Kidney Medicine

Hyperkalemia Incidence in Patients With Non-Dialysis Chronic Kidney Disease: A Large Retrospective Cohort Study From United States Clinical Care

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Rationale & Objective: Estimates of the incidence of hyperkalemia in patients with chronic kidney disease (CKD) vary widely. Our objective was to estimate hyperkalemia incidence in patients with CKD from routine clinical care, including by level of kidney damage or function and among important patient subgroups.

Study Design: Retrospective cohort study.

Setting & Participants: 1,771,900 patients with stage 1-4 CKD identified from the US Optum De-Identified electronic health records database.

Exposures or Predictors: Impaired kidney damage or function level at baseline based on urinary albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), respectively, and selected patient subgroups.

Outcomes: Hyperkalemia: 2 elevated serum potassium values (≥5.5 mmol/L) from the inpatient setting (2-24 hours apart) or outpatient setting (maximum 7 days apart), or 1 elevated serum potassium value plus pharmacotherapy initiation or hyperkalemia diagnosis (maximum 3 days apart).

Analytical Approach: Incidence rates of hyperkalemia were calculated. Estimates were stratified by UACR and eGFR level at baseline and patient subgroups.

Results: Over a mean follow-up of 3.9 years, the incidence of hyperkalemia was 3.37 events/100 person-years (95% confidence intervals, 3.36-3.38). Higher incidence rates were observed with increased UACR and lower eGFR. Highest rates were observed with UACR ≥3,500 (up to 19.1/100 person-years) irrespective of decreased eGFR level. High rates also occurred in patients with type 2 diabetes mellitus (T2DM, 5.43/100 person-years), heart failure (8.7/100 person-years), and those prescribed steroidal mineralocorticoid receptor antagonists (sMRAs, 7.7/100 person-years).

Limitations: Potential misclassification of variables from possible medical coding errors; potential data incompleteness issues if patients received care at institutions not included in Optum.

Conclusions: Hyperkalemia is a frequent occurrence in CKD, particularly in patients with T2DM, heart failure, or prescribed sMRAs, indicating the need for regular serum potassium and UACR monitoring in this patient population to help mitigate risk.

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Chronic kidney disease (CKD) is a significant cause of morbidity and mortality worldwide and by 2040 is projected to be the fifth global leading cause of years of life lost.[1,2] Hyperkalemia commonly develops in patients with impaired kidney function as a consequence of reduced potassium excretion[3,4] and is associated with more frequent hospitalizations, mortality, and potentially further renal decline.[5,6] Furthermore, the increased risk of hyperkalemia in patients using renin-angiotensin-aldosterone system inhibitors—the cornerstone of pharmacotherapy in slowing disease progression in patients with CKD—is well established.[7] Concerns about the actual or potential occurrence of hyperkalemia commonly leads to down-titration or discontinuation of these guideline-directed medications, which in turn is associated with worse clinical outcomes,[4,8] making long-term patient management challenging.

It is estimated that hyperkalemia occurs in approximately 12%-18% of patients with CKD[3] and up to 73% of patients with advanced CKD.[5] However, estimates outside the clinical trial setting vary widely in the literature depending on both the definition of hyperkalemia used and the profile of the patient population.[9] Additionally, estimates by level of kidney function (ie, estimated glomerular filtration rate [eGFR]) and, in particular, kidney damage (ie, albuminuria) from within the same study population, from real-world studies, are limited. Further information is therefore needed on this topic, including how estimates vary between patients with comorbid diabetes or heart failure, which are themselves risk factors for hyperkalemia and commonly occur in patients with CKD.[6,10-12] Aging populations and an increase in CKD risk factors (such as hypertension and obesity) have led to a growing number of patients with CKD worldwide, and this will inevitably lead to a corresponding increase in hyperkalemia.[13] This underscores the importance of building the knowledge base on this topic to help identify patients at high risk of developing hyperkalemia and guide appropriate patient management strategies. Therefore, we conducted a large population-based study that aimed to estimate the risk of hyperkalemia among patients with stage 1-4 CKD in clinical practice in the United States. The primary objectives were to estimate the incidence of hyperkalemia in patients with

PLAIN-LANGUAGE SUMMARY

People with chronic kidney disease (CKD) have a higher risk of illness, hospitalization, and death than those without CKD. Medicines that are commonly used to slow down CKD progression can sometimes lead to hyperkalemia, where levels of potassium in the blood are higher than normal and which can be potentially dangerous. Concerns about hyperkalemia have led some people with CKD to stop taking their medication. Our study of 1.7 million patients from the United States found that patients with severe kidney damage, as well as those with type 2 diabetes mellitus or heart failure, have a higher risk of hyperkalemia than other patients, indicating they are priority groups for having their potassium levels and level of kidney damage checked regularly.

stage 1-4 CKD, including by CKD stage, by eGFR, by urinary albumin-creatinine ratio (UACR), and among selected patient subgroups (including those with known hyperkalemia risk factors). A secondary objective was to evaluate the effect of changing the definition of hyperkalemia on these estimates.

METHODS

Study Design and Data Sources

This was a retrospective cohort study using data from the US Optum De-Identified electronic health records database, which holds patient-level longitudinal information for ~97 million individuals (either commercially insured, Medicare and Medicaid enrollees, or uninsured) of all ages seen at ~700 hospitals and ~7,000 clinics across the United States. Medical diagnoses are entered using *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (*ICD-9/10-CM*) codes, and medical procedures are entered using either *ICD-9/10* procedure codes, Current Procedural Terminology 4 or Healthcare Common Procedure Coding System codes. Prescriptions issued, hospital-administered medication, and self-reported over-the-counter medication use are also captured, and the data has particularly rich coverage of laboratory investigation results. The use of the Optum clinical electronic health record database was reviewed by the New England Institutional Review Board and was determined to be exempt from board approval because this research project did not involve human subjects research and only contains de-identified health information as described by the Health Insurance Portability and Accountability Act Privacy Rule. No direct identifiers of individuals, employers, households, or providers are included.[14]

Study Cohort

The study cohort included individuals aged ≥18 years with CKD stage 1-4 between January 1, 2009 and December 31, 2020, which was defined as ≥2 eGFR measurements of 15-60 mL/min/1.73 m^2 and/or ≥2 UACR measurements ≥30 mg/g, which were recorded between 90 and 365 days apart; the date of the second qualifying measurement was deemed confirmatory and set as the index date. eGFR and UACR measurements between the 2 qualifying measurements were required to be consistent (ie, most values must have fulfilled the same conditions). The time span of 90 to 365 days was based on KDIGO (Kidney Disease: Improving Global Outcomes) criteria that CKD is defined as abnormalities of kidney structure or function that are present for ≥3 months.[15] Of note, feasibility analyses showed that for 99.99% of the eGFR values, there was also a creatinine laboratory value reported on the same day. We therefore used the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula to calculate eGFR values from reported creatinine laboratory values and disregarded pre-calculated eGFR values to ensure a consistent eGFR definition.[16] Previous research has shown that patients with durable, pathological eGFR, UACR, or creatinine values, indicating impaired kidney function, commonly lack a respective diagnosis code for kidney disease, which illustrates the problem of CKD being a much underdiagnosed disease.[17-19] This provided the rationale for identifying patients with CKD from eGFR and UACR values and not CKD codes. Patients were also required to have ≥365 days of database activity before the index date. Patients with evidence of kidney failure, previous hemodialysis, or kidney transplantation (relevant code any time before the index date) were excluded. The overall study design is illustrated in Fig 1, and a flowchart depicting identification of the CKD study cohort is shown in Fig 2.

Chronic Kidney Disease Stage

We used eGFR and UACR measurements to calculate CKD stage at the index date in line with KDIGO guidelines,[15] using the closest recorded values from 1 year before the index date up to 14 days after. CKD stages were defined as follows: stage 1, index eGFR ≥90 mL/min/1.73 m^2 and index UACR ≥30 mg/g; stage 2, index eGFR ≥60 to <90 mL/min/1.73 m^2 and index UACR ≥30 mg/g; stage 3, index eGFR ≥30 to <60 mL/min/1.73 m^2; stage 4, index eGFR ≥15 to <30 mL/min/1.73 m^2. Level of impaired kidney function at baseline was categorized according to the index eGFR value (mL/min/1.73 m^2) as follows: G1, normal or high (≥90); G2, mildly decreased (60-89); G3a, mildly-moderately decreased (45-59); G3b, moderately-severely decreased (30-44); G4, severely deceased (15-29); G5, kidney failure (<15). Level of kidney damage at baseline was categorized according to the index UACR value (mg/g) as follows: A1, normal to mildly increased (<30); A2-1, moderately increased (30-200); A2-2, moderately increased (200-300); A3-1, severely increased (300-3,500); A3-2, severely increased (≥3,500).

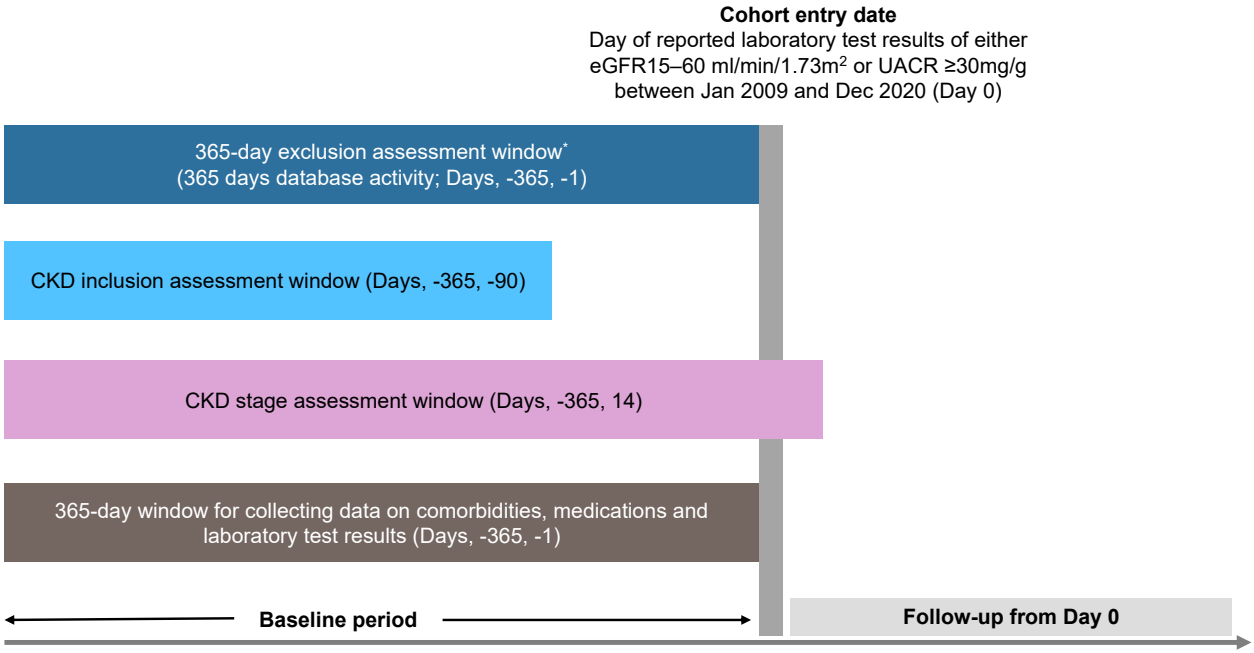

Figure 1. Depiction of the overall study design. *Exclusion criteria were not having ≥365 days database activity and/or evidence of kidney failure, previous hemodialysis, or kidney transplantation (relevant code any time before the index date [date of the second qualifying and confirmatory measurement]). Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

CKD Subgroups

We identified the following subgroups from the CKD cohort: patients with type 2 diabetes mellitus (T2DM), without T2DM or type 1 diabetes mellitus, patients with heart failure, patients prescribed steroidal mineralocorticoid receptor antagonists (sMRAs), patients prescribed

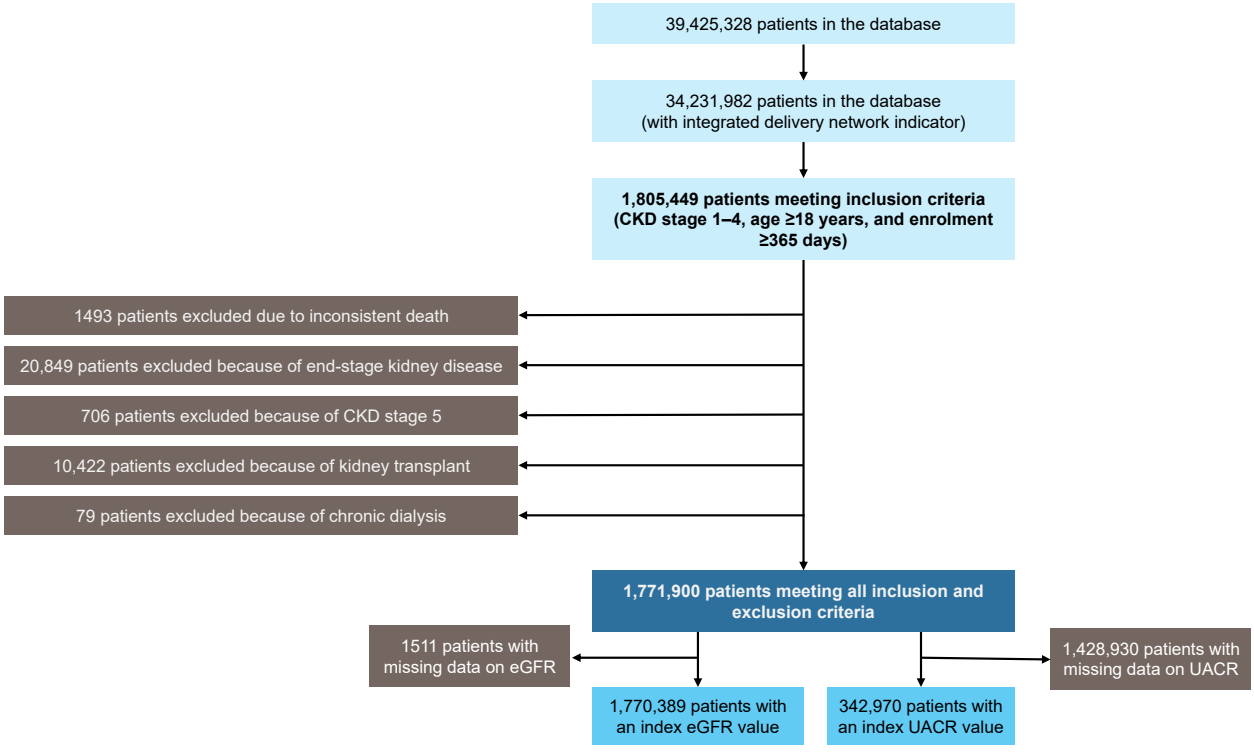

Figure 2. Flowchart depicting identification of the study cohort. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

renin angiotensin system inhibitors, and patients prescribed sodium/glucose cotransporter 2 inhibitors. Further details on the identification of the CKD subgroups can be found in Item S1.

Follow-up and Identification of Hyperkalemia Events

The CKD cohort was followed from the day after the index date until the end of data collection, the date the patient disenrolled, death, or the end of the study period (September 30, 2021), whichever came first. We defined an episode of hyperkalemia in 2 ways: either (1) 2 elevated inpatient serum potassium values (≥5.5 mmol/L) from the inpatient setting ≤2-24 hours apart or from the outpatient setting ≤7 days apart, or (2) 1 elevated serum potassium value plus either initiation of pharmacotherapy (eg, with intravenous calcium or insulin-glucose, nebulized albuterol, potassium binders) or diagnostic code for hyperkalemia ≤3 days apart. The date of the second event was defined as the date of hyperkalemia. We recorded all hyperkalemia events during the patient's follow-up with the assumption that those recorded within 7 days of each other referred to the same hyperkalemia event.

Patient Variables and Statistical Analysis

This was a descriptive study with no pre-specified hypotheses. We extracted information on patient demographics at the index date and information on comorbid conditions, medications prescribed, and clinical laboratory measurements (serum potassium and serum creatinine) recorded during the 365 days before the index date. Baseline characteristics of the CKD cohort and of each CKD subgroup were described using frequency counts and percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. For the time-to-first event analysis, we calculated incidence rates of hyperkalemia, expressed as events per 100 person-years; 95% confidence intervals (CIs) were determined using the Poisson distribution. Cumulative incidence curves with 95% CIs were produced using the Aalen-Johnsen estimator. We performed sensitivity analyses based on various modifications of the definition of a hyperkalemia event. First, we changed the qualifying serum potassium threshold to be 5.0 mmol/L. Second, a hyperkalemia event was redefined as a record of one inpatient/outpatient diagnosis of hyperkalemia. Third, it was specified as a record of ≥1 serum potassium measurement >5.5 mmol/L in an inpatient or outpatient record or the prescription of a potassium binder (sodium polystyrene sulfonate, calcium polystyrene sulfonate, sodium zirconium cylosilicate, or patiromer), or one inpatient or outpatient diagnosis of hyperkalemia. In a secondary analysis, we performed Cox proportional hazards regression adjusted for confounders (to identify independent risk factors for hyperkalemia for comparison with our descriptive analyses). Lastly, in a post hoc analysis, we explored hyperkalemia incidence rates according to ethnicity. Analyses were undertaken using R version 3.6.2 (R Core Team, 2022) using packages rms (version 6.3.0) and survival (version 3.4.0).[20]

RESULTS

CKD Cohort

A total of 1,771,900 patients met the inclusion criteria and were included in the CKD cohort; the median age was 75 years (IQR, 66-80), and 57.7% were female. Baseline comorbid conditions, medication use, and other characteristics are shown in Table 1. Median eGFR and UACR values were 47.9 mL/min/1.7 m^2 and 38 mg/g, respectively. eGFR values were available for 1,770,389 (>99.9%) patients, and UACR values were available for 342,970 (19.4%) patients. Data were missing on eGFR for 1,511 (<0.1%) patients and on UACR for 1,428,930 (80.6%) patients. The frequency distribution of UACR category according to eGFR category is shown in Table S1. Hypertension was the most prevalent comorbid condition occurring in 68.5% of the cohort; other commonly recorded conditions were hyperlipidemia (55.1%), T2DM (34.2%), and gastrointestinal disease (32.3%). Antihypertensives were the most prescribed medications (69.3%) followed by statins (45.7%) and antiarrhythmics (45.6%). Characteristics of the disease-related subgroups are shown in Table S2.

Hyperkalemia Events

During a mean follow-up of 3.9 years (median 3.5 years, IQR 1.7-5.8), 12.4% of the CKD cohort experienced ≥1 episode of hyperkalemia, among whom 69.3% experienced 1 event, 17.5% 2 events, and 13.2% ≥3 events. The incidence rate of hyperkalemia among the entire CKD cohort was 3.37 (95% CI, 3.36-3.38) events per 100 person-years. Higher incidence rates of hyperkalemia were observed with lower eGFR and with increased UACR values (Table 2, Fig 3), with the highest incidence rates observed in patients with UACR ≥3,500 largely irrespective of level of decreased eGFR (8.68-19.09/100 person-years; Table 3). In subgroup analyses (Table 4), higher incidence rates of hyperkalemia were seen among patients diagnosed with T2DM (5.43/100 person-years; 95% CI, 5.40-5.4), heart failure (8.7/100 person-years, 95% CI, 8.6-8.8), those with renin angiotensin system inhibitor use (4.03/100 person-years; 95% CI, 4.0-4.1), and those with sMRA use (7.66/100 person-years; 95% CI, 7.6-7.8) at baseline; cumulative incidence rates during follow-up are shown in Fig 4. The aforementioned findings were supported by results of the

Table 1. Baseline Characteristics of the CKD Study Cohort (N = 1,771,900)

Characteristic	N = 1,771,900
Demographics	
Age in years, median (IQR)	75 (66-80)
Females	1,022,051 (57.7%)
Ethnicity	
White	1,484,694 (83.8%)
African American	173,767 (9.8%)
Asian	20,053 (1.1%)
Other/missing	93,386 (5.3%)
Comorbid conditions	
Hypertension	1,213,878 (68.5%)
Hyperlipidemia	975,563 (55.1%)
Type 2 diabetes	605,099 (34.2%)
Gastrointestinal disease	571,947 (32.3%)
Coronary artery disease	426,000 (24.0%)
Heart failure	304,883 (17.2%)
Obesity	283,215 (16.0%)
Medications	
Antihypertensives	1,228,357 (69.3%)
Statins	810,065 (45.7%)
Antiarrhythmics	803,537 (45.4%)
Antiplatelets	565,003 (31.9%)
Anticoagulants	550,912 (31.1%)
Oral antidiabetics	446,953 (25.2%)
Index eGFR category, mL/min/1.73 m^2[a]	
G1, normal or high (≥90)	23,392 (1.3%)[a]
G2, mildly decreased (60-89)	40,385 (2.3%)[a]
G3a, mildly-moderately decreased (45-59)	989,091 (55.9%)[a]
G3b, moderately-severely decreased (30-44)	535,705 (30.3%)[a]
G4, severely deceased (15-29)	181,588 (10.3%)[a]
G5, kidney failure (<15)	228 (0.01%)[a,b]
Median (IQR) in mL/min/1.73 m^2	47.86 (38.93-54.46)[a]
Index UACR category, mg/g[b]	
A1 (normal to mildly increased [<30])	148,275 (43.2%)[c]
A2-1 (moderately increased [30-200])	127,732 (37.2%)[c]
A2-2 (moderately increased [200-300])	14,710 (4.3%)[c]
A3-1 (severely increased [300-3,500])	49,602 (14.5%)[c]
A3-2 (severely increased [≥3,500])	2,651 (0.8%)[c]
Median (IQR) in mg/g)	38 (12-132)[c]
Laboratory measurements	
Serum potassium in mmol/L, median (IQR)	4.3 (4.0-4.6)
Serum creatinine in mg/dL, median (IQR)	1.27 (1.09-1.5)

Note: Data are n (%) unless otherwise specified.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; UACR, urinary albumin-creatinine ratio.
[a]N = 1,770,389 patients had available eGFR information at the index date (note, 1,511 patients had missing data for eGFR).
[b]For each patient, their index eGFR value, index UACR value, and index CKD stage were assigned based on the laboratory value of the confirmatory event or the laboratory value closest to the index date during the baseline period or up to 14 days into the follow-up period. In some instances, in which patients were indexed based on 2 qualifying UACR values, the eGFR value closest to the index date was <15 mL/min/1.7 m^2 but, otherwise, they did not satisfy the exclusion criteria.
[c]N = 342,970 patients had available UACR information at the index date (note, 1,428,930 patients had missing data for UACR).

Cox regression analysis, after adjusting for confounders (Fig S1). Incidence rates of hyperkalemia were higher in each of the 3 sensitivity analyses, ranging from 9.39/100 person-years to 18.81/100 person-years (Table S3). In the post hoc analysis, the incidence of hyperkalemia was notably higher among patients of African American ethnicity (8.0/100 person-years; 95% CI, 7.9-8.2) than those of Asian (5.5/100 person-years; 95% CI, 5.2-5.9) or White (4.9/100 person-years; 95% CI, 4.9-5.0) ethnicity. Results of the multivariable adjusted Cox regression analysis confirmed African American ethnicity as an independent risk factor for hyperkalemia (Fig S1).

DISCUSSION

In this contemporary population-based study, we showed that hyperkalemia, specifically serum potassium >5.5 mmol/L, is a frequent occurrence in patients with CKD in routine US clinical care, and although its occurrence is notably higher in patients with reduced eGFR and elevated UACR, it is highest in those with severe albuminuria largely irrespective of their eGFR level. Furthermore, we observed that hyperkalemia occurs more frequently in patients with T2DM, heart failure, and those using sMRAs.

The incidence rate of hyperkalemia found in our CKD population (3.4 events/100 person-years) is similar to that reported by Jun et al,[21] who reported an incidence rate of 3.1/100 person-years among 20,184 adults with CKD (mean age 76.9 years) from general practice in Australia over a comparable follow-up time (median 3.9 years). Comparisons with other studies on this topic are more limited because of greater differences in the study population, follow-up duration, definition of hyperkalemia used, and how its occurrence was measured. Indeed, changing the definition of hyperkalemia in sensitivity analyses showed a doubling in the observed rate when applying the least restrictive definition. In their meta-analysis of observational studies, Humphrey et al[9] estimated the pooled mean prevalence of hyperkalemia among non-dialysis adult cohorts to be 8.9% when using a definition of serum potassium ≥5.5 mmol/L for hyperkalemia and 8.5% when using any hyperkalemia definition. Previous studies are consistent in reporting a higher incidence of hyperkalemia observed with decreasing eGFR[21-27] and increasing albuminuria[23,28] among patients with CKD. Our observation that the highest occurrence of hyperkalemia occurs in patients with severe albuminuria, largely irrespective of eGFR level, underscores the value of regular UACR monitoring in patients with CKD to evaluate hyperkalemia risk—a practice that is currently suboptimal.[29-31] Furthermore, this would help to guide the most appropriate management strategy for the individual (eg, a low potassium diet or use of potassium binders) to lower their serum

Table 2. Incidence Rates of Hyperkalemia in the CKD Cohort According to CKD Stage, eGFR Category, and Albuminuria Category

	Total (N)	Hyperkalemia Event, (%)	Cumulative Incidence, % (95% CI)	Incidence Rate per 100 Person-years (95% CI)
Total CKD cohort	1,771,900	220,339 (12.4%)	28.1% (27.7%-28.4%)	3.37 (3.4-3.4)
eGFR category (mL/min/1.73 m^2)	1,770,389			
G1, normal or high (≥90)	23,392	1,451 (6.2%)	18.3% (16.4%-20.2%)	1.32 (1.3-1.4)
G2, mildly decreased (60-89)	40,385	4,405 (10.9%)	28.2% (26.6%-29.8%)	2.48 (2.4-2.6)
G3a, mildly-moderately decreased (45-59)	989,091	94,170 (9.5%)	22.0% (21.6%-22.3%)	2.39 (2.4-2.4)
G3b, moderately-severely decreased (30-44)	535,705	79,090 (14.8%)	34.2% (33.6%-34.9%)	4.31 (4.3-4.3)
G4, severely decreased (15-29)	181,588	40,995 (22.6%)	52.6% (50.9%-54.3%)	8.80 (8.7-8.9)
G5, kidney failure (<15)	228	62 (27.2%)	74.9% (0.0%-93.9%)	9.37 (7.2-12.0)
Albuminuria category (mg/g)	342,970			
A1, normal to mildly increased (<30)	148,275	16,449 (11.1%)	25.0% (24.1%-25.9%)	2.52 (2.5-2.6)
A2-1, moderately increased (30-200)	127,732	16,807 (13.2%)	30.6% (29.6%-31.5%)	3.19 (3.2-3.2)
A2-2, moderately increased (200-300)	14,710	2,380 (16.2%)	40.4% (36.8%-43.8%)	4.15 (4.0-4.3)
A3-1, severely increased (300-3,500)	49,602	11,590 (23.4%)	52.7% (50.6%-54.8%)	6.70 (6.6-6.8)
A3-2, severely increased (≥3,500)	2,651	982 (37.0%)	77.3% (62.1%-86.4%)	13.81 (13.0-14.7)

Note: CKD stages, based on KDIGO guidelines,[15] were as follows: stage 1, index eGFR ≥90 and index UACR ≥30; stage 2, index eGFR ≥60 to <90 and index UACR ≥30; stage 3, index eGFR ≥30 to <60; stage 4, index eGFR ≥15 to <30.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urinary albumin-creatinine ratio.

potassium level and mitigate the risk of developing a potentially life-threatening arrhythmia.[32,33] Although we can postulate this could be because of factors such as inflammation, potassium homeostasis or retention, or tubular dysfunction; further research is needed to investigate this.

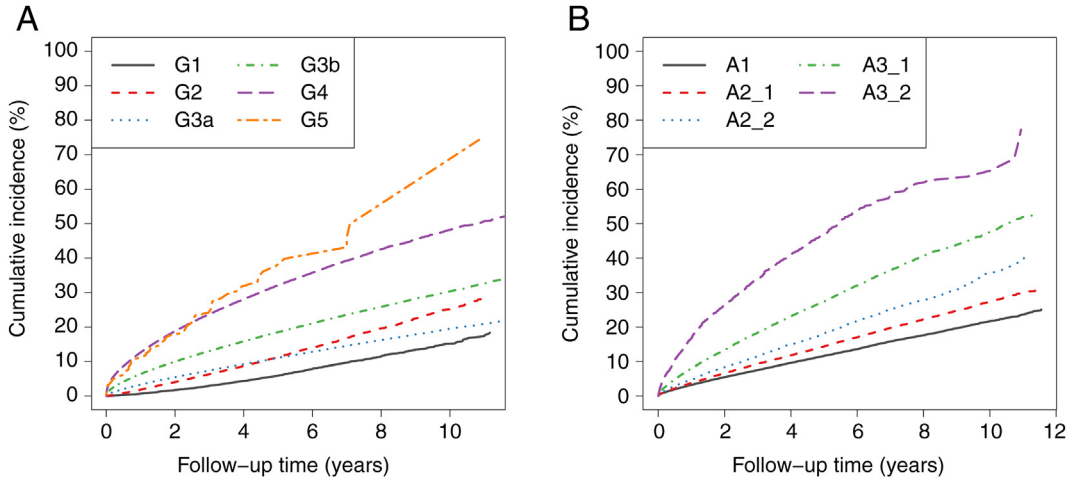

Figure 3. Cumulative incidence of hyperkalemia episodes in the CKD cohort according to (A) eGFR category and (B) albuminuria category. Note: eGFR categories (mL/min/1.73 m^2) at the index date were as follows: G1, normal/high ≥90; G2, mildly decreased 60-89; G3a, mildly-moderately decreased (45-59); G3b, moderately-severely decreased (30-44); G4, severely deceased (15-29); G5, kidney failure (<15). Albuminuria categories were based on index UACR values (mg/g) as follows: A1, normal to mildly increased (<30); A2-1, moderately increased (30-200); A2-2, moderately increased (200-300); A3-1, severely increased (300-3,500); A3-2, severely increased (≥3,500). Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 3. Heat Map Displaying Incidence Rates of Hyperkalemia per 100 Person-years According to eGFR and UACR Categories (Based on KDIGO Classification)

			Persistent Albuminuria Category Description and Range				
			A1	A2a	A2b	A3a	A3b
			Normal to Mildly Increased	Moderately Increased		Severely Increased	
eGFR Category (mL/min/1.73 m²)			<30 mg/g	30-200 mg/g	200-300 mg/g	300-3,500 mg/g	>3,500 mg/g
			Incidence Rate (95% CI) per 100 Person-years				
G1	Normal or high	≥90	—[a]	1.03 (0.97-1.11)	1.41 (1.18-1.67)	2.27 (2.07-2.48)	6.14 (3.85-9.30)
G2	Mildly decreased	60-89	—[a]	2.05 (1.97-2.13)	2.47 (2.22-2.75)	3.99 (3.78-4.21)	8.68 (6.57-11.25)
G3a	Mildly-to-moderately decreased	45-59	2.08 (2.04-2.12)	3.45 (3.37-3.53)	4.81 (4.50-5.13)	6.45 (6.24-6.65)	12.07 (10.67-13.61)
G3b	Moderately to severely decreased	30-44	3.24 (3.15-3.32)	5.08 (4.93-5.23)	6.29 (5.82-6.79)	9.24 (8.94-9.55)	14.46 (12.90-16.17)
G4	Severely decreased	15-29	5.51 (5.23-5.80)	7.79 (7.43-8.16)	8.49 (7.55-9.51)	12.42 (11.93-12.93)	19.1 (17.04-21.31)
G5	Kidney failure	<15	—[a]	6.05 (3.39-9.98)	8.53 (2.32-21.84)	11.87 (8.32-16.44)	11.06 (4.45-22.79)

Note: Increasing color intensity reflects higher risk of hyperkalemia.
Abbreviations: eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urinary albumin-creatinine ratio.
[a]No or insufficient data.

Consistent with previous reports is the higher hyperkalemia rates among members of our CKD cohort with T2DM,[21,22,24,25,34,35] heart failure,[21,22,35] and those prescribed sMRAs.[36-38] This also has clinical relevance because, in line with the literature,[10] diabetes and heart failure were common comorbid conditions in our CKD cohort, and it underscores the importance of routine serum potassium monitoring in these patients. With regard to sMRAs, it is well established that the potassium sparing effect of both spironolactone and eplerenone is the main factor limiting their wider use for cardiorenal protection.[39] With regard to the interesting finding from our post hoc analysis—that hyperkalemia incidence was notably higher in CKD patients of African American ethnicity than those of Asian or White ethnicity—we are unaware of other studies that have undertaken similar analyses; further data from other studies would be needed to decipher whether this patient population also represents a high-risk group.

Our study adds to the knowledge base in this field by means of evaluating the risk of hyperkalemia in a large real-world cohort of patients with stage 1-4 CKD (defined by eGFR and UACR KDIGO categories) undergoing routine clinical care, including the elderly and those with common comorbid conditions. Although other studies have evaluated hyperkalemia in specific CKD populations, the identification of important patient subgroups from within the same CKD cohort in our study enabled valid intergroup comparisons of hyperkalemia occurrence to be made. Our findings are generalizable to the US general population because the database includes patients who are representative of different geographical areas and covers commercially insured, Medicare and Medicaid enrollees, and uninsured patients. In addition, the inclusion of clinical data and high coverage of potassium and other laboratory measurements in the database (as opposed to relying solely on billing codes) make Optum electronic health records a suitable data source to study our research questions. We acknowledge, however, that UACR measurements were only available for a subset of patients in our CKD study cohort, and this was also the reason for the relatively low number of patients identified with CKD stage 1 or stage 2. Other limitations include potential misclassification of study variables because of possible coding errors and potential data incompleteness issues where patients may have received care at institutions not included in Optum electronic health records. Further, we cannot be sure that patients took their prescribed medications. However, there is no reason to believe that any of the abovementioned limitations will lead to misclassification of covariates in a differential manner across the study period or between patient groups.

In conclusion, our findings suggest that UACR levels are an important factor in hyperkalemia risk stratification, in addition to eGFR levels and other known risk factors. Moreover, they underscore the importance of routinely

Table 4. Incidence Rates of Hyperkalemia by CKD Subgroup

CKD Cohort/Subgroup	Hyperkalemia Events (%)	Cumulative Incidence, % (95% CI)	Incidence Rate per 100 Person-years (95% CI)
CKD with T2DM (N = 524,997)	96,266 (18.3%)	39.6% (39.0%-40.2%)	5.43 (5.40-5.47)
CKD without T2DM (N = 1,231,134)	119,739 (9.7%)	23.3% (22.9%-23.7%)	2.54 (2.53-2.56)
CKD with heart failure (N = 273,635)	54,825 (20.0%)	49.1% (47.4%-50.6%)	8.70 (8.62-8.77)
CKD prescribed sMRAs (N = 118,914)	24,558 (20.7%)	42.7% (40.9%-44.4%)	7.66 (7.57-7.76)
CKD prescribed with RASi (N = 863,183)	122,990 (14.3%)	31.5% (31.0%-32.0%)	4.03 (4.01-4.06)
CKD prescribed SGLT2is (N = 15,595)	1,562 (10.0%)	20.8% (18.5%-22.9%)	3.89 (3.70-4.09)
Total CKD cohort (N = 1,771,900)	220,339 (12.4%)	28.1% (27.7%-28.4%)	3.37 (3.36–3.38)

Note: N refers to the number of patients available for follow-up.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; RASi, renin angiotensin system inhibitor; SGLTi, sodium/glucose cotransporter 2 inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist; T2DM, type 2 diabetes mellitus.

monitoring both UACR and serum potassium levels in patients with CKD in clinical practice to help mitigate the development of hyperkalemia; particular attention should focus on patients with T2DM, heart failure, or prescribed sMRAs. Further studies are needed to study the associations between hyperkalemia and clinical outcomes in this patient population.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Multivariable adjusted Cox regression analysis for the association between patient variables and hyperkalemia.

Item S1: Methods: Identification of CKD Subgroups.

Table S1: Frequency Distribution of UACR Category According to eGFR Category.

Table S2: Baseline Characteristics of the CKD Subgroups.

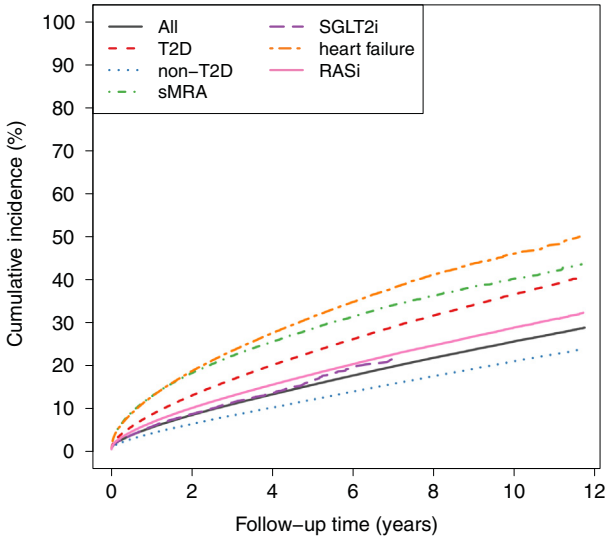

Figure 4. Cumulative incidence of hyperkalemia episodes in the total CKD cohort and CKD subgroups. Abbreviations: CKD, chronic kidney disease; DKD, diabetic kidney disease; RASi, renin angiotensin system inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist; SGLT2i, sodium/glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

Table S3: Incidence Rates of Hyperkalemia in Sensitivity Analyses (Changing Definition of Hyperkalemia From the Definition Used in the Main Analysis).

ARTICLE INFORMATION

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