Resolution and Recurrence of Hyperkalemia Among Adults in the UK

Laura Horne,[1] Akhtar Ashfaq,[1]* Sharon MacLachlan,[2] Marvin Sinsakul,[1] Lei Qin,[3] Robert LoCasale[1]

[1]Global Medical Affairs, AstraZeneca, Gaithersburg, MD, USA; [2]Real World Evidence, Evidera, London, UK; [3]Health Economics, AstraZeneca, Gaithersburg, MD, USA

*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 and is often associated with adverse clinical outcomes, including cardiac arrhythmias and mortality[2,3]
- The incidence of subsequent HiK following a primary event is unknown, as are the risk factors associated with the incidence of HiK recurrences
- Here, we report results from a retrospective, population-based analysis characterizing the incidence of primary and secondary HiK events and the associated risk factors for HiK recurrence among patients obtaining health care in England

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]

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 the initial HiK event, the frequency of HiK retesting (another K^+ laboratory value recording within 14 days of incident event), and the recurrence of HiK (second event of elevated serum K^+ any time after a documented return to normal serum K^+ concentration [<5.0 mmol/L]) after the initial HiK event
- Statistical analyses:
  - Incidence of initial HiK event and HiK recurrence 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 and were not adjusted for baseline differences across subgroups. Follow-up for each patient began at the time of incident HiK and ended at the earliest of the following: clinical outcome of interest, transfer out of practice, death, or end of the study period
  - Predictors of recurrence 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

Results

- A total of 195,178 patients with an incident HiK event were included and stratified by severity at time of event: K 5.0–≤5.5 (n = 177,945; 91.2%); K >5.5–≤6.0 (n = 14,020; 7.2%); and K >6.0 (n = 3213; 1.6%) (**Table 2**)

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.

- Only 5.8% of patients were retested for K^+ within 14 days of the initial event. Retests were numerically less common among patients with an incident HiK event of K 5.0–≤5.5 versus patients with an incident HiK event of K >5.5–≤6.0 or K >6.0 (**Table 3**). A subsequent HiK event of >5.5 mmol/L was experienced by greater proportions of patients with an incident HiK event of K >5.5–≤6.0 or K >6.0 versus K 5.0–≤5.5

Table 3. Few Patients Were Retested for K^+ Within 14 Days of Incident HiK Event

Parameter, n (%)	Overall (N = 194,035)	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)
Retest within 14 days	11,342 (5.8)	6922 (3.9)	3276 (23.4)	1144 (55.3)
Subsequent HiK event (≥5.0 mmol/L)[a]	3632 (32.0)	2045 (29.5)	1166 (35.6)	421 (36.8)
Subsequent HiK event K^+ concentration, mmol/L[a]				
5.0–≤5.5	—	1782 (87.1)	876 (75.1)	242 (57.5)
>5.5–≤6.0	—	228 (11.1)	249 (21.4)	98 (23.3)
>6.0	—	35 (1.7)	41 (3.5)	81 (19.2)

[a]Only in those patients who had a K^+ retest.
HiK, hyperkalemia; K^+, potassium.

- The overall incidence of HiK recurrence was 8.07 per 100 patient-years (PYs; n = 195,178) and was highest among patients who experienced incident HiK of K >6.0 (12.14 per 100 PYs; n = 3213) compared with patients who experienced incident HiK events of K 5.0–≤5.5 (7.82 per 100 PYs; n = 177,945) and K >5.5–≤6.0 (10.68 per 100 PYs; n = 14,020) in severity (no formal statistical comparisons made)
- Time-to-event analyses suggest that, in addition to age, important risk factors for HiK recurrence include comorbid type 1 or 2 diabetes and concomitant use of ACEis or MRAs (**Table 4**). Compared to patients with an incident HiK event of K 5.0–≤5.5, the hazard ratios of HiK recurrence for patients with an incident HiK event of K >5.5–≤6.0 or K >6.0 were both statistically significantly increased and similar to one another

Table 4. Predictors of HiK Recurrence Among Patients With an Incident HiK Event

Predictors	Adjusted HR (95% CI)
Age group, years	
18–29	REF
30–39	1.30 (1.13–1.48)
40–49	1.85 (1.64–2.08)
50–59	2.29 (2.04–2.58)
60–69	2.73 (2.43–3.07)
70–79	3.23 (2.87–3.64)
≥80	3.45 (3.06–3.89)
Baseline laboratory values	
Presence of eGFR	0.99 (0.99–0.99)
Comorbidity	
Ischemic heart disease	1.15 (1.11–1.18)
Arrhythmia (including AF)	1.10 (1.06–1.14)
Heart failure	1.10 (1.03–1.17)
Hypertension	1.23 (1.19–1.27)
Cerebrovascular disease	1.04 (1.00–1.08)
Peripheral arterial disease	1.10 (1.03–1.17)
Hyperlipidemia	1.04 (1.01–1.07)
Diabetes (types 1 and 2)	1.86 (1.81–1.91)
Chronic kidney disease	1.19 (1.15–1.23)
Obstructive lung disease	1.06 (1.03–1.09)
Liver disease	1.21 (1.15–1.28)
Concomitant medication	
NSAIDs	1.21 (1.17–1.25)
ACEis	1.27 (1.23–1.31)
ARBs	1.16 (1.12–1.21)
Loop diuretics	1.10 (1.06–1.15)
MRAs	1.74 (1.64–1.85)
Bendroflumethiazide	0.90 (0.86–0.93)
Indapamide	0.84 (0.75–0.94)
Severity of incident HiK event	
K 5.0–≤5.5	REF
K >5.5–≤6.0	1.39 (1.33–1.44)
K >6.0	1.34 (1.23–1.47)

ACEis, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CI, confidence interval; eGFR, estimated glomerular filtration rate; HiK, hyperkalemia; HR, hazard ratio; 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
- Since K^+ testing is part of a standard chemistry panel, retesting may have been conducted due to other medical reasons and not due to concern for HiK; furthermore, retesting done in the hospital setting would not have been captured
- By definition, recurrence of HiK required laboratory evidence of a return to normal serum K^+, which may not have been captured in CPRD if testing occurred during hospitalization or if the patient was not retested

Conclusions

- This study provides an overview of HiK in the general population primary care setting and demonstrates that, although HiK can be life threatening, few patients in England (<6.0%) were retested for K^+ within 14 days. However, retesting was more common among patients who experienced an initial HiK event of K >6.0
- Recurrent HiK of >5.5 mmol/L was more likely in patients with incident HiK events of >5.5 mmol/L
- A large number of patients who experience an initial HiK event experience recurrence following resolution. Therefore, these patients should be closely monitored for subsequent HiK events

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