Incidence of and Risk Factors for Hyperkalemia in Adults in the UK

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*At the time of the study

Introduction

- Hyperkalemia (HiK) is a potentially life-threatening electrolyte abnormality characterized by elevated serum potassium (K^+) concentrations[1]
- The severity of HiK increases as the serum K^+ concentration increases above normal[2,3]
- HiK frequently occurs in patients with progressive renal disease[2,3]
- Few studies have evaluated the incidence or prevalence of HiK, and published studies are generally limited to select patient populations. Estimates on the frequency of HiK vary based on the definition of HiK applied and patient characteristics, including comorbidities and medication use[4–6]
- Here, we report results from a retrospective, population-based analysis characterizing the incidence of and associated risk factors for incident HiK events among English patients seeking health care in a primary care setting

Methods

- Retrospective cohort and case-control analyses were conducted using patient data from the Clinical Practice Research Datalink (CPRD) database linked to the Hospital Episode Statistics (HES) database
  - CPRD is an electronic primary care database of >11 million anonymous longitudinal medical records across the UK and has established linkages to HES.[7] HES provides information on hospital/emergency department admissions and outpatient appointments at National Health Service hospitals in England[8]

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Aged ≥18 years • Record in linked CPRD/HES dataset • Incident HiK event (first occurrence of HiK event) defined as READ diagnosis code or a serum K^+ laboratory result ≥5.0 mmol/L in CPRD or ICD-10 codes for HiK in HES between 1/1/2009 and 12/31/2013	• Serum K^+ laboratory value ≥10.0 mmol/L • <365 days of observation time between the incident HiK event date and the current registration or up to standard dates • History of HiK before 1/1/2009 • Active cancer • Recent history of volume depletion/dehydration

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HiK, hyperkalemia; ICD-10, International Classification of Diseases, 10th Revision; K^+, potassium.

- Incident HiK events were stratified by severity and defined as:
  - K 5.0–≤5.5: serum K^+ concentration 5.0–≤5.5 mmol/L or CPRD diagnosis code for HiK with no laboratory results
  - K >5.5–≤6.0: serum K^+ concentration >5.5–≤6.0 mmol/L
  - K >6.0: serum K^+ concentration >6.0 mmol/L or HES diagnosis code for HiK, regardless of K^+ concentration
- A cohort analysis was used to determine the incidence of HiK
- A case-control analysis was used to identify demographic and clinical predictor factors of incident HiK (age, sex, laboratory test for estimated glomerular filtration rate [eGFR], concomitant medications, and comorbidities)
- Statistical analyses:
  - Incidence of initial HiK event was determined for the overall population and was stratified by range of K^+ values
  - Crude (unadjusted) incidence rates were calculated as the number of patients with the outcome of interest divided by the total number of patients seeking care. Follow-up for each patient ended at the earliest of the following: clinical outcome of interest, transfer out of practice, death, or end of the study period
  - Each patient with an incident HiK event was eligible to serve as a case. Up to 4 controls were selected for each case and matched on care setting of visit (eg, CPRD or HES), presence of ≥1 laboratory test of any time on visit date (for CPRD matches only), visit date (±3 months), age (±3 years), time since registration (±4 years), and sex. The visit date for the control patients served as the corresponding index date with the HiK event case date
  - For the risk factor analysis, conditional logistic regression analyses were used to estimate odds ratios and were adjusted using stepwise modeling, which are presented as adjusted odds ratios and 95% confidence intervals

Results

Table 2. Most Patients Experienced an Incident HiK Event of K 5.0–≤5.5

	Incident Cases of HiK, n (%)	Incidence of Initial HiK Event per 100 Patient-Years (95% CI)
Overall	195,178 (100.0)	2.86 (2.83–2.89)
Severity of incident HiK event		
K 5.0–≤5.5	177,945 (91.2)	2.61 (2.58–2.63)
K >5.5–≤6.0	14,020 (7.2)	0.21 (0.20–0.21)
K >6.0	3213 (1.6)	0.05 (0.04–0.05)

CI, confidence interval; HiK, hyperkalemia.

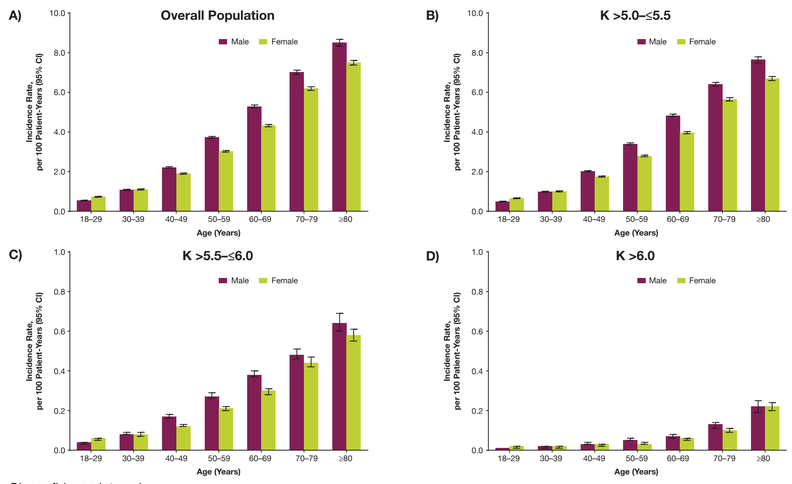
Table 3. Patient Demographics and Baseline Characteristics

	Overall (N = 195,178)	Severity of Incident HiK Event		
		K 5.0–≤5.5 (n = 177,945)	K >5.5–≤6.0 (n = 14,020)	K >6.0 (n = 3213)
Age, years, mean (SD)	60.6 (16.6)	60.5 (16.5)	60.7 (17.0)	63.7 (18.7)
Female, %	52.1	52.2	51.2	52.3
BMI, kg/m², mean (SD)	28.3 (6.1)	28.4 (6.1)	27.9 (6.1)	27.8 (6.7)
eGFR, mL/min/1.73 m², mean (SD)	80.5 (21.1)	80.6 (20.9)	79.7 (22.0)	78.2 (23.9)
Comorbidities, %				
Hypertension	50.7	50.7	48.8	58.1
Hyperlipidemia	19.6	19.7	18.0	22.1
Obstructive lung disease	18.3	18.2	18.6	22.5
Chronic kidney disease	17.9	17.7	17.5	27.9
Ischemic heart disease	12.8	12.6	12.4	20.7
Diabetes (types 1 and 2)	12.5	12.5	11.8	14.7
Arrhythmia (including AF)	9.5	9.3	9.7	18.6
AF	6.8	6.6	7.4	15.4
Cerebrovascular disease	6.5	6.3	6.9	12.9
Myocardial infarction	5.2	5.1	5.0	9.3
Liver disease	3.8	3.7	4.2	9.2
Heart failure	2.2	2.1	2.5	9.0
Peripheral arterial disease	1.8	1.8	1.9	3.5
RAASi use, %				
Never	64.8	64.8	67.1	57.7
Current	30.5	30.7	28.6	28.9
Former	4.7	4.6	4.4	13.4
Concomitant medication, %				
ACE inhibitors	22.5	22.7	21.3	20.0
NSAIDs	9.3	9.3	9.3	7.7
ARBs	7.9	8.0	7.1	7.8
Thiazide diuretics	7.3	7.3	6.6	8.4
Bendroflumethiazide	5.9	5.9	5.4	6.3
Indapamide	0.7	0.7	0.6	1.1
Hydrochlorothiazide	0.5	0.5	0.4	0.6
Chlorthalidone	0.2	0.1	0.2	0.2
Loop diuretics	5.9	5.7	6.9	12.6
MRAs	2.0	1.9	2.8	5.5
Antibiotics	1.6	1.5	2.2	3.3

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; HiK, hyperkalemia; MRAs, mineralocorticoid receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; RAASi, renin–angiotensin–aldosterone system inhibitor; SD, standard deviation.

- A total of 195,178 patients with an incident HiK event were included in the analysis (**Table 3**)
  - The proportion of patients with prespecified baseline comorbidities was greatest among patients with an incident HiK event of K >6.0, with heart failure being roughly 4-fold more common and chronic kidney disease (CKD) and other cardiovascular-related diseases being roughly 2-fold more common relative to patients with K 5.0–≤5.5 and K >5.5–≤6.0
  - Use of prespecified concomitant medications was fairly similar across K^+ concentration strata, with the majority of patients using angiotensin-converting enzyme (ACE) inhibitors
  - Use of loop diuretics and mineralocorticoid receptor antagonists (MRAs) were roughly 2-fold more common among patients with K >6.0 relative to those with K 5.0–≤5.5 and K >5.5–≤6.0

Figure 1. The Incidence of HiK Increases With Increasing Age, Regardless of Sex or Incident HK Event Severity



CI, confidence interval.

- Important risk factors for an incident HiK event include the presence of an eGFR value and concomitant use of ACE inhibitors, angiotensin receptor blockers, and MRAs although many patients with HiK never had RAASi. (**Table 4**). Antibiotic use and increasing age appeared to protect against HiK

Table 4. Predictors of Incident HiK Event in English Patients

Predictors	Odds Ratio (95% CI)	
	Unadjusted	Stepwise Adjusted
Sex		
Male	REF	REF
Female	0.89 (0.88–0.90)	1.08 (1.07–1.10)
Age range, years		
18–29	REF	REF
30–39	1.07 (1.04–1.10)	0.86 (0.83–0.89)
40–49	1.15 (1.12–1.19)	0.68 (0.66–0.71)
50–59	1.41 (1.37–1.45)	0.68 (0.66–0.70)
60–69	1.60 (1.56–1.65)	0.67 (0.65–0.69)
70–79	1.76 (1.72–1.81)	0.60 (0.58–0.62)
≥80	1.77 (1.73–1.83)	0.62 (0.59–0.64)
Smoking status		
Never	REF	REF
Current	1.05 (1.04–1.06)	1.17 (1.15–1.18)
Former	1.40 (1.39–1.42)	1.26 (1.24–1.27)
Unknown	0.72 (0.66–0.77)	1.32 (1.20–1.44)
Measured baseline laboratory values		
BUN	1.12 (1.05–1.19)	0.70 (0.66–0.75)
eGFR	31.49 (30.51–32.52)	29.81 (28.84–30.80)
Comorbidity		
Ischemic heart disease	1.63 (1.61–1.66)	0.85 (0.83–0.87)
Arrhythmia (including AF)	1.33 (1.31–1.36)	0.91 (0.89–0.93)
Heart failure	1.94 (1.87–2.02)	0.89 (0.84–0.94)
Hypertension	2.29 (2.27–2.32)	0.88 (0.87–0.90)
Cerebrovascular disease	1.31 (1.29–1.34)	0.93 (0.91–0.96)
Peripheral arterial disease	1.71 (1.64–1.78)	1.13 (1.08–1.19)
Hyperlipidemia	1.42 (1.41–1.44)	0.85 (0.84–0.87)
Diabetes (types 1 and 2)	1.97 (1.94–2.01)	0.95 (0.93–0.97)
Chronic kidney disease	1.69 (1.67–1.71)	1.04 (1.02–1.06)
Obstructive lung disease	0.92 (0.91–0.93)	0.95 (0.93–0.96)
Liver disease	1.13 (1.10–1.17)	0.93 (0.90–0.96)
Concomitant medication		
ACE inhibitors	15.11 (14.80–15.43)	13.63 (13.31–13.95)
ARBs	14.56 (14.05–15.09)	15.89 (15.27–16.54)
Antibiotics	0.32 (0.31–0.33)	0.33 (0.32–0.34)
Loop diuretics	2.79 (2.72–2.86)	1.39 (1.34–1.44)
MRAs	17.47 (16.17–18.88)	7.77 (7.06–8.54)
Bendroflumethiazide	1.86 (1.82–1.90)	0.85 (0.83–0.88)
Hydrochlorothiazide	2.46 (2.26–2.67)	0.83 (0.75–0.93)
Indapamide	1.45 (1.36–1.54)	0.57 (0.52–0.62)

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; MRAs, mineralocorticoid receptor antagonists; REF, reference value.

Limitations

- Analysis was limited to available data in the linked CPRD/HES dataset and does not include emergency care data. However, this study describes overall incidence of HiK in a general population and is not limited to patients who had experienced severe events
- The dataset may not reflect the totality of patients hospitalized for or with HiK as the HES only provides diagnosis codes (no laboratory values); clinical diagnoses were not adjudicated; and transient HiK cases occurring before the study start may not have been captured if laboratory testing was done only during periods of normal serum K^+ levels

Conclusions

- The overall incidence of a first HiK event was a common condition among patients seeking health care services in England (2.86 per 100 patient-years), and most HiK cases were K 5.0–≤5.5
- Patients with an incident HiK event of K >6.0 generally had a greater comorbidity burden (eg, atrial fibrillation, cardiac arrhythmia, CKD, and hypertension) than those with less severe incident HiK
- The strongest risk factor for HiK is the presence of an eGFR laboratory value, demonstrating the importance of renal function monitoring and decreased kidney function in HiK development
- Use of essential medications (eg, renin–angiotensin–aldosterone inhibitors [RAASis] and diuretics) for common comorbid conditions, such as hypertension and heart failure, also contribute to HiK incidence in these complex patients
- Because patients with multiple comorbidities, RAASi prescriptions, and those who are tested for eGFR are at increased risk of HiK, frequent K^+ monitoring may be indicated for these patients

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