/or decreasing sodium intake.[8]

The 2021 Kidney Disease: Improving Global Outcomes Guidelines recommend that renin-angiotensin system inhibitors (RASi) be used as the first-line antihypertensive drug in patients with CKD,[9] but there is no clear recommendation for the second-line antihypertensive therapy in CKD, largely because of a lack of trial evidence. The uncertainty about the choice of therapy possibly explains the considerable variation observed in the patterns of use of antihypertensive drugs in persons with CKD worldwide.[10] Some guidelines suggest the use of a calcium channel blocker (CCB) or a diuretic.[11,12] Diuretic therapy may offer additional advantages over CCB therapy: beyond their antihypertensive and natriuretic properties, diuretics are known to potentiate the renoprotective[13–20] and cardioprotective[21] effects of RASi in CKD. They may also decrease blood pressure variability, a factor associated with poor kidney and cardiovascular outcomes.[22] Finally, the kaliuretic effect of diuretics could be of value to patients with CKD and hypertension in whom RAS blockade optimization is hampered by hyperkalemia. On the contrary, dihydropyridine CCB therapy induces an increase in proteinuria[23] and may potentially promote long-term CKD progression.

However, the long-term effects of diuretics in patients with CKD or whether they offer any advantage over CCBs as antihypertensive therapy is essentially unknown. Pivotal randomized trials were often small,[13,17,18,20] did not evaluate KRT, and/or focused on short-term effects of surrogate end points.[13,17,20,24–26] They neither evaluated drug efficacy as a second-line of therapy[24,27,28] nor, in general, failed to include patients with advanced CKD.[24–26,28] Some observational studies have attempted to compare clinical outcomes of diuretics with those of CCBs, but they may be limited by low sample sizes, confounding by indication bias,[29–31] lack of stratification by kidney function,[29,32] or lack of consideration of concomitant use of RASi.[33,34] The ACCOMPLISH (Avoiding Cardiovascular events through COmbination therapy in Patients LIving with Systolic Hypertension) trial, conducted in 11,506 patients at high cardiovascular risk but a low risk of CKD progression (<10% with estimated glomerular filtration rate [eGFR] < 60 ml/min per 1.73 m^2 and <1.5% with albumin-to-creatinine ratio > 30 mg/mmol), showed that compared with RASi/diuretic use, RASi/CCB use was associated with a lower risk of cardiovascular[26] and kidney[25] (i.e., composite of doubling in serum creatinine, eGFR < 15 ml/min per 1.73 m^2, or dialysis) events. However, no difference was observed between treatment groups for all-cause and cardiovascular mortality in the total ACCOMPLISH population, and no clear benefit was observed for kidney events in the subset of 1093 patients with moderate CKD at enrollment, which may be attributed to low power.

With the aim to help inform decisions on the choice of antihypertensive drug for patients with moderate to advanced CKD, we emulated a target trial comparing the risk of long-term outcomes of nephrologist-referred patients who initiated diuretic or CCB therapy on top of RASi therapy.

METHODS

Data source
We used data from the Swedish Renal Registry, a nationwide registry collecting longitudinal information of patients with all-cause CKD attending routine nephrology specialist care in Sweden. According to the registry protocol, patients should be enrolled when reaching an eGFR of <30 ml/min per 1.73 m^2 but encourage enrollment at earlier stages of CKD. Registrations of subsequent outpatient visits to nephrology care are thereafter performed, until death, emigration from the country, or start of KRT. The Swedish Renal Registry collects information on outpatient nephrology visits, including laboratory tests and clinical data. Via each citizen's unique personal identification number, the Swedish Renal Registry was then linked to other national registries, such as the Swedish Prescribed Drug Registry, which provides complete information on prescribed drugs dispensed at any Swedish pharmacies; the National Patient Register, a government-run registry that collects all in- and outpatient specialist diagnoses issued; and the National Death Registry, with virtually no loss to follow-up. The study was approved by the Swedish Ethical Review Authority (project numbers 2018/1591-31/2 and 2022-04594).

Study design and patient selection
We emulated a pragmatic clinical trial comparing the effect of initiating diuretics versus CCBs in patients with moderate to advanced CKD.[35] Explicit emulation of a target trial prevents common biases in pharmacoepidemiology studies,[36] such as immortal time bias and prevalent user bias, and makes the analysis of observational studies more transparent.[37] The protocol of the target trial and its emulation are specified in Supplementary Table S1. Eligible individuals were adult patients with CKD stages G3–G5 (eGFR < 60 ml/min per 1.73 m^2) who, between January 1, 2007, and May 1, 2022, had long-term treatment with good adherence to RASi (i.e., angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) and initiated a diuretic (thiazide, thiazide-like diuretic, or loop diuretic) or a CCB (dihydropyridine or nondihydropyridine; Supplementary Figure S1). *Good adherence to RASi* was defined as a proportion of days covered >75% within the year before the initiation of a diuretic or CCB. To capture therapies that were started because of hypertension management and not because of cardiovascular disease, we excluded patients with any in- or outpatient cardiovascular disease events in the 6 months before therapy initiation. Patients with a history of kidney transplantation or dialysis and those who initiated diuretic and CCB therapy simultaneously were also excluded. Look-back periods for eligibility criteria are specified in Supplementary Figure S2.

Treatment strategies and covariates
In our main analysis, the treatment strategies of interest were "initiation of a diuretic" versus "initiation of a CCB" in an intention-to-treat approach. *New initiation* was defined as the first dispensation recorded without dispensation of either drug in the previous 6 months. The date of the first dispensation constituted the index date and the start of follow-up (Supplementary Figure S2). Because changes in the pattern of antihypertensive therapy are common in the course of CKD, we also

conducted a supporting analysis comparing risks associated with the cumulative drug exposure over time.

Covariates were derived at index date and included age, sex, comorbidities, ongoing medications, clinical assessments, and recent health care use (Supplementary Table S2). Comorbidities considered the underlying cause of CKD,[38] diabetes mellitus, hypertension, coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, arrythmia, and liver disease. Ongoing medications included potassium-sparing diuretics, β-blockers, α-blockers, vasodilators, antidiabetic drugs, lipid-modifying agents, and nonsteroidal anti-inflammatory drugs. Clinical assessments included systolic and diastolic blood pressure, body mass index, GFR estimated with the 2009 creatinine-based Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, urinary albumin-to-creatinine ratio (ACR), hemoglobin, serum albumin, and serum potassium. Office blood pressure was measured at each outpatient visit, either through automated oscillometric device or manually according to the standard procedure at each nephrology clinic.[39] Because blood pressure was measured for clinical decision making in routine practice, the procedure followed the general guidelines of using an adapted sized cuff in a patient comfortably seated in a quiet room, after 5 minutes of rest. Recent health care use was used as a marker of overall disease burden and included the number of hospitalizations for any cause in the previous year as well as the number of hospitalizations in the previous 6 months for hyperkalemia or acute kidney injury.

Outcomes
The primary study outcome was the occurrence of major adverse kidney events (MAKE),[40] a composite of *initiation of KRT* (defined as start of maintenance dialysis or preemptive kidney transplantation), experiencing a decline in eGFR ≥ 40% from baseline, or experiencing an eGFR of <15 ml/min per 1.73 m^2. Each component of MAKE was also analyzed separately.

The secondary outcomes were all-cause mortality, cardiovascular and noncardiovascular death, and major adverse cardiovascular events (MACE; a composite of cardiovascular death, hospitalization for myocardial infarction, or stroke). We also evaluated repeated blood pressure measurements over the study period in the weighted population and represented them graphically by treatment group.

Safety outcomes were adverse events known to be associated with diuretic therapy, including hospitalizations and outpatient specialist care for acute kidney injury, hyperkalemia, hypokalemia, and hyponatremia. Outcome definitions are detailed in Supplementary Table S2. For each outcome, patients were followed from inclusion to the occurrence of event, death, or end of follow-up (May 1, 2022).

Statistical analyses
Main analyses. To control for baseline confounders, we used propensity score weighting, which targets an average treatment effect on the treated.[41] A multivariable logistic regression model was used to calculate the probability of receiving a diuretic or a CCB as a function of the baseline covariates listed above. Confounders were *a priori* selected on the basis of clinical knowledge and by consensus among study authors. Balance was considered appropriate if the standardized mean difference between treatment groups was <0.1 (10%) after propensity score weighting.

Weighted cumulative incidence curves were estimated using the Aalen-Johansen method. Weighted cause-specific Cox proportional hazards models were used to estimate hazard ratios (HRs) for the association between diuretic or CCB initiation and outcomes, and accounting for competing risks between MAKE and death and between MACE and death. Robust variance estimation was used to calculate 95% confidence intervals (CIs) after propensity score weighting. The proportional hazards assumption was checked using log(–log[S]) plots and Schoenfeld residuals against time. The interpretation of these methods in the presence of the competing risk of death is as follows: the Aalen-Johansen estimator estimates the total effect of the treatment on the outcome. Under strong assumptions, the cause-specific HRs can be interpreted as the direct effect of the treatment on the outcome (i.e., the effect of the treatment on the outcome that is not mediated by death), where death is considered a censoring event.[42,43]

Most study covariates had no missing values, but body mass index, serum potassium, and ACR were missing in ∼30% of patients. Because these clinical assessments are part of the routine monitoring of patients with CKD, we assumed missing to be at random and due to a lack of reporting to the registry. Indeed, characteristics of patients with versus without ACR measurements were not different (Supplementary Table S3). We then performed multiple imputations by chained equations using 50 imputed data sets with 20 iterations.

Subgroup analyses. To evaluate the consistency of our results, we performed prespecified subgroup analyses and tested interactions between treatment and age (≥75 years vs. <75 years), sex, presence versus absence of diabetes, systolic blood pressure (<120, [120–140], [140–160], ≥160 mm Hg), eGFR (≥30 ml/min per 1.73 m^2 vs. <30 ml/min per 1.73 m^2), and ACR (>30 mg/mmol vs. ≤30 mg/mmol).

Supporting analysis. Hypertension problems are common and intrinsic to the progression of CKD, naturally resulting in changes in the pattern of antihypertensive therapy in the course of CKD. To account for temporal and permanent discontinuations of therapy, switches across medication groups, and enrichments, we evaluated the total time drug exposure by modeling the cumulative use of each medication (see details in Supplementary Methods). In short, for each patient and at each dispense, we calculated the cumulative defined daily doses of diuretics and CCBs dispensed since the beginning of therapy. Then, the association between the cumulative use of diuretics, CCBs, and outcomes was analyzed using weighted Cox models and represented graphically. Their relative risk-benefit was compared by calculating the ratio of the HRs ($HR_{diuretics}$/HR_{CCBs}) per 1000 defined daily dose delivered.

Sensitivity analyses. (i) We redefined the window of no dispensation that determines eligibility from 6 to 12 months ($n = 2705$); (ii) we performed cause-specific Cox models considering the first outcome between MAKE, MACE, and death to assess the direct effect of the exposure and each outcome,[42,43] especially as hypertension and fluid overload are mainly treated by modulating ultrafiltration in dialysis; (iii) we repeated our main analysis in people free of cardiovascular disease at baseline ($n = 3656$), (iv) with any dispensation of RASi in the 4 months prior without consideration of adherence ($n = 6334$), (v) as well as with ($n = 5799$) and without ($n = 5555$) considering potassium-sparing diuretics in the diuretic group. (vi) Finally, we modeled negative control outcomes (including the most frequent causes of cancer [breast, prostate, lung, and colorectal cancers], gastritis/duodenitis with or without ulcer, cholecystis, and sigmoiditis) to study the influence of potential unmeasured confounders on our effect estimates. Although unmeasured confounders may predict the risk of negative outcomes, we did not expect the initiation of a diuretic or a CCB to cause or prevent them.[44]

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting of observational studies.[45] All statistical analyses were performed using R 3.6.3 software (https://cran.r-project.org/).

RESULTS

Baseline characteristics of patients with diuretics versus CCBs

We identified 5875 patients with nondialysis CKD stages 3–5 who, under long-term RASi treatment, started a diuretic or a CCB (Supplementary Figure S3). Their median age was 71 [interquartile range (IQR): 60–78] years; 64% ($N = 3779$) were men; eGFR was 26 [IQR: 20–34] ml/min per 1.73 m^2; and ACR was 31 [IQR: 6–116] mg/mmol. Of these, 3165 patients started a diuretic (including 2993, 163, and 9 users of loop diuretics, thiazides, or both, respectively) and 2710 started a CCB (including 2678 users of dihydropyridine CCBs and 32 of non-dyhydropyridine CCBs). Compared with new users of CCBs, patients on diuretics were older, were more often men, and had a higher prevalence of both atheromatous and nonatheromatous cardiovascular diseases (Supplementary Table S4). After weighting, all baseline characteristics were well balanced between the 2 groups (Table 1; Supplementary Figure S4).

Comparative effectiveness of diuretics versus CCBs on study outcomes

During a median follow-up of 6.3 years (IQR: 3.2–9.7 years), blood pressure remained stable and did not differ between the 2 groups of treatment (Supplementary Figure S5). A total of 2549 patients experienced MAKE, 1178 had a MACE, and 2299 patients died. After weighting, diuretic therapy was associated with a lower risk of MAKE (HR for diuretics vs. CCBs use 0.87 [95% CI 0.77–0.97]), which was consistent across each single component: KRT (HR 0.77 [95% CI 0.66–0.88]), ≥40% decline in eGFR (HR 0.80 [95% CI 0.71–0.91]), and eGFR < 15 ml/min per 1.73 m^2 (HR 0.84 [95% CI 0.74–0.96]; Table 2 and Figure 1; Supplementary Figure S6). The 5-year absolute risk of MAKE was lower in diuretic than in CCB users (49.4% [95% CI 47.2%–51.7%] vs. 54.2% [95% CI 50.8%–57.8%]; risk difference −4.80% [95% CI −8.95% to −0.66%]), with higher magnitudes at 8 and 10 years (Supplementary Table S5).

We did not observe any significant difference in the risk of all-cause mortality between diuretic and CCB use (HR 1.07 [95% CI 0.94–1.23]), both for noncardiovascular (HR 1.02 [95% CI 0.87–1.20]) and for cardiovascular (HR 1.19 [95% CI 0.94–1.50]) death. The risk of MACE (HR 1.14 [95% CI 0.96–1.36]) did not differ between therapies (Table 3 and Figure 1; Supplementary Figure S6). In absolute terms, the 5-year risk differences of MACE (4.50% [95% CI 0.84%–8.11%]) and all-cause mortality (4.20% [95% CI 0.192%–8.15%]) favored CCB users, but decreased at 8 and 10 years (Supplementary Table S5).

Supporting analyses

Modeling the total time drug exposure of each treatment provided consistent results with our main analysis. Compared with cumulative CCB use, cumulative diuretic use was associated with a lower risk of CKD progression (ratio of HR per each 1000 defined daily dose delivered: 0.89 [95% CI 0.85–0.94] for MAKE and 0.86 [95% CI 0.81–0.91] for KRT), with a similar risk of all-cause mortality (ratio of HR 1.02 [95% CI 0.98–1.06]) and MACE (ratio of HR 1.02 [95% CI 0.97–1.09]; Supplementary Figure S7).

Subgroup and sensitivity analyses

We observed in general no major differences in HR estimates across subgroups of age, sex, diabetes, systolic blood pressure, eGFR, or ACR (Figure 2; Supplementary Figures S8–S10). However, subgroup analyses might suggest somewhat stronger renoprotection for diuretics in older patients, those with higher blood pressure, or those with eGFR < 30 ml/min per 1.73 m^2.

Results were similar across sensitivity analyses (Supplementary Tables S6 and S7), and we did not observe differences in the risk of negative control outcomes between both therapies (Supplementary Table S8).

Potential adverse drug events, including acute kidney injury, hypokalemia, hyperkalemia, and hyponatremia, were not different between patients initiating diuretic therapy and those initiating CCB therapy (Supplementary Table S9).

DISCUSSION

In this large nationwide observational study of nephrologist-referred patients with CKD stages G3–G5 who initiated antihypertensive therapy on top of guideline-recommended RASi, we observed that compared with CCB therapy, diuretic therapy is associated with a lower risk of CKD progression and a similar risk of death and MACE. The association was consistent across the single components of our composite kidney outcome definition—including the hard end point of KRT—across subgroups of patients when evaluating the total time drug exposure and after considering death as a competing risk.

Our results are in line with the findings from small-scale studies reporting a synergy between diuretics and RASi in renoprotection.[13–20] Our results are novel and cannot be directly compared with preceding trials evaluating the impact of diuretic use, whose characteristics and findings are summarized in Supplementary Table S10. These trials were most often conducted in patients with a low risk of CKD progression[25,26,28,32] and investigated diuretics against no use,[33] as the first-line therapy,[24,34,46] or without cotreatment with RASi,[24,28,33,34,46] and these were not always consistent. We overcame some of the identified limitations of previous studies by selecting nephrologist-referred patients with moderate to advanced CKD, by having a long-term follow-up, and by evaluating a composite kidney outcome that is robust and includes kidney failure. We argue that previous studies have focused on short-term changes in eGFR/albuminuria, which are surrogate end points and may be affected by the reversible hemodynamic increase in serum creatinine often seen at the start of diuretics[17,18,47,48] or by the early vasodilatory effect of CCBs on renal afferent arterioles,[49,50] which may result in a higher initial eGFR,[51] but a higher long-term

Table 1 | Characteristics of the study population by treatment strategy after propensity score weighting

Characteristic	RASi + diuretic (*n* = 3165)	RASi + CCB (*n* = 3130)	SMD (%)
Demographics and clinical data			
Age, yr	73 [63–80]	72 [63–78]	2.0
Sex: woman	1229 (38.8)	1294 (41.4)	5.2
Body mass index, kg/m^2	28.4 [24.8–32.4]	28.3 [25.1–32.2]	5.4
Systolic BP, mm Hg	134 [120–148]	137 [125–150]	9.8
Diastolic BP, mm Hg	78 [70–84]	80 [70–85]	6.9
Medical history			
Diabetes mellitus	1312 (41)	1333 (43)	2.3
Myocardial infarction	410 (13)	405 (13)	0.0
Heart failure	614 (19)	580 (19)	2.2
Arrhythmia	511 (16)	476 (15)	2.6
Peripheral vascular disease	208 (7)	198 (6)	1.0
Cerebrovascular disease	212 (7)	195 (6)	2.0
Coronary artery disease	725 (23)	700 (22)	1.3
Primary cause of kidney disease			
Diabetic kidney disease	690 (22)	706 (23)	1.8
Glomerulonephritis	461 (15)	480 (15)	2.1
Nephroangiosclerosis or renovascular nephropathy	754 (24)	722 (23)	1.8
Others or unknown	1260 (40)	1223 (39)	1.5
Liver disease	77 (2)	82 (3)	1.1
Biological values			
Hemoglobin, g/dl	12.4 [11.4–13.5]	12.4 [11.2–13.5]	3.5
eGFR, ml/min per 1.73 m^2	26 [20–33]	26 [19–33]	1.9
eGFR, ml/min per 1.73 m^2			3.4
45–60	240 (8)	226 (7)	
30–45	872 (27)	832 (27)	
15–30	1666 (53)	1663 (53)	
<15	387 (12)	409 (13)	
ACR, mg/mmol	18 [4–95]	30 [6–118]	0.3
ACR, mg/mmol			16.4
A1: <3	645 (21)	522 (17)	
A2: 3–29	1181 (37)	1032 (33)	
A3: ≥30	1339 (42)	1576 (50)	
Serum potassium, mmol/l	4.5 [4.1–4.9]	4.5 [4.2–4.9]	0.9
Serum albumin, g/l	37 [34–40]	37 [34–39]	2.0
Medications			
RASi	3165 (100)	3130 (100)	0.0
β-Blockers	1947 (62)	1932.4 (62)	0.5
Potassium-sparing diuretics	244 (8)	201 (6)	5.0
α-Blockers	278 (9)	320 (10)	4.9
Vasodilators	18 (1)	51 (2)	10.3
NSAIDs	136 (4)	107 (3)	4.6
Lipid-lowering drugs	1886 (60)	1804 (58)	4.0
Health care use			
In the year before the index date			
Hospitalization for any cause	1041 (33)	1035 (33)	0.4
Hospitalization for any cause, no.	0.0 [0.0–1.0]	0.0 [0.0–1.0]	2.1
In the 6 months before the index date			
Hospitalization for hyperkalemia	0 (0)	0 (0)	0.0
Hospitalization for AKI	21 (1)	16 (1)	1.9

ACR, urinary albumin-to-creatinine ratio; AKI, acute kidney injury; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; RASi, renin-angiotensin system inhibitor; SMD, standardized mean difference.
Continuous variables are presented as median [interquartile range] and categorical variables as *n* (%).

increase in albuminuria,[23] and may not result in improved long-term clinical kidney outcomes.[23,24] Interestingly, our evaluation of safety outcomes did not show any increased risk of acute kidney injury or electrolyte disorders, which are adverse effects of diuretics that may be perceived as a barrier to its use. Subgroup analyses suggest somewhat

Table 2 | Primary study outcomes: weighted HRs for the association between diuretic use versus CCB use and adverse kidney outcomes

| Kidney outcomes	No. of events	Person-years	Crude IR (95% CI)	Weighted HR[a] (95% CI)
MAKE (composite)				
Overall	2549	16,667	15.3 (14.7–15.9)	
RASi + CCB	1261	7350	17.2 (16.2–18.1)	Reference
RASi + diuretic	1288	9317	13.8 (13.1–14.6)	0.87 (0.77–0.97)
Single components of MAKE				
Kidney replacement therapy				
Overall	1689	20,526	8.2 (7.8–8.6)	
RASi + CCB	862	9062	9.5 (8.9–10.2)	Reference
RASi + diuretic	827	11,464	7.2 (6.7–7.7)	0.77 (0.66–0.88)
≥40% decline in eGFR				
Overall	1902	15,239	12.5 (11.9–13.1)	
RASi + CCB	960	6647	14.4 (13.5–15.4)	Reference
RASi + diuretic	942	8592	11.0 (10.3–11.7)	0.80 (0.71–0.91)
eGFR < 15 ml/min per 1.73 m^2				
Overall	1700	14,203	12.0 (11.4–12.6)	
RASi + CCB	838	6338	13.2 (12.3–14.1)	Reference
RASi + diuretic	862	7865	11.0 (10.2–11.7)	0.84 (0.74–0.96)

CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IR, incidence rate per 100 patient-year; MAKE, major adverse kidney event; RASi, renin-angiotensin system inhibitor.
[a]Weighted for age, sex, diabetes, hypertension, body mass index, underlying nephropathy, history of ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, arrythmia, liver disease, systolic and diastolic blood pressure, hemoglobin, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, serum potassium, serum albumin, β-blockers, potassium-sparing diuretics, α-blockers, vasodilators, statins, hospitalization in the previous 6 months for hyperkalemia, acute kidney injury, and number of hospitalizations for any cause.

stronger renoprotection for diuretics in older patients, those with higher blood pressure, or those with eGFR < 30 ml/min per 1.73 m^2, which may be plausible and explained by a higher salt sensitivity related to a hyporeninism-hypoaldosteronism hormonal profile.

Although the ACCOMPLISH trial also compared RASi/CCB use with RASi/diuretic use,[25,26] the study population was quite different from that of our study (see Supplementary Table S11 for a head-to-head comparison between the ACCOMPLISH trial and our study), which may explain the different findings. ACCOMPLISH was prematurely terminated because of early demonstration of cardiovascular superiority—mainly on coronary disease—of CCBs over thiazides, with risks of all-cause mortality, stroke, and heart failure being not different. This early termination possibly affected the power of secondary kidney outcomes. Although the analysis of kidney events favored CCBs over thiazides,[25] effects were mostly attributed to the single end point of doubling of creatinine and were no longer significant in the <10% of patients with CKD.[25] This leaves a clinical
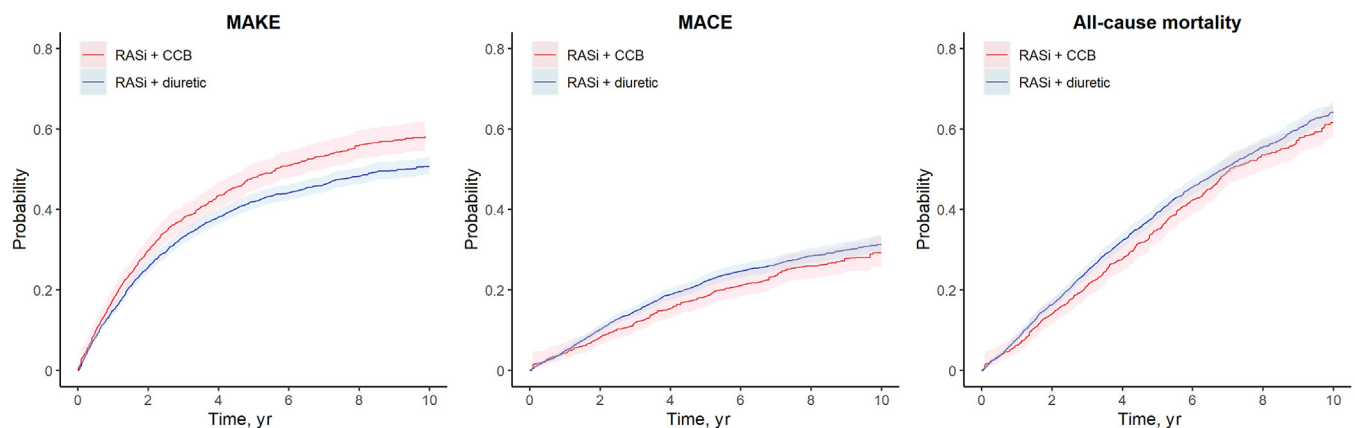
Figure 1 | Weighted cumulative incidence curves for major adverse kidney events (MAKE), major adverse cardiovascular events (MACE), and all-cause mortality according to treatment. Cumulative incidence curves were estimated with the Aalen-Johansen estimator to take into account competing risks between MAKE, MACE, and all-cause mortality. Cumulative incidence curves were weighted for age, sex, diabetes, hypertension, body mass index, underlying nephropathy, history of ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, arrythmia, liver disease, systolic and diastolic blood pressure, hemoglobin, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, serum potassium, serum albumin, β-blockers, potassium-sparing diuretics, α-blockers, vasodilators, statins, hospitalization in the previous 6 months for hyperkalemia, acute kidney injury, and number of hospitalizations for any cause. CCB, calcium channel blocker; RASi, renin-angiotensin system inhibitor.

Table 3 | Secondary study outcomes: weighted HRs for the association between diuretic use versus. CCB use, MACE, and death

| Outcomes	No. of events	Person-years	Crude IR (95% CI)	Weighted HR[a] (95% CIs)
All-cause death				
Overall	2299	27,927	8.2 (7.9–8.6)	
RASi + CCB	808	12,849	6.3 (5.9–6.7)	Reference
RASi + diuretic	1491	15,078	9.9 (9.4–10.4)	1.07 (0.94–1.23)
Non-CV death				
Overall	1570	27,927	5.6 (5.3–5.9)	
RASi + CCB	584	12,849	4.5 (4.2–4.9)	Reference
RASi + diuretic	986	15,078	6.5 (6.1–7.0)	1.02 (0.87–1.20)
CV death				
Overall	729	27,927	2.6 (2.4–2.8)	
RASi + CCB	224	12,849	1.7 (1.5–2.0)	Reference
RASi + diuretic	505	15,078	3.3 (3.1–3.7)	1.19 (0.94–1.50)
MACE				
Overall	1178	26,408	4.5 (4.2–4.7)	
RASi + CCB	422	12,191	3.5 (3.1–3.8)	Reference
RASi + diuretic	756	14,216	5.3 (4.9–5.7)	1.14 (0.96–1.36)

CCB, calcium channel blocker; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 patient-year; MACE, major adverse cardiovascular event; RASi, renin-angiotensin system inhibitor.
[a]Weighted for age, sex, diabetes, hypertension, body mass index, underlying nephropathy, history of ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, arrythmia, liver disease, systolic and diastolic blood pressure, hemoglobin, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, serum potassium, serum albumin, β-blockers, potassium-sparing diuretics, α-blockers, vasodilators, statins, hospitalization in the previous 6 months for hyperkalemia, acute kidney injury, and number of hospitalizations for any cause.

knowledge gap for patients with CKD stages 3–5, where choices of antihypertensive treatment are not defined and that the present study tries to address.

Pathophysiological hypotheses that may explain the observed protective effect of diuretics on CKD progression include the following: (i) a decrease in renal venous pressure, possibly slowing impairment of renal microcirculation and improving renal filtration[52]; (ii) a decrease in intraglomerular pressure slowing glomerulosclerosis and CKD progression; (iii) a decrease in pressure-independent alterations of structure and function of large arteries[4,53–55]; (iv) both thiazides and loop diuretics potentiate anti-albuminuria properties of RASi,[13–19] likely mediated by diuretic-induced volume depletion and hemodynamic changes[18]; and finally, (v) in patients with heart failure, diuretics improve cardiac filling pressures and venous congestion, resulting in better long-term kidney outcome.[56] Furthermore, we cannot exclude the possibility that an adverse effect of CCBs might contribute to explain our results. Indeed, despite a higher eGFR after treatment initiation,[51] CCBs may be associated with an increase in albuminuria[23] and a subsequent faster CKD progression,[23,24] because of an increase in intraglomerular pressure consecutive to afferent arteriole vasodilation and loss of autoregulation.[49,50]

We did not observe any lower risk of death or MACE for any of the treatment strategies, which is consistent with other trials—except ACCOMPLISH—comparing diuretics versus CCBs (with[57] or without[24,28,34,46] cotreatment with RASi) and with a large observational study conducted in patients with diabetes who were treated with a thiazide or a CCB on top of
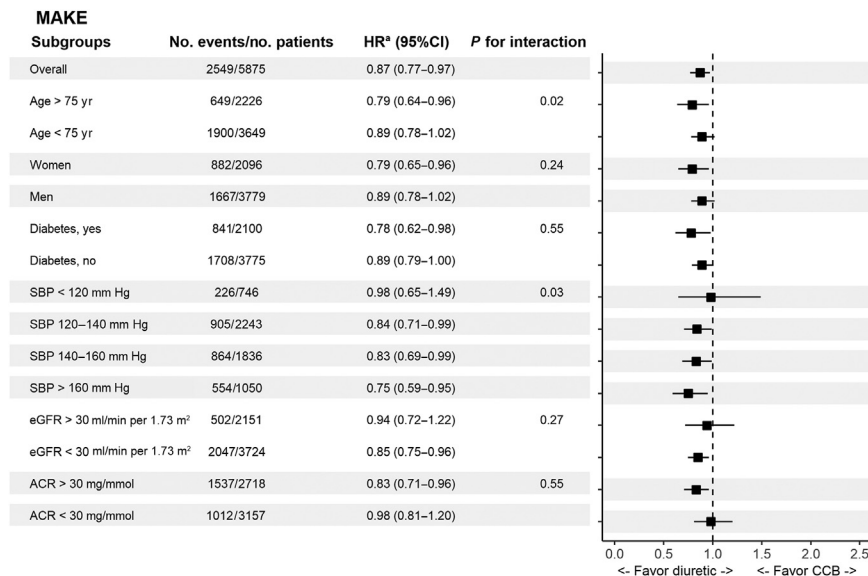
Figure 2 | Subgroup analyses: weighted hazard ratios (HRs) for the association between diuretic use versus calcium channel blocker (CCB) use and major adverse kidney events (MAKE). [a]Weighted for age, sex, diabetes, hypertension, body mass index, underlying nephropathy, history of ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, arrythmia, liver disease, systolic (SBP) and diastolic blood pressure, hemoglobin, estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (ACR), serum potassium, serum albumin, β-blockers, α-blockers, vasodilators, potassium-sparing diuretics, statins, hospitalization in the previous 6 months for hyperkalemia, acute kidney injury, and number of hospitalization for any cause. CI, confidence interval.

a 6-month therapy with RASi.[32] Although not statistically significant, we notice that the risks of MACE and cardiovascular death were somewhat higher in diuretic users than in CCB users whereas the difference in risk was null for non-cardiovascular death. Studying the impact of diuretic prescription on cardiovascular and death outcomes in CKD in observational studies is challenging because of confounding by indication bias. Fluid overload, for instance, may increase the risk of heart failure and subsequent risk of death from cardiovascular disease. A previous study[58] reported a higher risk of heart failure hospitalization in patients with CKD using diuretics versus nonuse (sub-distribution HR 1.83 [95% CI 1.43–2.32]), a counterintuitive finding attributed by the authors to unmeasured confounding by indication. In contrast, we expect this bias to less strongly affect kidney outcomes, given that delay of CKD progression is not an indication for neither therapy.

Our findings have implications for clinical practice and future research, suggesting that a diuretic could be proposed in CKD on top of RASi.[59,60] However, diuretics are often poorly and/or inadequately prescribed, mainly because diuretic prescription is challenging as it may induce an acute decrease in kidney function at start,[61] which may lead to discontinue or reduce the diuretic dose, and in turn cause fluid overload and poor long-term prognosis.[60] Taken together with the strong differences worldwide in nephrology practices for diuretic prescription,[10] this study highlights the need for clearer guidelines for diuretic management in patients with CKD. Diuretics efficaciously and safely reduce extracellular fluid volume and blood pressure if the dosage is carefully adjusted at the onset of the treatment[60,62] to avoid intravascular volume depletion from inadequate plasma refilling, potentially leading to a clinically relevant increase in serum creatinine.[13]

Strengths of our analysis include its large sample size, nationwide capture with long follow-up, careful design, robustness across various supporting and sensitivity analyses, and the unique setting involving real-world patients from a country with universal tax-funded health care, which minimizes selection bias from disparate access to health care. Our study also has limitations, starting by its observational nature, which is prone to residual confounding. The number of patients using thiazides was small, possibly reflecting the guideline-recommended advice not to use thiazides in patients with eGFR < 30 ml/min per 1.73 m^2. This prevented us from analyzing loop diuretics and thiazides separately. Moreover, previous beliefs that thiazide diuretics are not effective in advanced CKD may have influenced the decision to start one or the other medication in our study. We tried to minimize this confounding through propensity score weighting for a large array of identified confounders. However, we cannot rule out the possibility that loop diuretics may have been prescribed for other indications uncontrolled in our analysis, such as clinically evident volume overload, which may explain the magnitude of our cardiovascular disease–related outcomes. We used an intention-to-treat

approach and assumed that initiated treatment was continued, which may lead to bias toward the null. Our modeling of total time drug exposure nevertheless shows consistent findings and strengthens our confidence in the results. Another limitation is that adverse events were evaluated by issued diagnoses based on hospitalizations and outpatient specialist care data, but electrolyte disorders not recognized with diagnoses may have been missed. Finally, Sweden has traditionally limited ethnic diversity, which may preclude generalizability of our findings to other ethnicities.

To conclude, results of this large real-world observational study suggest that in patients with CKD stages G3–G5, compared with CCB therapy, diuretic therapy on top of RASi may further slow CKD progression, beyond their antihypertensive effect. Combined with our current understanding of the deleterious effect of volume overload,[1–7] these findings provide the rationale to initiate a clinical trial comparing these 2 antihypertensive treatment strategies in patients with CKD.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods. Supporting analysis of cumulative drug exposure over time.
Supplementary Table S1. Brief protocol of the pragmatic target trial and its emulation using data from the Swedish Renal Registry.
Supplementary Table S2. Definitions of comorbidities, medications, and outcomes.
Supplementary Table S3. Characteristics of patients with versus without available value of urinary albumin-to-creatinine ratio.
Supplementary Table S4. Characteristics of the study population before propensity score weighting.
Supplementary Table S5. Absolute risks and risk difference of major adverse kidney events (MAKE), major adverse cardiovascular events (MACE), and all-cause mortality.
Supplementary Table S6. Characteristics of new users of diuretics versus calcium channel blockers, new user being redefined as no dispensation of either drug in the previous 12 months.

Supplementary Table S7. Sensitivity analyses: weighted hazard ratios for the association between diuretic use versus calcium channel blocker use and adverse outcomes.

Supplementary Table S8. Negative control outcomes: weighted hazard ratios for the association between diuretic use versus calcium channel blocker use and hospitalization for gastrointestinal diseases or cancer.

Supplementary Table S9. Weighted hazard ratios for the association between diuretic use versus calcium channel blocker use and adverse events.

Supplementary Table S10. Main characteristics and findings from randomized controlled trials and observational studies comparing diuretics and calcium channel blockers as antihypertensive treatment.

Supplementary Table S11. Head-to-head comparison between the patients enrolled and the findings of the ACCOMPLISH trial and the present observational study.

Supplementary Figure S1. Selection of the study population.

Supplementary Figure S2. Study design following the graphical display recommended by the reporting guidelines for observational studies by Schneeweiss *et al.*[63]

Supplementary Figure S3. Flowchart of the study population.

Supplementary Figure S4. Covariates balance.

Supplementary Figure S5. Changes in blood pressure during follow-up according to treatment group.

Supplementary Figure S6. Weighted cumulative incidence curves for kidney replacement therapy (KRT), cardiovascular (CV) mortality, and non-CV mortality according to treatment.

Supplementary Figure S7. Weighted hazard ratios for the association between the cumulative dose use of diuretics and calcium channel blockers (CCBs) and adverse outcomes.

Supplementary Figure S8. Hazard ratios (HRs) for the association between diuretic use (vs. calcium channel blocker use) and all-cause mortality according to subgroups.

Supplementary Figure S9. Hazard ratios (HRs) for the association between diuretic use (vs. calcium channel blocker use) and kidney replacement therapy (KRT) according to subgroups.

Supplementary Figure S10. Hazard ratios (HRs) for the association between diuretic use (vs. calcium channel blocker use) and major adverse cardiovascular events (MACE [composite outcome of the following 3 criteria: cardiovascular death, hospitalization for myocardial infarction, or stroke]) according to subgroups.

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