Clinical Outcomes Associated With Hyperkalemia in Adults in the UK

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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]
- Although it is known that HiK is associated with adverse clinical outcomes (ie, cardiac arrhythmias and mortality),[2,3] the incidence of these outcomes following an incident HiK event is unknown
- Here, we report results from a retrospective, population-based analysis characterizing the incidence of and risk factors for adverse clinical outcomes following an incident HiK event among English patients receiving health care

Methods

- Retrospective cohort 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[4]
  - HES provides information on hospital/emergency department admissions and outpatient appointments at National Health Service hospitals in England[5]
  - Data were further linked to the Office for National Statistics mortality database to obtain information on mortality

Table 1. Inclusion and Exclusion Criteria

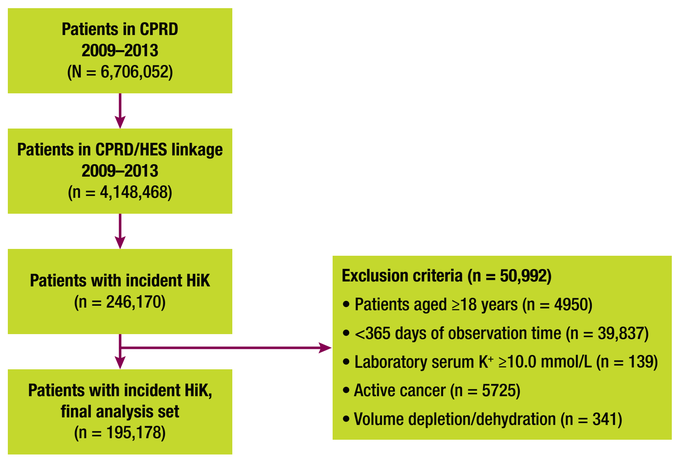
Inclusion Criteria	Exclusion Criteria
• Aged ≥18 years • Record in linked CPRD/HES dataset • Incident HiK event (first occurrence of HiK event) defined as READ diagnosis code or a serum K^+ laboratory result ≥5.0 mmol/L in CPRD or ICD-10 codes for HiK in HES between 1/1/2009 and 12/31/2013	• Serum K^+ 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 incidence of adverse clinical outcomes following an incident HiK event
- Adverse clinical outcomes of interest were HiK recurrence (second event of elevated serum K^+ any time after a documented return to serum K^+ <5.0 mmol/L after the incident HiK event), heart failure, cardiac arrhythmia, cardiac arrest, declining kidney function, acute kidney injury, dialysis, all-cause mortality, and all-cause hospitalization
- Statistical analyses:
  - Incidence of adverse clinical outcomes of interest following an incident HiK event was determined for the overall population and was stratified by incident event serum K^+ concentration
  - Crude 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
  - Baseline predictors of clinical outcomes of interest were identified using a Cox proportional hazards model, and variables identified as significant in the stepwise analysis are presented as adjusted hazard ratios with 95% confidence intervals (CIs)

Results

Figure 1. Identification of Study Participants



CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HiK, hyperkalemia.

Table 2. 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.

- Of the 195,178 patients included in the analysis, an incident HiK event of K 5.0–≤5.5, K >5.5–≤6.0, and K >6.0 was experienced by 91.2%, 7.2%, and 1.6% of patients, respectively (**Table 2**)
  - 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 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
- Of the negative clinical outcomes investigated, all-cause hospitalization, HiK recurrence, and decline in kidney function occurred at the highest incidence in the overall population (**Table 3**). The incidence (95% CI) of HiK recurrence (8.07 [7.98–8.16]) was much higher than the incidence of primary incident HiK event (2.86 [2.83–2.89])

Table 3. Incidence Rate of Adverse Clinical Outcomes Following HiK Increases With Severity of Incident HiK Event

	Incidence Rate (95% CI) per 100 Patient-Years			
	Overall	K 5.0–≤5.5	K >5.5–≤6.0	K >6.0
HiK recurrence	8.07 (7.98–8.16)	7.82 (7.73–7.91)	10.68 (10.28–11.08)	12.14 (11.14–13.21)
Heart failure	0.61 (0.59–0.64)	0.60 (0.58–0.63)	0.64 (0.55–0.74)	1.38 (1.07–1.75)
Cardiac arrhythmia	1.07 (1.03–1.10)	1.05 (1.02–1.09)	1.13 (1.01–1.26)	1.83 (1.46–2.27)
Cardiac arrest	0.14 (0.13–0.15)	0.13 (0.12–0.15)	0.17 (0.12–0.22)	0.44 (0.28–0.66)
Decline in kidney function	6.68 (6.60–6.76)	6.54 (6.45–6.62)	7.36 (7.04–7.69)	14.61 (13.46–15.83)
Acute kidney injury	1.26 (1.23–1.30)	1.18 (1.15–1.22)	1.87 (1.71–2.03)	4.09 (3.52–4.72)
Dialysis	0.14 (0.13–0.15)	0.12 (0.11–0.13)	0.21 (0.16–0.27)	1.55 (1.23–1.94)
All-cause mortality	2.73 (2.68–2.78)	2.51 (2.46–2.56)	3.83 (3.61–4.05)	12.57 (11.63–13.56)
All-cause hospitalization	14.14 (14.01–14.27)	13.86 (13.73–13.99)	15.53 (15.03–16.03)	28.93 (27.22–30.72)

CI, confidence interval; HiK, hyperkalemia.

- Age, liver disease, obstructive lung disease, heart failure, and the use of loop diuretics were strong predictors of cardiac arrhythmia, cardiac arrest, and death following an incident HiK event (**Table 4**). Other important covariates for arrhythmia and death included ischemic heart disease and the use of MRAs

Table 4. Predictors of Cardiac Arrhythmia, Cardiac Arrest, and Death Among Patients With Incident HiK Event

	Stepwise Adjusted Odds Ratio (95% CI)		
Predictor	Cardiac Arrhythmia	Cardiac Arrest	Death
Sex			
Male	REF	REF	REF
Female	0.70 (0.65–0.75)	0.59 (0.5–0.7)	0.87 (0.83–0.90)
Age group, years			
18–29	REF	REF	REF
30–39	1.08 (0.58–2.02)	0.83 (0.32–2.14)	1.58 (0.92–2.71)
40–49	1.52 (0.88–2.62)	0.64 (0.27–1.51)	3.14 (1.95–5.08)
50–59	2.94 (1.74–4.96)	1.25 (0.57–2.76)	6.19 (3.87–9.90)
60–69	6.83 (4.08–11.43)	1.81 (0.83–3.91)	13.36 (8.39–21.27)
70–79	15.52 (9.28–25.96)	3.19 (1.48–6.91)	30.23 (19.00–48.11)
≥80	33.18 (19.82–55.56)	6.21 (2.86–13.51)	91.03 (57.21–144.86)
Smoking status			
Never	REF	REF	REF
Current	1.22 (1.10–1.34)	1.80 (1.43–2.28)	1.86 (1.76–1.96)
Former	1.04 (0.97–1.11)	1.20 (1.00–1.45)	1.07 (1.02–1.11)
Unknown	1.29 (0.79–2.12)	1.71 (0.55–5.37)	1.91 (1.53–2.37)
Baseline laboratory values			
eGFR	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)
Comorbidity			
Ischemic heart disease	1.42 (1.31–1.54)	—	1.12 (1.07–1.17)
Arrhythmia (including AF)	—	1.33 (1.07–1.64)	1.33 (1.27–1.39)
Heart failure	1.32 (1.12–1.56)	1.65 (1.22–2.24)	1.38 (1.29–1.48)
Hypertension	1.11 (1.03–1.19)	—	—
Cerebrovascular disease	1.27 (1.16–1.40)	—	1.60 (1.53–1.68)
Peripheral arterial disease	1.29 (1.11–1.50)	1.72 (1.25–2.36)	1.43 (1.32–1.54)
Hyperlipidemia	0.86 (0.80–0.93)	—	0.79 (0.76–0.83)
Diabetes (types 1 and 2)	—	1.57 (1.30–1.91)	1.27 (1.21–1.33)
Chronic kidney disease	—	—	1.09 (1.05–1.15)
Obstructive lung disease	1.36 (1.26–1.46)	1.32 (1.09–1.59)	1.36 (1.31–1.42)
Liver disease	1.47 (1.26–1.72)	2.05 (1.50–2.79)	2.01 (1.87–2.17)
Concomitant medication			
NSAIDs	—	1.32 (1.01–1.71)	—
ACE inhibitors	—	—	0.77 (0.74–0.80)
ARBs	—	—	0.66 (0.62–0.70)
Antibiotics	—	—	1.50 (1.38–1.65)
Loop diuretics	1.78 (1.61–1.97)	2.12 (1.69–2.66)	1.87 (1.78–1.97)
MRAs	1.36 (1.15–1.61)	—	1.23 (1.14–1.32)
Bendroflumethiazide	1.17 (1.06–1.30)	—	—
Chlorthalidone	—	—	1.45 (1.07–1.97)

Parameters that were evaluated but not included in the final stepwise-adjusted model are represented as a dash.
ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CI, confidence interval; eGFR, estimated glomerular filtration rate; MRAs, mineralocorticoid receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; REF, reference value.

Limitations

- Analysis was limited to available data in the linked CPRD/HES dataset and primarily captures HiK in the outpatient setting, as laboratory data are not available in HES
- 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 could not be captured
- Incidence rates for adverse clinical outcomes were not adjusted for differences in baseline characteristics, including HiK severity

Conclusions

- Patients with a more severe incident HiK event are more likely than those with less severe incident HiK to experience recurrent HiK events and adverse clinical outcomes such as all-cause hospitalization and decline in kidney function
- Age, comorbid liver disease, obstructive lung disease, diabetes, or cardiovascular disease (heart failure, arrhythmia, cerebrovascular disease, and peripheral arterial disease) and the use of loop diuretics were strong predictors of negative clinical outcomes, including death, following an HiK event
- Future studies are needed to assess how HiK treatments that specifically reduce K^+ to normal levels affect clinical outcomes in at-risk patients and the ongoing management of high risk co-morbid conditions

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