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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Consequences of Recurrent Hyperkalemia on Cardiovascular Outcomes and Mortality

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ABSTRACT

BACKGROUND Hyperkalemia (HK) has been linked to serious cardiovascular (CV) outcomes, but the impact of recurrent HK on these outcomes is ill-defined.

OBJECTIVES This study evaluated mortality and CV outcomes associated with recurrent HK vs normokalemia in patients with chronic kidney disease (CKD) and in a subset of patients with co-occurring heart failure (HF).

METHODS REVOLUTIONIZE III was a retrospective cohort study of adults (aged ≥18 years) diagnosed with stage 3/4 CKD, with or without HF in Optum's deidentified Market Clarity database (January 2016 to August 2022). Patients with recurrent HK (≥2 events) were exactly and propensity score-matched to patients with normokalemia (no serum [K+] <3.5 or >5.0 mmol/L or HK diagnosis ever). The primary endpoint was all-cause mortality; secondary endpoints were CV outcomes including major adverse CV events plus (major adverse cardiovascular event or hospitalization with heart failure [MACE+]; defined as all-cause mortality or hospitalized myocardial infarction, stroke, or HF and hospitalized arrhythmia). Cause-specific Cox proportional hazard models were used to compare outcomes between cohorts.

RESULTS The study included 6,337 matched pairs overall, including 2,129 with HF. Characteristics of the samples were well-balanced. Recurrent HK was associated with higher risks of all-cause mortality (HR overall: 1.29 [95% CI: 1.20-1.38]; HF substudy: 1.30 [95% CI: 1.18-1.44]), MACE+ (overall: 1.53 [95% CI: 1.43-1.65]; HF substudy: 1.45 [95% CI: 1.29-1.64]), and hospitalized arrhythmia (overall: 1.94 [95% CI: 1.74-2.16]; HF substudy: 1.85 [95% CI: 1.55-2.21]) compared with normokalemia.

CONCLUSIONS In patients with CKD, recurrent HK increased the risks of all-cause mortality, MACE+, and hospitalized arrhythmia compared with normokalemia, including in a subset of patients with HF. (JACC Adv. 2024;3:101331)

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ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

CV = cardiovascular

eGFR = estimated glomerular filtration rate

EHR = electronic health record

HF = heart failure

HK = hyperkalemia

MACE = major adverse cardiovascular event

MACE+ = major adverse cardiovascular event plus

RAASi = renin-angiotensin-aldosterone system inhibitor

SMD = standardized mean difference

UACR = urine albumin-creatinine ratio

Hyperkalemia (HK), an electrolyte disorder characterized by abnormally high levels of serum potassium (K+), is an established complication of reduced renal function in patients with chronic kidney disease (CKD) or acute renal failure.[1] Serious clinical outcomes of HK include muscle weakness, paralysis, cardiovascular (CV) abnormalities (eg, conduction abnormalities, arrhythmia, and atrial fibrillation), and death.[2,3]

In the United States, the prevalence of HK is 1.6% in the general population but higher in individuals with certain comorbid conditions such as hypertension (2.6%), stage 3 CKD (5.0%), and heart failure (HF) (9.6%).[4] CKD is a known risk factor for HK recurrence,[5] defined as ≥2 HK events (serum K+ concentration >5.0 mEq/l) ≥7 days apart; in 1 study, over one-half of patients with stage 3 or 4 CKD had recurrent HK over a 6-month follow-up period.[6] Additionally, among patients diagnosed with HF who had an HK episode, the proportion experiencing a second, third, or fourth HK episode was 43%, 54%, and 60%, respectively.[7] Thus, patients with CKD including those with concomitant HF are at high risk of recurrent HK.

HK, CKD, and CV outcomes are interconnected through regulatory mechanisms that govern the CV and renal systems including the renin-angiotensin-aldosterone system.[3] As such, renin-angiotensin-aldosterone system inhibitors (RAASis), beta-blockers, and other pharmacologic agents used to treat HF and CKD can contribute to the development of HK.[8-11] Among new RAASi users who experienced an HK event, more than one-third of (37%) had a recurrence within 6 months; the rates were even higher in patients with CKD (40%) and chronic HF (49%).[5] The occurrence and recurrence of HK has been identified as a risk factor for poor renal outcomes, CV events, and death in patients with CKD and HF.[7,12-19] Previous research has demonstrated an increased risk of adverse CV outcomes in patients with CKD,[13,18,20] but it is unclear how this is impacted by recurrent HK in patients with stage 3 or 4 CKD.

Given the potentially fatal consequences, determining the risk of severe clinical outcomes associated with HK recurrence in patients with CKD—especially those with additional cardiorenal risk—is important so that appropriate management strategies can be implemented. To this end, the present study investigated the clinical impact of HK recurrence in CKD by comparing mortality (primary endpoint) and CV outcomes (secondary endpoint) between patients with stage 3 or 4 CKD diagnosed with HK and those with normokalemia, and in substudies of patients with HF, hypertension, RAASi use, and proteinuria.

METHODS

DATA SOURCE. Data for this study were from Optum's deidentified Market Clarity Data, which deterministically links U.S. medical and pharmacy claims with electronic health record (EHR) data (January 1, 2016 to August 31, 2022). All patients in the datacut were screened for study inclusion/exclusion criteria. As the data were deidentified, no institutional review board waiver of the requirement for informed consent was required per article 45 §CFR 164.514(e).

STUDY DESIGN. REVOLUTIONIZE III (Real-world value of leveraging the use of long-term anti-hyperkalemia treatment to normalize potassium) is a retrospective, matched observational study of patients with stage 3 or 4 CKD without or with HF comparing morality and CV outcomes between patients with recurrent HK vs normokalemia. A schematic of the study design is shown in Supplemental Figure 1. The index date was defined separately for each cohort (described below). The baseline period was the 12-month period preceding the index date, and the follow-up was the period spanning from the index date and to the earliest of death, occurrence of a relevant CV outcome, or end of data availability. Patients were required to have continuous medical and pharmacy insurance coverage during baseline.

PATIENT SELECTION. Recurrent HK was identified using a claims-based algorithm as in previous work.[7,18,21] First, HK episodes consisting of ≥1 HK diagnosis and ≥1 K+ laboratory result indicating HK (K+ >5.0 mmol/L) occurring within a span of 7 days were identified; the earliest eligible HK episode meeting all sample selection criteria was selected as the index HK episode. Patients were classified as having recurrent HK if they had either an HK diagnosis or K+ >5 mmol/L within the 12 months preceding the index HK episode. The index date was the day after the end of the healthcare encounter for the index HK episode. Patients were indexed not on the first HK event, but on the first recurrence of HK in the data (index HK episode) to avoid introducing immortal time bias (ie, by definition, recurrence constitutes ≥2 HK events, and the time between the first and recurring HK event would introduce person-time when the occurrence of death is not permitted).

For the normokalemia cohort, a random K+ laboratory result indicating normokalemia (K+ ≥3.5 and ≤5.0 mmol/L) that met all inclusion criteria was

identified. The index date was defined as the day after the healthcare encounter in which this result occurred.

Additional inclusion criteria for all patients were at least 1 estimated glomerular filtration rate (eGFR) value ≤59 mL/min/1.73 m^2 and 1 stage 3 or 4 CKD diagnosis during the baseline period, and aged ≥18 years on the index date. Patients that had undergone organ or stem cell transplantation or had a diagnosis of end-stage kidney disease or stage 5 CKD and/or eGFR <15 mL/min/1.73 m^2 during the baseline period were excluded. Patients in the normokalemia cohort were also required to have no record of K+ <3.5 or >5.0 mmol/L and no HK diagnosis at any time.

COHORT MATCHING AND SUBSTUDIES. Recurrent HK and normokalemia cohorts were matched 1:1 using a 2-step process of exact and propensity score matching. First, patients with recurrent HK and those with normokalemia were exactly matched on the following key baseline characteristics: diagnosis of CKD stage (3 or 4) on the index date; treatment with an RAASi on or within 90 days before the index date; occurrence of CV outcomes during baseline; urine albumin-creatinine ratio (UACR) ≥30 mg/g (yes/no/unavailable); UACR ≥300 mg/g (yes/no/unavailable); diagnosis of HF; diagnosis of hypertension; and diagnosis of type II diabetes mellitus during the baseline period. A logistic regression model that predicted recurrent HK vs normokalemia based on baseline characteristics was used to generate the propensity score. An algorithm[22] was used to select demographical and clinical variables that were included in the propensity score calculation. Patients were matched 1:1 within each coarsened exact match category using the propensity score and by caliper matching using a caliper of 0.01. For each CV outcome, matched pairs with that outcome during baseline were excluded from the analysis sample.

Subgroup analyses were conducted among patients diagnosed with HF during the baseline period (HF substudy), hypertension during the baseline period (hypertension substudy), RAASi use on or within 90 days preceding the index date (RAASi substudy), and laboratory-confirmed proteinuria (UACR ≥30 mg/g; proteinuria substudy).

STUDY ENDPOINTS. Study endpoints included all-cause mortality and CV outcomes. CV outcomes included major adverse cardiovascular events [MACEs], defined as all-cause mortality or hospitalization with myocardial infarction or stroke; major adverse cardiovascular events plus (MACE+), defined as all components of MACE or hospitalization with HF; and hospitalization with arrhythmia. All-cause mortality, MACE+, and hospitalized arrhythmia outcomes were assessed in the overall sample and the HF, hypertension, RAASi, and proteinuria substudies. MACE was assessed in the overall population.

Time to RAASi discontinuation was assessed in the RAASi substudy.

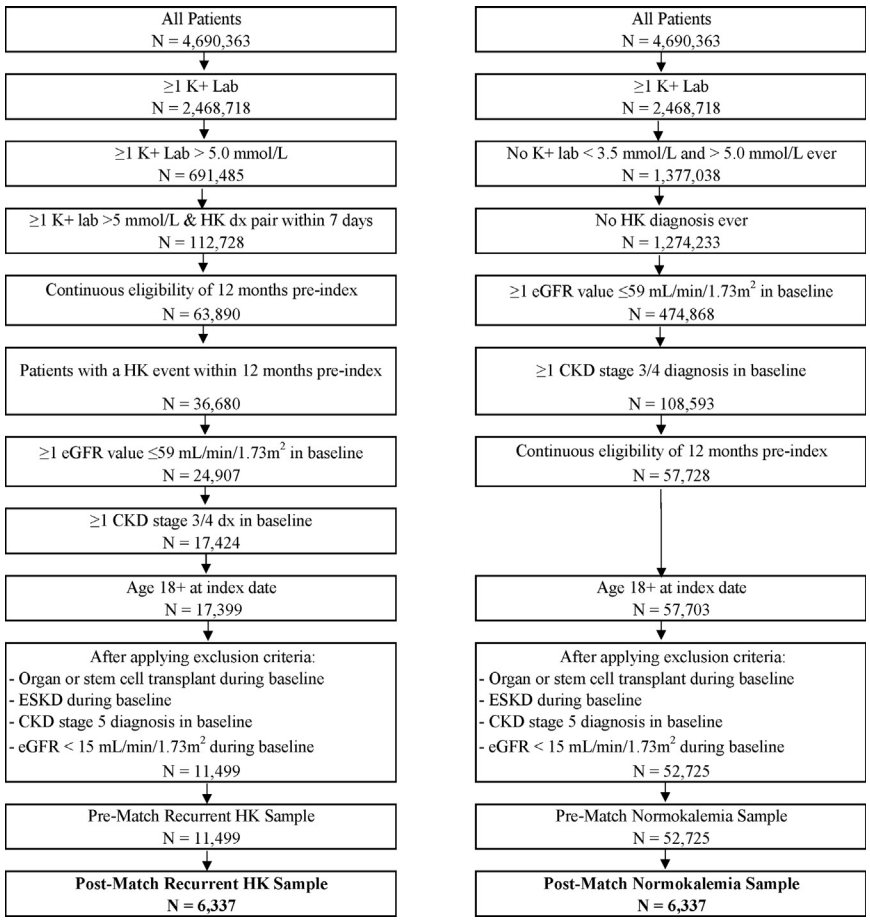
DATA ANALYSIS. Patient baseline characteristics including demographics, comorbidities, medications (including HK treatments and RAASi use), and laboratory values were summarized descriptively using mean ± SD and median (IQR) for continuous variables and count (percentage) for categorical variables. Matched patient characteristics were compared between cohorts using standardized mean difference (SMD); the cohorts were considered well-balanced if the SMD was <0.20.

All-cause mortality, MACE, MACE+, hospitalization with arrhythmia, and RAASi discontinuation during the follow-up period were described by Kaplan-Meier analysis and compared using adjusted cause-specific Cox proportional hazard models. In the Cox models, robust sandwich variance estimators were used to account for correlations between matched pairs, and HRs and 95% CIswere reported. *P* values <0.05 were considered statistically significant.

In the Kaplan-Meier analyses for CV outcomes, patients were censored at the end of data availability, end of the enrollment period, use of a K+ binder for ≥7 days in the outpatient setting, or death (for the hospitalization with arrhythmia analysis only). For each CV outcome, components of the event were also descriptively summarized. These were determined for the first identified event that a patient experienced postindex and were not mutually exclusive, as a patient could have a diagnosis code for more than 1 event on the same day. For the arrhythmia outcomes, patients were identified as having either atrial fibrillation or other arrhythmias (paroxysmal tachycardia, ventricular tachycardia, atrial flutter, ventricular flutter, ventricular fibrillation, and all other arrhythmias).

In the time to RAASi discontinuation analysis, discontinuation was defined as the first gap >90 days between the end of one recorded fill and the beginning of the next fill. The discontinuation date was the last date covered by the days of supply for the RAASi record before discontinuation. Patients were censored at the end of data availability, end of the enrollment period, use of a K+ binder for ≥7 days in the outpatient setting, death, or if they did not have ≥90 days of continuous enrollment following

FIGURE 1 Sample Selection for Recurrent HK and Normokalemia Cohorts



Before matching, there were 11,499 patients with recurrent hyperkalemia and 52,725 with normokalemia; 6,337 matched pairs were included in the analysis. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HK = hyperkalemia; K+ = potassium.

the treatment end date (as their discontinuation status would be unknown).

All analyses were conducted using R 3.6.3.

RESULTS

PATIENT SAMPLES. The prematched samples included 11,499 eligible patients with recurrent HK and 52,725 with normokalemia (Figure 1). After exact and propensity score matching, there were 6,337 matched pairs in the overall sample for the mortality analysis (Table 1). From this sample, 5,839 matched pairs were included in the MACE sample, 5,258 were included in the MACE+ sample, and 5,485 were included in the hospitalization with arrhythmia sample. The substudy of patients with HF included 2,129 matched pairs; additional substudies were 2,939 matched pairs with RAASi use at the index date, 5,973 with a hypertension diagnosis during baseline, and 918 matched pairs with proteinuria during baseline. The mean follow-up time was 1.78 ± 1.33 years for the overall mortality analysis sample and ranged from 1.53 ± 1.27 to 1.94 ± 1.35 years in the substudies.

KEY BASELINE CHARACTERISTICS. As expected, baseline characteristics were similar and well-balanced between the normokalemia and recurrent HK cohorts in the overall sample and were generally similar in the HF substudy (Table 1). Full baseline characteristics for the other substudies are presented in the Supplemental Appendix. In the overall mortality analysis sample, the mean (SD) age was 73.3 ± 11.3 years; 52.3% of patients were male and the majority were White (77.8%) and had Medicare

TABLE 1 Baseline Characteristics of the Overall Population and Heart Failure Substudy in the Mortality Sample

	Overall Population			Heart Failure Substudy		
	Normokalemia (n = 6,337)	Recurrent HK (n = 6,337)	SMD[2]	Normokalemia (n = 2,129)	Recurrent HK (n = 2,129)	SMD[2]
Demographics						
Age (y)	73.2 ± 11.3	73.4 ± 11.3	0.018	75.6 ± 10.7	75.8 ± 10.3	0.026
Female	3,049 (48.1%)	2,994 (47.2%)	0.017	962 (45.2%)	1,029 (48.3%)	0.063
Race			0.020			0.062
Caucasian	4,926 (77.7%)	4,932 (77.8%)		1,646 (77.3%)	1,652 (77.6%)	
African American	825 (13.0%)	792 (12.5%)		302 (14.2%)	314 (14.7%)	
Asian	100 (1.6%)	105 (1.7%)		16 (0.8%)	24 (1.1%)	
Other/unknown	486 (7.7%)	508 (8.0%)		165 (7.8%)	139 (6.5%)	
Insurance type (medical)			0.041			0.040
Medicare	4,201 (66.3%)	4,243 (67.0%)		1,517 (71.3%)	1,526 (71.7%)	
Commercial	1,316 (20.8%)	1,337 (21.1%)		330 (15.5%)	347 (16.3%)	
Medicaid	480 (7.6%)	414 (6.5%)		181 (8.5%)	166 (7.8%)	
Unknown	340 (5.4%)	343 (5.4%)		101 (4.7%)	90 (4.2%)	
Region			0.049			0.058
Midwest	3,312 (52.3%)	3,194 (50.4%)		1,110 (52.1%)	1,160 (54.5%)	
Northeast	1,190 (18.8%)	1,281 (20.2%)		393 (18.5%)	360 (16.9%)	
South	1,042 (16.4%)	1,097 (17.3%)		364 (17.1%)	354 (16.6%)	
West	591 (9.3%)	575 (9.1%)		186 (8.7%)	190 (8.9%)	
Unknown	202 (3.2%)	190 (3.0%)		76 (3.6%)	65 (3.1%)	
BMI (kg/m^2)						
Available BMI score	5,313 (83.8%)	5,697 (89.9%)		1,748 (82.1%)	1,954 (91.8%)	
Mean ± SD	31.7 ± 7.6	30.7 ± 7.7	0.133	32.0 ± 8.5	31.2 ± 8.2	0.099
CKD stage by diagnosis code[3] at index						
CKD stage 3	5,058 (79.8%)	5,058 (79.8%)	0.000	1,705 (80.1%)	1,705 (80.1%)	0.000
CKD stage 4	1,279 (20.2%)	1,279 (20.2%)	0.000	424 (19.9%)	424 (19.9%)	0.000
Comorbidities						
CCI	3.5 ± 2.2	3.6 ± 2.2	0.027	5.2 ± 1.9	5.3 ± 2.0	0.012
Hypertension	5,973 (94.3%)	5,973 (94.3%)	0.000	2,109 (99.1%)	2,109 (99.1%)	0.000
Type II diabetes	3,999 (63.1%)	3,999 (63.1%)	0.000	1,395 (65.5%)	1,395 (65.5%)	0.000
Coronary artery disease	2,495 (39.4%)	2,524 (39.8%)	0.009	1,408 (66.1%)	1,409 (66.2%)	0.001
Acute kidney injury	2,300 (36.3%)	2,310 (36.5%)	0.003	1,132 (53.2%)	1,156 (54.3%)	0.023
Congestive heart failure	2,129 (33.6%)	2,129 (33.6%)	0.000	2,129 (100.0%)	2,129 (100.0%)	0.000
Peripheral vascular disease	2,004 (31.6%)	2,157 (34.0%)	0.051	1,045 (49.1%)	1,119 (52.6%)	0.070
Cerebrovascular disease	1,336 (21.1%)	1,337 (21.1%)	0.000	634 (29.8%)	663 (31.1%)	0.030
Stroke[4]	934 (14.7%)	887 (14.0%)	0.021	441 (20.7%)	464 (21.8%)	0.026
Myocardial infarction	823 (13.0%)	831 (13.1%)	0.004	571 (26.8%)	571 (26.8%)	0.000
Deep vein thrombosis	272 (4.3%)	262 (4.1%)	0.008	129 (6.1%)	130 (6.1%)	0.002
Any coronary revascularization	195 (3.1%)	133 (2.1%)	0.062	140 (6.6%)	93 (4.4%)	0.097
Pulmonary embolism	157 (2.5%)	138 (2.2%)	0.020	87 (4.1%)	79 (3.7%)	0.019
Arterial embolism/thrombosis	72 (1.1%)	77 (1.2%)	0.007	40 (1.9%)	45 (2.1%)	0.017
Deep vein thrombophlebitis	54 (0.9%)	47 (0.7%)	0.012	31 (1.5%)	23 (1.1%)	0.034
Any MACE	498 (7.9%)	498 (7.9%)	0.000	388 (18.2%)	388 (18.2%)	0.000
Any MACE+	1,079 (17.0%)	1,079 (17.0%)	0.000	969 (45.5%)	969 (45.5%)	0.000
Any hospitalized cardiac dysrhythmia[5]	852 (13.4%)	852 (13.4%)	0.000	682 (32.0%)	682 (32.0%)	0.000
Atrial fibrillation	643 (10.1%)	647 (10.2%)	0.002	525 (24.7%)	539 (25.3%)	0.015
Other cardiac dysrhythmia	469 (7.4%)	499 (7.9%)	0.018	382 (17.9%)	398 (18.7%)	0.019

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medical insurance coverage (66.6%). Patients in the HF substudy had similar demographics except for a slightly higher mean age.

In the overall sample, most patients had a diagnosis of stage 3 CKD at index (79.8%) whereas a smaller proportion had stage 4 (20.2%). The median (IQR) outpatient eGFR laboratory value closest to the index date was lower in the recurrent HK cohort than in the normokalemia cohort (39.4 [IQR: 30.4-48.4] vs 45.3 [IQR: 35.7-53.6] mL/min/1.73 m^2; SMD = 0.042). In the recurrent HK cohort, 46.0% of patients had mild HK (K+ >5 to <5.5 mmol/L) at the index episode, 35.4%

TABLE 1 Continued

	Overall Population			Heart Failure Substudy		
	Normokalemia (n = 6,337)	Recurrent HK (n = 6,337)	SMD[2]	Normokalemia (n = 2,129)	Recurrent HK (n = 2,129)	SMD[2]
Laboratory values closest to index date						
Outpatient eGFR (mL/min/1.73 m^2)						
Mean ± SD	45.6 ± 42.4	42.4 ± 98.2	0.042	43.8 ± 13.3	42.3 ± 92.0	0.023
Median (IQR)	45.3 (35.7-53.6)	39.4 (30.4-48.4)		44.0 (34.1-52.6)	38.8 (30.4-48.3)	
Potassium						
≤5 mmol/L (normokalemia)	6,337 (100.0%)	280 (4.4%)	6.578	2,129 (100.0%)	167 (7.8%)	4.847
>5-<5.5 mmol/L (mild HK)	0 (0.0%)	2,912 (46.0%)		0 (0.0%)	947 (44.5%)	
5.5-<6.0 mmol/L (moderate HK)	0 (0.0%)	2,243 (35.4%)		0 (0.0%)	691 (32.5%)	
≥6 mmol/L (severe HK)	0 (0.0%)	902 (14.2%)		0 (0.0%)	324 (15.2%)	
RAASi use						
RAASi use at index date	2,939 (46.4%)	2,939 (46.4%)	0.000	926 (43.5%)	926 (43.5%)	0.000
Any RAASi use during baseline	4,330 (68.3%)	4,755 (75.0%)	0.149	1,447 (68.0%)	1,621 (76.1%)	0.183
ACEI	2,332 (36.8%)	3,063 (48.3%)	0.235	776 (36.4%)	975 (45.8%)	0.191
ARB	2,034 (32.1%)	1,761 (27.8%)	0.094	674 (31.7%)	664 (31.2%)	0.010
ARNI	74 (1.2%)	115 (1.8%)	0.053	73 (3.4%)	115 (5.4%)	0.096
DRI	6 (0.1%)	5 (0.1%)	0.005	0 (0.0%)	<5 (<0.2%)	0.061
MRA	503 (7.9%)	903 (14.2%)	0.202	334 (15.7%)	569 (26.7%)	0.273
Other medications						
Beta-blockers	3,729 (58.8%)	3,734 (58.9%)	0.002	1,604 (75.3%)	1,668 (78.3%)	0.071
NSAIDs	1,122 (17.7%)	1,143 (18.0%)	0.009	353 (16.6%)	381 (17.9%)	0.035
UACR[6] laboratory values						
Urine albumin creatinine ratio (mg/g)	270.5 ± 615.1	296.1 ± 677.7	0.040	208.5 ± 476.5	204.7 ± 536.4	0.007
Available UACR (%)	1,645 (26.0%)	1,645 (26.0%)	0.040	259 (12.2%)	259 (12.2%)	0.007
UACR ≥30 mg/g	918 (14.5%)	918 (14.5%)	0.000	141 (6.6%)	141 (6.6%)	0.000
UACR ≥300 mg/g	318 (5.0%)	318 (5.0%)	0.000	39 (1.8%)	39 (1.8%)	0.000

Values are mean ± SD, n (%), or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; DRI = direct renin inhibitor; eGFR = estimated glomerular filtration rate; HK = hyperkalemia; MACE = major adverse cardiac event; MACE+ = major adverse cardiac event plus; MRA = mineralocorticoid receptor antagonist; NSAIDs = nonsteroidal anti-inflammatory drugs; RAASi = renin-angiotensin-aldosterone system inhibitors; SMD = standardized mean difference; UACR = urine albumin-creatinine ratio.

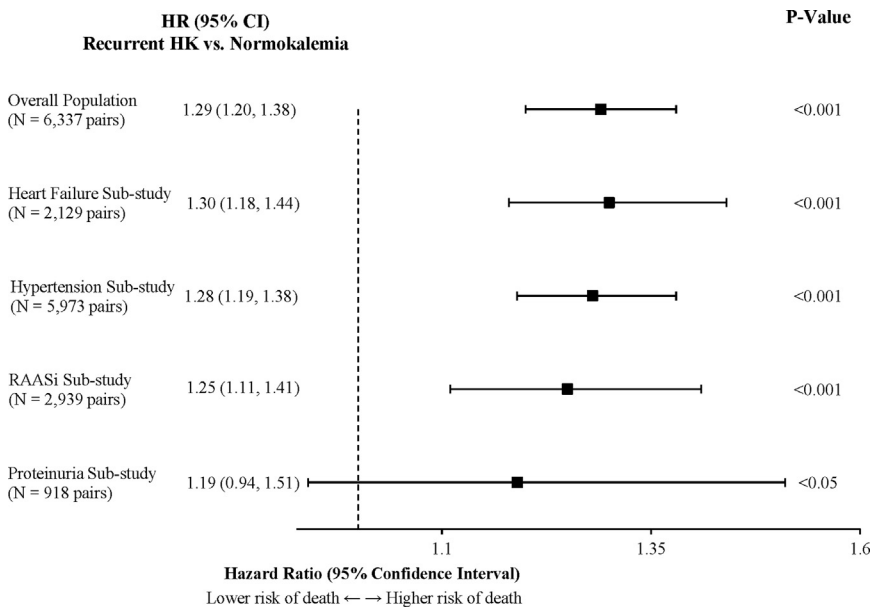
had moderate HK (K+ >5.5 to <6 mmol/L), and 14.2% had severe HK (≥6 mmol/L). The mean Charlson Comorbidity Index was 3.6 ± 2.2; common comorbidities in the overall mortality sample were hypertension (94.3% in both cohorts), type II diabetes (63.1% in both cohorts), coronary artery disease (recurrent HK: 39.8%, normokalemia: 39.4%), congestive HF (33.6% in both cohorts), and peripheral vascular disease (recurrent HK: 34.0%, normokalemia: 31.6%) (all SMDs <0.100). Patients in the HF substudy had a similar comorbidity profile and laboratory values, except that Charlson Comorbidity Index was higher and a smaller proportion had proteinuria.

In the overall mortality sample, 46.4% of patients had RAASi use on or in the 90 days preceding the index date. During baseline, 68.3% of patients with normokalemia and 75.0% with recurrent HK had RAASi use (SMD = 0.149). UACR was available for 26.0% of patients in both cohorts; the mean UACR was 291.6 ± 677.7 mg/g in patients with recurrent HK and 270.5 ± 615.1 mg/g in those with normokalemia.

MORTALITY. In the overall sample, the risk of all-cause mortality was 1.29 times higher for the recurrent HK cohort than for the normokalemia cohort (95% CI: 1.20-1.38; $P < 0.001$) (**Figure 2**). The results were similar and statistically significant in the HF substudy (1.30 times HF for patients with recurrent HK; 95% CI: 1.18-1.44) (**Figure 3**) and other substudies (hypertension, RAASi, proteinuria), with HRs ranging from 1.19 (proteinuria) to 1.28 (hypertension) (Supplemental Figures 2 to 5).

CV OUTCOMES. Patients with recurrent HK had a higher risk of CV outcomes than those with normokalemia (**Central Illustration**). In the overall sample, patients with recurrent HK had a 1.40 times higher risk of MACE than those with normokalemia (95% CI: 1.31-1.50; $P < 0.001$) (**Figure 4**). Death was the most common MACE for both cohorts (60.5% and 66.9%, respectively). For MACE+, the risk was 1.53 times higher in the recurrent HK cohort compared with the normokalemia cohort (95% CI: 1.43-1.65; $P < 0.001$); in the HF substudy, the risk was 1.45 times higher for

FIGURE 2 HRs for All-Cause Mortality



HRs and 95% CIs comparing recurrent hyperkalemia and normokalemia cohorts are presented for all-cause mortality in the overall population and heart failure, hypertension, renin-angiotensin-aldosterone system inhibitor, and proteinuria substudies. HK = hyperkalemia.

patients with recurrent HK (95% CI: 1.29-1.64; $P < 0.001$) (Figure 3). The results were consistent and statistically significant in all other substudies, with HRs ranging from 1.46 to 1.58. In the overall sample, HF was the most common MACE+ component in the recurrent HK cohort (45.9%), followed by death (37.3%); in the normokalemia cohort, death was more common than HF (48.6% vs 35.9%).

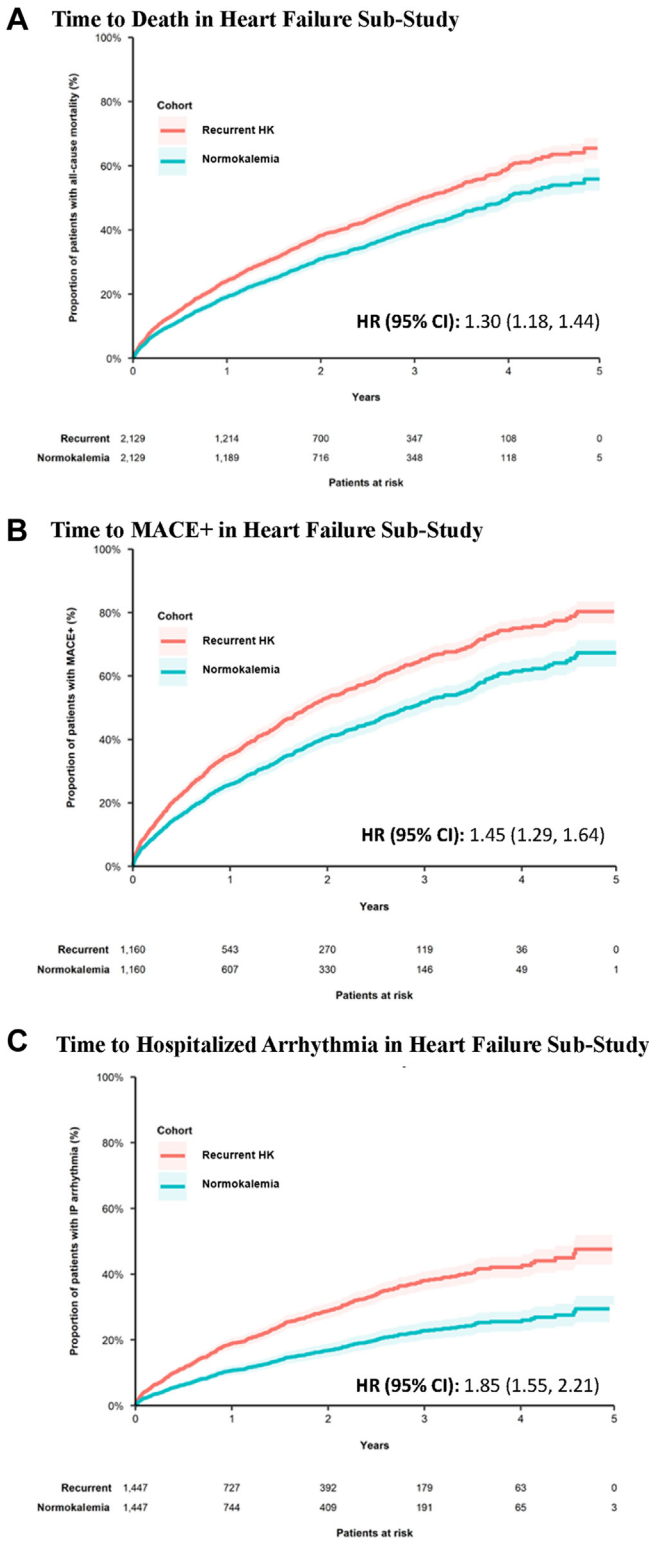
HK recurrence was associated with a 1.94 times higher risk of hospitalization with arrhythmia than normokalemia (95% CI: 1.74-2.16; $P < 0.001$) (Figure 5). The results were similar in the HF substudy (1.85 times higher risk for patients with recurrent HK; 95% CI: 1.55-2.21; $P < 0.001$) (Figure 3) and in all other substudies, for which HRs ranged from 1.84 (RAASi) to 1.96 (proteinuria). In both the overall population and HF substudy, the most common type of arrhythmia event was atrial fibrillation (overall: 59.2% in recurrent HK cohort and 68.0% in normokalemia cohort; HF substudy: 66.7% and 71.5%, respectively), with a large proportion of patients also experiencing other arrhythmias (overall: 53.1% for recurrent HK and 46.4% for normokalemia; HF substudy: 48.0% and 47.7%, respectively).

RAASi DISCONTINUATION. Among matched pairs with RAASi use on the index date, patients with recurrent HK had a 1.72 times higher risk of RAASi discontinuation than those with normokalemia (95% CI: 1.59-1.85; $P < 0.001$) (Figure 6). The median time to RAASi discontinuation was 1.19 (95% CI: 1.11-1.26) years for the recurrent HK cohort and 2.57 (95% CI: 2.39-2.87) years for the normokalemia cohort.

DISCUSSION

HK is a common complication of CKD that increases the risk of CV events and death. However, the impact of repeated HK episodes on these outcomes has not been systematically investigated. This was addressed in the present study by comparing the risks of mortality and CV outcomes between patients in the United States with stage 3 or 4 CKD with recurrent HK and those with normokalemia. Analyses were also conducted in separate substudies of patients with HF and other cardiorenal risk factors. The results showed that patients with recurrent HK had significantly higher risks of all-cause mortality and CV outcomes than those with normokalemia. The results were robust and consistent across all substudies, including in patients with HF, hypertension, RAASi use, and proteinuria during baseline. These findings demonstrate that recurrent HK has serious adverse consequences for moderate or severe CKD, and that

FIGURE 3 Kaplan-Meier Curves for Cardiovascular Outcomes in the Heart Failure Substudy



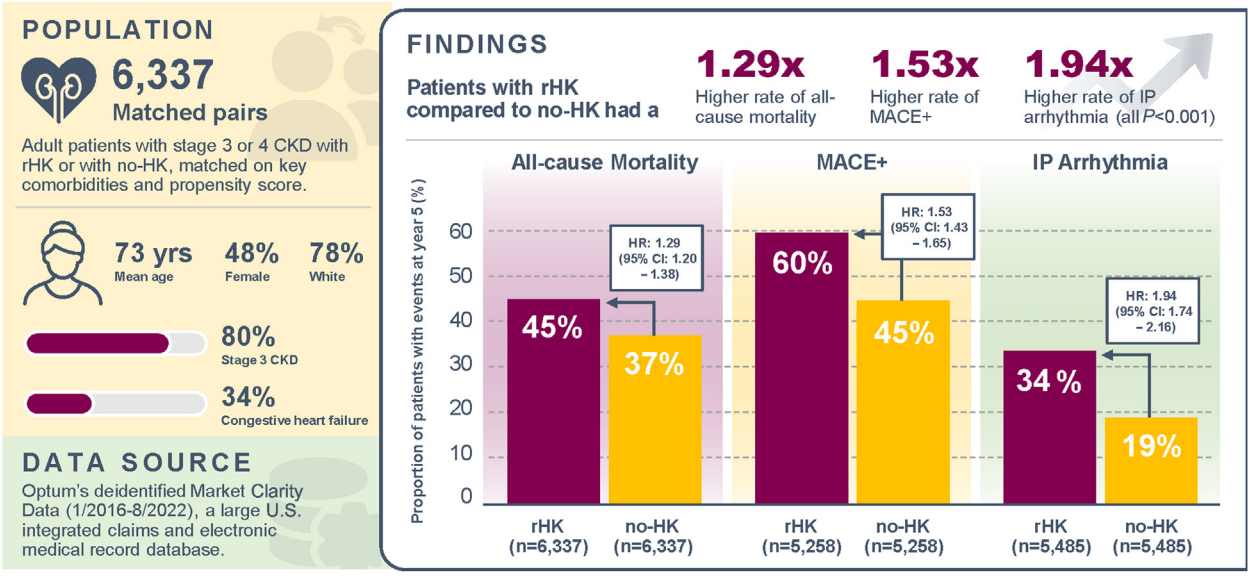
Median time to death, major adverse cardiovascular event or hospitalization with heart failure, and hospitalized arrhythmia in the heart failure substudy were compared Between patients with recurrent hyperkalemia and those with normokalemia. (A) Time to death in heart failure substudy. (B) Time to MACE+ in heart failure substudy. (C) Time to hospitalized arrhythmia in heart failure substudy. HK = hyperkalemia; IP = inpatient; MACE+ = major adverse cardiovascular events plus.

restoring K+ homeostasis in these patients is critical to ensure the best possible prognosis.

This is the first study to evaluate the impact of recurrent HK on mortality and CV outcomes in patients with stage 3 or 4 CKD without or with HF and other cardiorenal risk factors. Previous studies conducted in the United States and other countries have shown that HK increases the risks of CV outcomes (hospitalization for cardiac events, HF, ventricular arrhythmia, and MACE) and all-cause and CV-related mortality in patients with CKD and/or HF.[12-19,23] Our results extend these findings by showing that repeated episodes of HK increases these risks compared with normokalemia. In the overall population, recurrent HK was associated with a ~30% higher risk of all-cause mortality and higher risks of MACE (40%), MACE+ (>50%), and hospitalization with arrhythmia (>90%). Consistent with the earlier finding that any HK was associated with increased risk of mortality and adverse clinical outcomes,[13,14] we also found that the risks of mortality and CV outcomes were higher for recurrent HK than for normokalemia in patients with HF, hypertension, RAASi use, and proteinuria. Elevated K+ levels can cause CV events through various mechanisms such as inducing cardiac arrhythmia by disrupting myocardial action potentials.[3] It also stimulates the secretions of aldosterone,[24] which can damage the heart and kidneys and promote CV disease progression and CKD.[25-27]

Importantly, our results revealed higher risks of CV outcomes and death with HK recurrence across a range of HK severities. Most (>80%) patients in this study had mild ([K+] >5.0 to <5.5 mmol/L) or moderate (5.5 to <6.0 mmol/L)[28] HK. A systematic review of 123 studies examining risk factors or clinical outcomes of HK found that serum K+ in the range of 5.5 to 6.0 mmol/L was associated with an increased risk of MACE, whereas values between 5.0 and 5.5 mmol/L increased the risk of all-cause mortality in patients with CKD and HF.[15] A UK study found that over 10% of patients with mild HK had 4 or more episodes.[17] These results suggest that mild HK may not be adequately managed, eventually becoming a recurring condition. This is supported by the observation that in a cohort of patients with CKD, the proportion that experienced another episode increased with each successive HK event,[18] ie, 43% of patients with a first HK event had a second event; in this subset of patients, 57% had a third event and of this group, 64% had a fourth event.[18] Collectively, the available evidence suggests that in patients with stage 3 or 4 CKD, serum K+ should be closely monitored over the long term and elevated levels should be normalized to

CENTRAL ILLUSTRATION **Consequences of Recurrent Hyperkalemia on Cardiovascular Outcomes and Mortality**



Bakris G, et al. JACC Adv. 2024;3(11):101331.

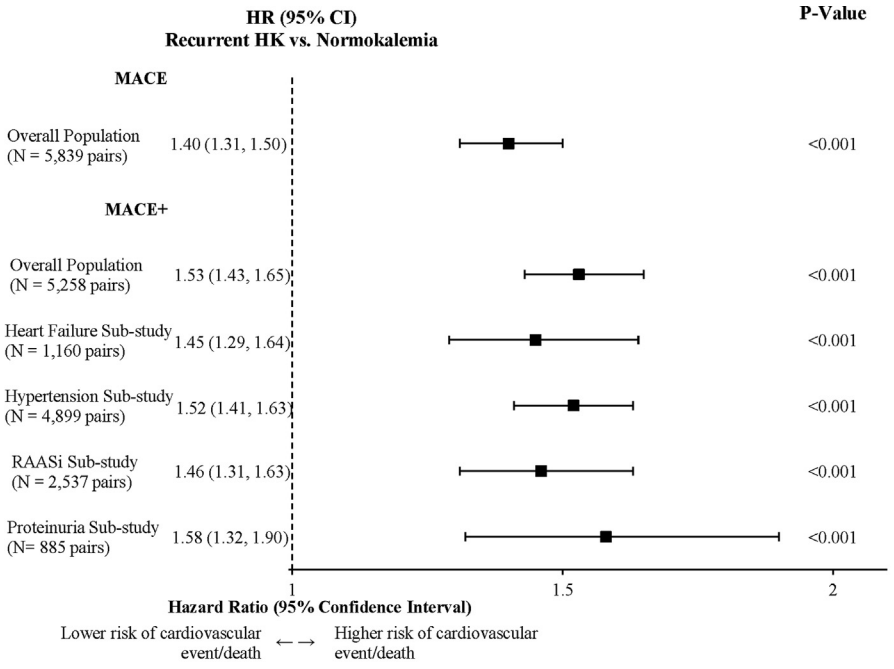
In a matched cohort study, patients with chronic kidney disease and recurrent hyperkalemia experienced significantly higher risks of mortality, major adverse cardiovascular event or hospitalization with heart failure, and inpatient cardiac arrhythmia compared to patients with chronic kidney disease and no-hyperkalemia. CV outcomes included MACE+ and IP cardiac arrhythmia. Proportions in the figures are the proportion of patients with the events at year 5 based on Kaplan-Meier analyses. Funding or this research was provided by AstraZeneca. CKD = chronic kidney disease; CV = cardiovascular; HK = hyperkalemia; IP = inpatient; MACE+ = major adverse cardiovascular events plus (stroke, myocardial infarction or heart failure occurring in the inpatient setting or all-cause mortality); No-HK = normokalemia; rHK = recurrent hyperkalemia.

prevent recurring episodes of HK and potentially severe clinical outcomes.

These study results can inform the management of patients with CKD and CV disorders who use RAASis for disease management. A network meta-analysis of 119 randomized controlled trials evaluating RAASi use in patients with CKD showed that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers decreased the odds of MACE, with angiotensin-converting enzyme inhibitors also reducing the odds of all-cause and CV-related mortality compared with placebo.[20] The occurrence of HK in patients with CKD or HF treated with RAASis is typically managed by dose reduction or more frequently, treatment discontinuation.[17,23,29,30] In a study of patients in Australia with CKD receiving RAASi, the first occurrence of HK led to dose reduction in 10% of patients and discontinuation in 37%.[30] Similarly, in a U.S. EHR study of patients with CKD or HF receiving RAASis at the maximum dose, the rate of RAASi treatment discontinuation after a mild HK event was higher than the rate of dose reduction (22% vs 16%),[29] despite the guideline recommendation to lower the dose rather than halt treatment following an elevation in K+ level.[8] Notably, the rates of dose reduction and discontinuation in the mild HK group were comparable to those in patients with moderate/severe HK (21% and 26%, respectively),[29] implying that even mild HK can cause physicians to change RAASi prescribing practices to prevent CKD and CV disease progression. Among patients with RAASi use at index in this study, recurrent HK was associated with higher risks of RAASi discontinuation compared with normokalemia, which may explain the higher risks of CV outcomes in the recurrent HK cohort. Although we did not assess the impact of RAASi discontinuation on CV outcomes, other investigators have shown that RAASi discontinuation after HK was associated with a higher rate of all-cause mortality compared with treatment persistence (27% vs 17%).[31]

A key strength of this study was that it was designed to minimize reverse causation, which is important as many possible outcomes of HK such as HF are also known to cause HK. The methodology employed here allowed a unidirectional relationship to be established between HK and CV outcomes of

FIGURE 4 HRs and Event Breakdown for MACE and MACE+

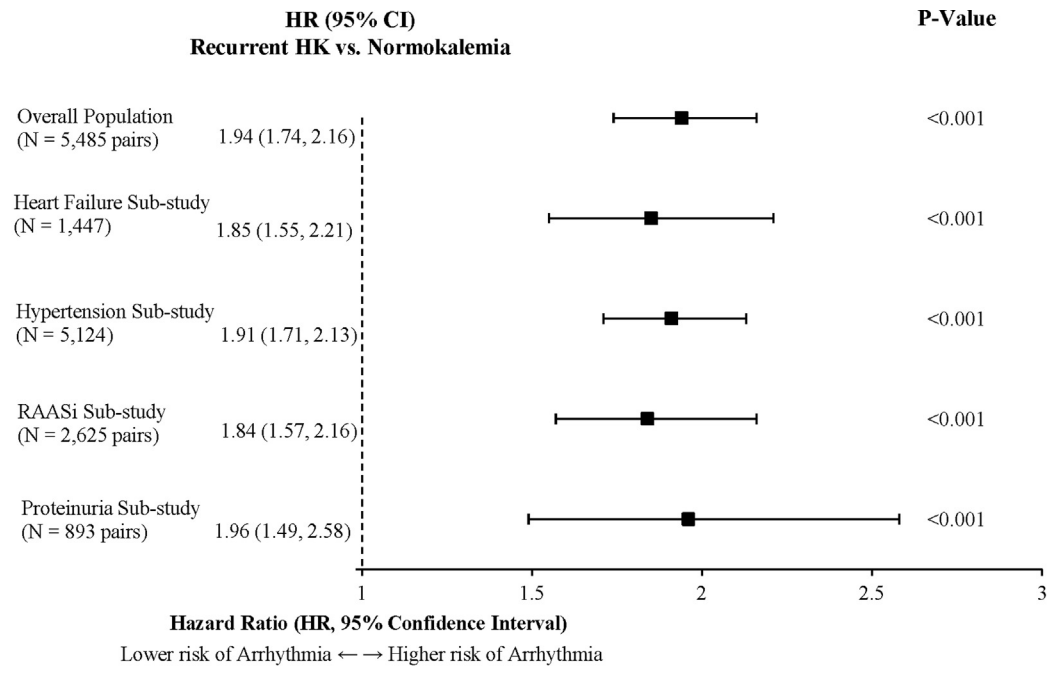


MACE and MACE+ Event Breakdown (Out of Patients with Event)

Outcome	Population (N Patients with Event)	Outcome Component	Recurrent HK	Normokalemia
MACE	Overall (Recurrent HK: 1,804; Normokalemia: 1,280)	Death	1,092 (60.5%)	856 (66.9%)
		Myocardial infarction	393 (21.8%)	203 (15.9%)
		Stroke	348 (19.3%)	232 (18.1%)
MACE+	Overall (Recurrent HK: 1,803; Normokalemia: 1,204)	Heart failure	828 (45.9%)	432 (35.9%)
		Death	673 (37.3%)	585 (48.6%)
		Myocardial infarction	256 (14.2%)	140 (11.6%)
		Stroke	238 (13.2%)	169 (14.0%)
	Heart Failure Sub-study (Recurrent HK: 583; Normokalemia: 436)	Heart failure	362 (62.1%)	212 (48.6%)
		Death	183 (31.4%)	200 (45.9%)
		Myocardial infarction	73 (12.5%)	44 (10.1%)
		Stroke	47 (8.1%)	42 (9.6%)
	Hypertension Sub-study (Recurrent HK: 1,706; Normokalemia: 1,149)	Heart failure	790 (46.3%)	419 (36.5%)
		Death	633 (37.1%)	552 (48.0%)
		Myocardial infarction	246 (14.4%)	136 (11.8%)
		Stroke	221 (13.0%)	161 (14.0%)
	RAASi Sub-study (Recurrent HK: 750; Normokalemia: 530)	Heart failure	373 (49.7%)	207 (39.1%)
		Death	238 (31.7%)	236 (44.5%)
		Myocardial infarction	121 (16.1%)	69 (13.0%)
		Stroke	99 (13.2%)	77 (14.5%)
	Proteinuria Sub-study (Recurrent HK: 291; Normokalemia: 182)	Heart failure	132 (45.4%)	72 (39.6%)
		Death	90 (30.9%)	75 (41.2%)
		Myocardial infarction	53 (18.2%)	24 (13.2%)
		Stroke	48 (16.5%)	26 (14.3%)

HRs and 95% CIs comparing recurrent hyperkalemia and normokalemia cohorts are presented for major adverse cardiovascular events and major adverse cardiovascular event or hospitalization with heart failure in the overall population and heart failure, hypertension, renin-angiotensin-aldosterone system inhibitor, and proteinuria substudies. The distribution of major adverse cardiovascular events and major adverse cardiovascular event or hospitalization with heart failure events are reported by cohort. HK = hyperkalemia; MACE = major adverse cardiovascular event; MACE+ = major adverse cardiovascular events plus hospitalization for heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor.

FIGURE 5 HRs and Event Breakdown for Hospitalized Arrhythmia

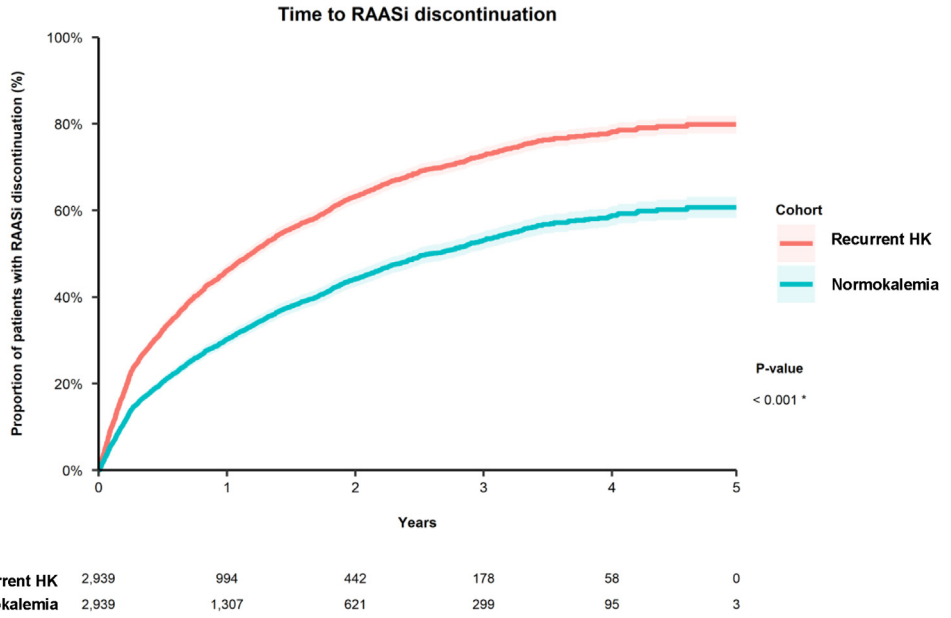


Arrhythmia Event Breakdown (Out of Patients with Event)			
Population (N Patients with Event)	**Outcome Component**	**Recurrent HK**	**Normokalemia**
Overall (Recurrent HK: 919; Normokalemia: 478)	Atrial fibrillation	544 (59.2%)	325 (68.0%)
	Other arrhythmias	488 (53.1%)	222 (46.4%)
Heart Failure Sub-study (Recurrent HK: 354; Normokalemia: 193)	Atrial fibrillation	236 (66.7%)	138 (71.5%)
	Other arrhythmias	170 (48.0%)	92 (47.7%)
Hypertension Sub-study (Recurrent HK: 870; Normokalemia: 459)	Atrial fibrillation	518 (59.5%)	311 (67.8%)
	Other arrhythmias	461 (53.0%)	217 (47.3%)
RAASi Sub-study (Recurrent HK: 412; Normokalemia: 225)	Atrial fibrillation	246 (59.7%)	154 (68.4%)
	Other arrhythmias	228 (55.3%)	102 (45.3%)
Proteinuria Sub-study (Recurrent HK: 149; Normokalemia: 74)	Atrial fibrillation	91 (61.1%)	49 (66.2%)
	Other arrhythmias	72 (48.3%)	37 (50.0%)

HRs and 95% CIs comparing recurrent hyperkalemia and normokalemia cohorts are presented for arrhythmia in the overall population and heart failure, hypertension, renin-angiotensin-aldosterone system inhibitor, and proteinuria substudies. The distribution of arrhythmia events are reported by cohort. HK = hyperkalemia; RAASi = renin-angiotensin-aldosterone system inhibitor.

interest by defining HK status during the baseline period and assessing each CV outcome during follow-up only in patients who did not experience that outcome during baseline. The study design also minimized potential confounding by using a rigorous double-matching method that controlled for baseline CKD stage, eGFR, and other potential confounding factors. Other strengths include the use of an adjudicated and closed claims and EHR database, which provided a rich data set of all encounters covered by multiple payer types including Medicare for many eligible patients. The study sample was thus representative of patients with CKD and recurrent HK or normokalemia in the United States, unlike clinical trial populations. Finally, this is the first real-world study to examine the impact of recurrent HK on CV

FIGURE 6 Median Time to RAASi Discontinuation in the RAASi Substudy



	Total patients	Patients with RAASi discontinuation	Median time to discontinuation (years), 95% CI	Patients with RAASi discontinuation, 95% CI				
				Year 1	Year 2	Year 3	Year 4	Year 5
All patients	5,878	2,622	1.75 (1.68, 1.82)	38.1% (37.1%, 39.1%)	53.7% (52.6%, 54.8%)	63.0% (61.7%, 64.2%)	68.6% (67.1%, 70.1%)	38.1% (37.1%, 39.1%)
Recurrent HK	2,939	1,537	1.19 (1.11, 1.26)	46.1% (44.6%, 47.6%)	63.3% (61.5%, 64.9%)	72.7% (71.0%, 74.4%)	78.2% (76.3%, 80.0%)	NA
Normokalemia	2,939	1,085	2.57 (2.39, 2.87)	30.3% (28.8%, 31.7%)	44.2% (42.4%, 46.0%)	53.1% (51.0%, 55.1%)	58.9% (56.6%, 61.0%)	60.8% (58.2%, 63.1%)

Median time to renin-angiotensin-aldosterone system inhibitor discontinuation in patients with renin-angiotensin-aldosterone system inhibitor use was compared between patients with recurrent hyperkalemia and those with normokalemia. HK = hyperkalemia; RAASi = renin-angiotensin-aldosterone system inhibitor.

outcomes and all-cause mortality in patients with later-stage CKD, including those with additional cardiorenal risk.

STUDY LIMITATIONS. The main limitation of this study is that the claims data set lacked some variables of interest. Clinical and laboratory values related to CV and renal status were unavailable, including ejection fraction, natriuretic peptide levels, electrocardiogram readings, CKD etiology, and cause of death. A second limitation is that UACR was available for only ~30% of patients in the overall sample, which reduced the number of matched pairs in the proteinuria substudy. Finally, continuous enrollment in a health plan was an inclusion criterion for the study sample; patients who did not meet this requirement—ie, because of a change in employment status—were excluded. If the demographic or clinical characteristics of excluded patients differed from those of the overall population, then the results may not be generalizable. However, this is not expected to affect the study findings given that the required period of continuous enrollment was relatively short.

CONCLUSIONS

Recurrent HK in patients with stage 3 or 4 CKD increased the risk of all-cause mortality and CV outcomes compared with normokalemia. The same was observed in the substudies of patients with HF, hypertension, RAASi use, and proteinuria. These results highlight the importance of long-term monitoring and early and appropriate treatment of HK in patients

with later-stage CKD to prevent HK recurrence and severe clinical outcomes.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Long-term monitoring and early and appropriate treatment of HK in patients with later-stage CKD is warranted to prevent HK recurrence and severe clinical outcomes.

TRANSLATIONAL OUTLOOK: This study found that HK was associated with higher risks of CV outcomes and mortality compared with normokalemia in patients with CKD who were using RAASi, but additional studies are needed to determine whether treatment of HK decreases the risk of these outcomes.

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KEY WORDS administrative claims study, chronic kidney disease, heart failure, hypertension, major adverse cardiovascular events, normokalemia, proteinuria, recurrent hyperkalemia, renin-angiotensin-aldosterone inhibitor

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.