Real-World Clinical Burden and Economic Assessment Associated with Hyperkalaemia in a Large Integrated Healthcare System: A Retrospective Analysis

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Abstract

Background: Hyperkalaemia (HK) is a serious and potentially life-threatening condition. Both acute and chronic conditions may alter potassium homeostasis. Our aim is to describe HK incidence, clinical outcomes, and associated resource use within a large, integrated healthcare system.

Methods: Adult patients seen at Intermountain Healthcare facilities with a serum potassium (sK) result between January 1, 2003 and December 31, 2018 were retrospectively studied. Descriptive assessment of a population with HK, defined by any sK >5.0 mmol/L and HK frequency and severity to associated resource use and characteristics of HK predictors were made. Multivariable Cox hazard regression was used to evaluate HK to outcomes.

Results: Of 1,208,815 patients included, 13% had HK. Compared to no-HK, HK patients were older (60 ± 18 vs 43 ± 18 years, $P < 0.001$), male (51% vs 41%, $P < 0.001$), and had greater disease burden (Charlson Comorbidity Index 3.5 ± 2.8 vs 1.7 ± 1.4 , $P < 0.001$). At 3 years, more HK patients experienced major adverse cardiovascular events (MACEs) (19% vs 3%, $P < 0.001$), persisting post-adjustment (multivariable hazard ratio = 1.60, $P < 0.001$). They incurred higher costs for emergency department services ($\$552 \pm 7,574$ vs $\$207 \pm 1,930$, $P < 0.001$) and inpatient stays ($\$10,956 \pm 93,026$ vs $\$1,477 \pm 21,423$, $P < 0.001$). HyperK Risk Scores for the derivation and validation cohorts were: 44% low-risk, 45% moderate-risk, 11% high-risk. Strongest HK predictors were renal failure, dialysis, aldosterone blockers, diabetes, and smoking.

Conclusion: Within this large system, HK was associated with a large clinical burden, affecting over 1 in 10 patients; HK was also associated with increased 3-year MACE risk and higher medical costs. Although risk worsened with more severe or persistently recurring HK, even mild or intermittent HK episodes were associated with significantly greater adverse clinical outcomes and medical costs. The HyperK Score predicted patients who may benefit from closer management to reduce HK risk and associated costs.

Background

Hyperkalaemia (HK), typically defined as a serum potassium (sK) concentration > 5 or > 5.5 mmol/L, is a serious medical condition that can lead to life-threatening cardiac arrhythmias and sudden cardiac death [1–3]. It can result from various acute and chronic conditions that affect potassium (K^+) homeostasis, but commonly occurs in patients with chronic kidney disease (CKD) with comorbidities such as heart failure (HF), diabetes mellitus (DM), and hypertension (HTN) [1–3]. HK is a condition often seen in the emergency department (ED) and may present with noncardiac symptoms (eg, altered mental status, confusion, muscle cramps and weakness, fatigue, paresthesias) [4]. Thus, HK may go unrecognized with few or no obvious symptoms prior to cardiac arrhythmias and/or sudden cardiac arrest [5, 6].

A recent retrospective study evaluating the 5-year prevalence of HK in approximately 1.7 million patients found that 47.6% of patients with CKD (stages 3 and 4) and HF had at least 1 HK event compared to 8.5% of patients without comorbid CKD, end-stage renal disease, HF, or DM [7]. Moreover, optimal treatment regimens for these underlying diseases often include renin-angiotensin-aldosterone system inhibitors

(RAASI's), which further increase HK risk [8]. Furthermore, given the chronic and progressive nature of CKD, patients with or without comorbidities are at long-term risk for HK [3, 7]. HK management options have historically lacked proven efficacy for chronic use (eg, dietary K⁺ intake reduction, loop diuretics, dose reduction, or discontinuation of RAASI's).

HK incidence and subsequent clinical and economic outcomes within a large healthcare system have not previously been fully described. This study describes the prevalence of HK within the Intermountain Healthcare population, assesses associated clinical and economic impacts, and employs a predictive risk tool to identify vulnerable at-risk subsets who may benefit from better HK management.

Methods

A retrospective, observational database analysis of electronic medical records from Intermountain Healthcare was performed to describe the clinical and economic burden of HK. Intermountain Healthcare is a large, nonprofit, electronically integrated healthcare network consisting of hospitals, clinics, and a system of health insurance plans. Intermountain Healthcare provides services to approximately 60% of the population of Utah, and parts of Idaho and Nevada. This study was approved by the Intermountain Healthcare institutional review board.

To be included, patients were ≥ 18 years of age, had ≥ 2 nonurgent care or ED encounters at least 2 years apart, and had at least one nonspurious sK between January 1, 2003 and December 31, 2018.

Patients were stratified into one of two groups: no-HK (all sK ≤ 5.0 mmol/L) or HK (at least one sK > 5.0 mmol/L). They were further classified based on HK frequency or severity. Frequency of HK was characterized as transient (1 occurrence of sK > 5.0 mmol/L), intermittent (> 1 occurrence of sK > 5.0 mmol/L, but $< 50\%$ of reported results), or persistent (sK > 5.0 mmol/L for $> 50\%$ of reported results). Severity categories were based on index sK: mild HK (sK > 5.0 – 5.5 mmol/L), moderate HK (sK > 5.5 – 6.4 mmol/L), or severe HK (sK > 6.4 mmol/L). Baseline characteristics assessed included age, sex, traditional cardiovascular (CV) risk factors, prior diagnoses, and medications. Discrete variables were presented as frequencies and continuous variables as means and standard deviations. However, if characteristics were found to be nonnormally distributed, the median and interquartile ranges were reported. The student's t-test, analysis of variance, and chi-square statistic were used to characterize the populations, and where appropriate, nonparametric test were used.

Follow-ups at 1 and 3 years were assessed from electronic medical records. Univariable and multivariable logistic and Cox Hazard regression analyses were used for outcomes evaluation. Multivariable models used baseline and clinical characteristics, test results, and medications to adjust for group differences. Final multivariable models retained significant and confounding variables with odds ratios (ORs) and hazard ratios (HRs) reported. A *P*-value of ≤ 0.05 was deemed significant. To determine data accuracy, means and frequencies were compared to prior like-studies for similarity and trends.

Annualized ED and inpatient visits in the follow-up period were quantified and stratified by the presence or absence of HK.

A risk score, termed the HyperK Score, was created in a randomly divided derivation cohort (70% of the population) and then applied in a validation cohort (30% of the population). It was derived by multiplying the β -coefficient for each of the significant and confounding variables, rounding to the nearest integer, and summing the values. The risk score was then stratified into risk categories of low ($< 90\%$ sensitivity threshold), moderate ($\geq 90\%$ sensitivity threshold but $< 90\%$ specificity threshold), and high ($\geq 90\%$ specificity threshold). Receiver operator characteristic curves were used to determine the area under the curve c-statistic from risk score data. Overall risk scores were applied to compare c-statistics and associated 95% confidence intervals (CIs).

Role of the Funding Source

The sponsor had a role in the study design, conduct of the study, data interpretation, and decision to publish. The findings and conclusions in this article are those of the authors, who are responsible for its contents.

Results

A total of 1,208,815 patients met the study criteria, with 161,849 (13%) having HK. Compared to patients without HK, HK patients were older (mean age 60 ± 18 years vs 43 ± 18 years), more often male (51% vs 41%), had a higher Charlson Comorbidity Index (CCI; 3.5 ± 2.8 vs 1.7 ± 1.4 ; $P < 0.001$), and were more likely to have renal insufficiency (16.3% vs 0.7%; $P < 0.001$). Atherosclerotic CV disease (CVD), HF, and atrial fibrillation were among the highest prior diagnoses in patients with HK (21%, 20%, and 14%, respectively) and significantly higher than in the no-HK group (4%, 2%, and 2%, respectively). Baseline characteristics stratified by the presence of HK are presented in Table 1. At baseline, all assessed medication use was more common in the HK group, K^+ -binder use was low overall ($< 1\%$); sodium polystyrene sulfonate (SPS) was used in 0.4% of patients with HK and 0.04% of patients without HK ($P < 0.001$); and patiromer use was insufficient to evaluate. At 3-year follow-up, major adverse CV events (MACEs) were higher in the HK vs no-HK group (18.8% vs 3.2%; $P < 0.001$), which persisted after adjustment (multivariable HR = 1.60; $P < 0.001$; Table 1, Fig. 1A).

Table 1
Overall Population – Baseline Characteristics and Post-Index Outcomes

	No-HK n = 1,046,966	HK n = 161,849
Mean age (years)*	43 ± 18	60 ± 18
< 65 years	86%	56%
65–74 years	8%	20%
≥ 75 years	6%	24%
Sex (male)*	41%	51%
CCI*	1.7 ± 1.4	3.5 ± 2.8
Mean baseline sK (mmol/L)*,†	4.07 ± 0.39	5.38 ± 0.48
Traditional CV Risk Factors		
Hypertension*	20%	63%
Hyperlipidaemia*	17%	55%
Diabetes*	7%	33%
Smoking*	13%	26%
Renal insufficiency*	0.7%	16%
BMI, kg/m ² , n = 662,888*	28.4 ± 7.4	29.7 ± 8.1
BMI ≥ 30	33%	40%
Maximum SBP (mm Hg)*	139.2 ± 71.6	162.8 ± 73.7

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P < 0.001$.

†Taken within ± 1 month of index date (baseline sK level).

‡MACE is the composite of death, MI, stroke, and HFH.

	No-HK n = 1,046,966	HK n = 161,849
EF (%)*	60.9 ± 10.2	58.0 ± 12.9
Prior Diagnoses		
ASCVD*	4%	21%
CAD*	1%	7%
MI*	0.6%	4%
Stroke*	0.3%	2%
TIA*	0.7%	4%
PVD*	0.1%	1.0%
Heart failure*	2%	20%
Atrial fibrillation*	2%	14%
Baseline Medications		
Statin*	7%	39%
Other anti-diabetic*	1%	10%
Insulin*	2%	24%
Metformin*	3%	18%
Sulfonylurea*	1%	11%
NSAID*	39%	62%
ACEi*	8%	39%
ARB*	3%	16%
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.		
Models adjusted by baseline characteristics, risk factors, and medications.		
* $P < 0.001$.		
†Taken within ± 1 month of index date (baseline sK level).		
‡MACE is the composite of death, MI, stroke, and HFH.		

	No-HK n = 1,046,966	HK n = 161,849
Aldosterone inhibitor*	0.6%	6%
Beta-blocker*	6%	32%
Diuretic*	9%	42%
CCB*	4%	22%
Furosemide*	3%	24%
Torsemide*	0.1%	1.2%
SPS*	0.04%	0.4%
Patiromer	0%	0%
3-Year Post-Index Outcomes (n = 1,128,582)		
	n = 983,409	n = 145,173
MACE*	3.2%	18.8%
Death*	2.9%	16.7%
MI*	0.05%	0.2%
Stroke*	0.2%	0.9%
HFH*	0.2%	2.8%
Multivariable Hazard Ratio (95% CI) for 3-Year MACE [‡]		
No-HK vs HK*		1.60 (1.57, 1.63)
Post-Index Average Costs/Year (n = 1,208,815)		

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P < 0.001$.

[†]Taken within ± 1 month of index date (baseline sK level).

[‡]MACE is the composite of death, MI, stroke, and HFH.

	No-HK n = 1,046,966	HK n = 161,849
ED	\$207 ± 1,930	\$552 ± 7,574
Cost ± SD*	11 (0, 187)	56 (0, 408)
Median (IQR)		
Inpatient	\$1,477 ± 21,423	\$10,956 ± 93,026
Cost ± SD*	0 (0, 740)	0 (0, 4585)
Median (IQR)		
Age ≥ 60 years Post-Index Average Costs/Year (n = 290,972)		
ED	\$222 ± 2,747	\$561 ± 7,098
Cost ± SD*	18 (0, 219)	72 (0, 444)
Median (IQR)		
Inpatient	\$3,765 ± 35,137	\$13,844 ± 109,257
Cost ± SD*	0 (0, 2307)	1,277 (0, 6678)
Median (IQR)		
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.		
Models adjusted by baseline characteristics, risk factors, and medications.		
*P< 0.001.		
†Taken within ± 1 month of index date (baseline sK level).		
‡MACE is the composite of death, MI, stroke, and HFH.		

Table 2 describes baseline characteristics and outcomes by HK frequency. Persistent HK represented only 3% of the total HK population, whereas a large majority showed either intermittent or transient patterns (45% and 52%, respectively). Relative to other HK patterns, persistent HK was more common in older patients (mean age 68 ± 17 years) and was the dominant pattern (40%) in those age ≥ 75 years. Persistently recurring HK was also associated with the highest CCI (4.3 ± 3.1) as well as greater rates of renal insufficiency (30%) and HF (30%). At baseline and relative to more frequent patterns, all medication use was generally lowest among transient HK, with the exception of nonsteroidal anti-inflammatory drugs

(NSAIDs). SPS use was low in each group (0.1% of transient HK, 0.7% of intermittent HK, 1% of persistent HK). Substantially higher than other patterns, 3-year MACE was highest (44.8%) with persistently recurring HK, achieving statistical significance (persistent vs transient HK multivariable HR = 2.31 [95% CI, 2.20, 2.43], $P < 0.001$). A smaller difference was observed between less frequently occurring patterns (intermittent vs transient HK multivariable HR = 1.02 [95% CI, 0.99, 1.05], $P =$ not significant; Table 2, Fig. 1B). Each of the four individual MACE components (death, myocardial infarction [MI], stroke, and HF hospitalization) influenced risk.

Table 2
HK Frequency – Baseline Characteristics and Post-index Outcomes

	Transient n = 82,307 (52%)	Intermittent n = 72,382 (45%)	Persistent n = 5,150 (3%)
Mean age (years)*	57 ± 19	63 ± 16	68 ± 17
< 65 years	64%	48%	40%
65–74 years	16%	24%	20%
≥ 75 years	20%	28%	40%
Sex (male)*	49%	53%	56%
CCI*	3.1 ± 2.7	3.8 ± 2.8	4.3 ± 3.1
Mean baseline sK (mmol/L)*,†	5.3 ± 0.5	5.4 ± 0.5	5.6 ± 0.6
Traditional CV Risk Factors			
Hypertension*	52%	74%	73%
Hyperlipidaemia*	49%	63%	55%
Diabetes*	23%	43%	43%
Smoking*	24%	29%	27%
Renal insufficiency*	10%	23%	30%
BMI ≥ 30	37%	43%	40%
Maximum SBP* (mm Hg)	158 ± 82	168 ± 64	168 ± 49
EF (%)*	58 ± 13	57 ± 14	58 ± 13

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P < 0.001$.

†Taken within ± 1 month of index date (baseline sK level).

‡MACE is the composite of death, MI, stroke, and HFH.

	Transient n = 82,307 (52%)	Intermittent n = 72,382 (45%)	Persistent n = 5,150 (3%)
Prior Diagnoses			
ASCVD*	15%	26%	25%
CAD*	5%	10%	9%
MI*	3%	5%	4%
Stroke*	1%	2%	2%
TIA*	3%	4%	4%
PVD*	0.7%	1%	1%
Heart failure*	13%	27%	30%
Atrial fibrillation*	10%	17%	19%
Baseline Medications			
Statin*	33%	46%	41%
Other anti-diabetic*	6%	13%	14%
Insulin*	17%	32%	33%
Metformin*	13%	22%	23%
Sulfonylurea*	7%	16%	18%
NSAID*	61%	65%	59%
ACEi*	30%	47%	48%
ARB*	13%	20%	18%
Aldosterone inhibitor*	25%	39%	37%
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.			
Models adjusted by baseline characteristics, risk factors, and medications.			
* $P < 0.001$.			
†Taken within ± 1 month of index date (baseline sK level).			
‡MACE is the composite of death, MI, stroke, and HFH.			

	Transient n = 82,307 (52%)	Intermittent n = 72,382 (45%)	Persistent n = 5,150 (3%)
Beta-blocker*	4%	9%	8%
Diuretic*	33%	52%	50%
CCB*	17%	27%	28%
Furosemide*	17%	32%	34%
Torsemide*	0.7%	2%	2%
SPS*	0.1%	0.7%	1%
Patiromer	0%	0%	0%
3-Year Post-Index Outcomes (n = 145,173)			
	n = 73,036	n = 67,486	n = 4,651
MACE*,‡	14.8%	21.3%	44.8%
Death*	14.1%	17.7%	44.2%
MI*	0.1%	0.3%	0.04%
Stroke*	0.6%	1.2%	0.5%
HFH*	0.9%	5%	1.8%
Multivariate Hazard Ratio (95% CI) for 3-Year MACE [‡]			
Persistent vs transient HK*		2.31 (2.20, 2.43)	
Intermittent vs transient HK		1.02 (0.99, 1.05)	
Post-Index Average Costs/Year			

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P < 0.001$.

[†]Taken within ± 1 month of index date (baseline sK level).

[‡]MACE is the composite of death, MI, stroke, and HFH.

	Transient n = 82,307 (52%)	Intermittent n = 72,382 (45%)	Persistent n = 5,150 (3%)
ED			
Cost ± SD*	\$422 ± 4,221	\$620 ± 2,305	\$1,737 ± 37,846
Median (IQR)	0 (0, 274)	165 (0, 580)	0 (0, 70)
1-year visit* (primary diagnosis)	0.01%	0.3%	0.7%
Inpatient			
Cost ± SD*	\$5,047 ± 51,691	\$16,478 ± 108,826	\$30,011 ± 245,519
Median (IQR)	0 (0, 1347)	2681 (0, 9661)	0 (0, 1488)
1-year visit* (primary diagnosis)	0.004%	0.3%	0.9%
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.			
Models adjusted by baseline characteristics, risk factors, and medications.			
* $P < 0.001$.			
†Taken within ± 1 month of index date (baseline sK level).			
‡MACE is the composite of death, MI, stroke, and HFH.			

Table 3 identifies baseline characteristics and post-index outcomes by HK severity. Of total HK patients, only 3% had severe HK; most had mild (81%) or moderate (16%) HK. Severity patterns were similar across age groups. Moderate and severe HK were associated with higher baseline disease burden based on CCI. At baseline, SPS use was low regardless of HK severity (0.8% each of moderate and severe HK, 0.3% of mild HK). MACE risk at 3 years positively correlated with HK severity; multivariable HR was 1.31 (95% CI, 1.23, 1.40; $P < 0.001$) for severe vs mild groups and 1.29 (95% CI, 1.25, 1.33; $P < 0.001$) for moderate vs mild groups (Table 3, Fig. 1C). Death and HF hospitalization were the primary drivers of MACE risk.

Table 3
HK Severity – Baseline Characteristics and Post-Index Outcomes

	Mild HK n = 131,509 (81%)	Moderate HK n = 25,380 (16%)	Severe HK n = 4,960 (3%)
Mean age (years)*	60 ± 18	60 ± 19	58 ± 19
< 65 years	56%	55%	59%
65–74 years	20%	19%	18%
≥ 75 years	24%	26%	23%
Sex (male)*	51%	50%	48%
CCI*	3.2 ± 2.7	3.9 ± 2.9	4.1 ± 3.0
Mean baseline sK (mmol/L)*,†	5.2 ± 0.1	5.8 ± 0.2	7.3 ± 1.1
Traditional CV Risk Factors			
Hypertension*	62%	65%	65%
Hyperlipidaemia*	56%	51%	47%
Diabetes*	32%	36%	37%
Smoking*	25%	29%	33%
Renal insufficiency*	14%	24%	38%
BMI ≥ 30	40%	40%	40%
Maximum SBP (mm Hg)*	162 ± 77	166 ± 59	166 ± 52
EF (%)*	38 ± 13	57 ± 14	58 ± 13
Prior Diagnosis			
ASCVD*	20%	22%	19%
CAD*	7%	8%	7%
MI*	3%	4%	3%
Stroke*	1%	2%	2%
TIA*	4%	4%	3%
PVD*	1%	1%	0.9%
Heart failure*	18%	24%	26%
Atrial fibrillation*	13%	16%	17%

	Mild HK n = 131,509 (81%)	Moderate HK n = 25,380 (16%)	Severe HK n = 4,960 (3%)
Baseline Medications			
Statin*	40%	37%	33%
Other anti-diabetic	10%	10%	9%
Insulin*	23%	29%	31%
Metformin [‡]	18%	17%	16%
Sulfonylurea*	11%	12%	10%
NSAID*	63%	61%	60%
ACEi*	38%	39%	36%
ARB	16%	16%	15%
Aldosterone inhibitor*	6%	8%	9%
Beta-blocker*	31%	34%	32%
Diuretic*	41%	46%	45%
CCB*	21%	24%	23%
Furosemide*	23%	29%	30%
Torsemide*	1%	2%	1%
SPS*	0.3%	0.8%	0.8%
Patiromer	0%	0%	0%
3-Year Post-Index Outcomes (n = 145,173)			
	n = 117,902	n = 22,879	n = 4392
MACE* [§]	17.2%	25.1%	27.9%
Death*	15.2%	22.7%	25.9%
MI	0.2%	0.2%	0.2%
Stroke	0.9%	1%	0.7%
HFH*	2.6%	3.6%	3.3%
Multivariable Hazard Ratio (95% CI) for 3-Year MACE [§]			
Moderate vs mild HK*	1.29 (1.25, 1.33)		

	Mild HK n = 131,509 (81%)	Moderate HK n = 25,380 (16%)	Severe HK n = 4,960 (3%)
Severe vs mild HK*		1.31 (1.23, 1.40)	
Post-Index Annualized Acute Care Trends			
ED			
Mean cost ± SD*	\$519 ± 7,819	\$701 ± 6,936	\$668 ± 2,100
Median (IQR)	54 (0, 391)	67 (0, 477)	68 (0, 554)
1-year visit* (primary diagnosis)	0.1%	0.4%	0.7%
Inpatient			
Mean cost ± SD*	\$9,626 ± 73,418	\$16,328 ± 155,262	\$18,743 ± 125,932
Median (IQR)	0 (0, 4235)	0 (0, 6222)	788 (0, 7332)
1-year visit* (primary diagnosis)	0.1%	0.4%	1.1%
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.			
Models adjusted by baseline characteristics, risk factors, and medications.			
* $P \leq 0.001$.			
†Taken within ± 1 month of index date (baseline sK level).			
‡ $P \leq 0.01$.			
§MACE is the composite of death, MI, stroke, and HFH.			

ED and inpatient costs in the HK and no-HK groups were compared (Table 1), with substantial divergence of medians and median ranges in older patients. In the overall HK population, average annual costs were \$552 ± 7,574 for ED and \$10,956 ± 93,026 for inpatient visits; in the no-HK group, costs were \$207 ± 1,930 for ED and \$1,477 ± 21,423 for inpatient visits. Notably, in patients age ≥ 60 years, average annual ED and inpatient costs were significantly higher in HK patients (\$561 ± 7,098 for ED and \$13,844 ± 109,257 for inpatient) relative to those without HK (\$222 ± 2,747 for ED and \$3,765 ± 35,137 for inpatient) (Table 1).

Higher HK frequency correlated with greater ED and inpatient costs (Table 2), with greatest impact on inpatient costs. For transient, intermittent, and persistent HK patterns, ED costs were $\$422 \pm 4,221$, $\$620 \pm 2,305$, and $\$1,737 \pm 37,846$, respectively; and inpatient costs were $\$5,047 \pm 51,691$, $\$16,478 \pm 108,826$, and $\$30,011 \pm 245,519$, respectively. For patients with a primary diagnosis of HK, visits within 1 year increased in parallel with greater HK frequency.

Increasing severity showed similar trend patterns but with lower magnitudes of cost increases (Table 3). The severe-HK group incurred the highest mean annual inpatient costs ($\$18,743 \pm 125,932$; $P < 0.001$) and 1-year hospitalization rate (1.1%; $P < 0.001$). The moderate-HK group averaged the highest annual ED costs ($\$701 \pm 6,936$; $P < 0.001$), albeit a modest numeric difference from other groups.

The general trends suggest that inpatient costs trended upward with both severity and frequency of HK, while ED costs trended upward with frequency but not severity. Persistently recurring HK diverged from other frequencies and any severity with regard to impact on both ED and inpatient costs.

A HyperK Risk Score was calculated for a total of 1,077,306 patients using clinical risk predictors from standard factors from the electronic health record. Baseline characteristics among the derivation and validation cohorts are shown in Table 4. Of patients who were given HyperK Risk Scores, 754,109 (70.0%) were in the derivation cohort. Within the derivation cohort, 732,936 (97.2%) did not have HK (defined as $sK < 5.0$ mmol/L) and 21,173 (2.8%) had HK (defined as $sK > 5.5$ mmol/L). Among the derivation cohort, 334,504 (44.4%) were considered low-risk, 337,335 (44.7%) were moderate, and 82,270 (10.9%) were high-risk. 323,197 (30.0%) were applied in a validation cohort, of which 314,030 (97.2%) did not have HK and 9,167 (2.8%) had HK ($sK > 5.5$ mmol/L). Patients with an intermediate sK between > 5.0 and 5.5 mmol/L were excluded. In the validation cohort, 143,328 (44.3%) were low-risk, 144,990 (44.9%) were moderate, and 34,879 (10.8%) were high-risk.

Table 4
HyperK – Baseline Characteristics

	Derivation n = 754,109	Validation n = 323,197
Mean age (years)	43.1 ± 18.4	43.0 ± 18.4
< 65 years	85.1%	85.2%
65–74 years	8.4%	8.3%
≥ 75 years	6.5%	6.5%
Sex (male)*	41.7%	41.5%
Hypertension	21.5%	21.4%
Hyperlipidaemia	18.0%	17.9%
Diabetes	7.4%	7.3%
Smoking	13.0%	12.9%
ASCVD	4.2%	4.1%
Heart failure	2.6%	2.6%
Atrial fibrillation	2.5%	2.5%
Renal failure	1.5%	1.5%
Dialysis*	0.2%	0.2%
ACEi	5.6%	5.6%
ARB	2.2%	2.2%
Beta-blocker	4.5%	4.5%
Aldosterone	0.6%	0.6%
NSAID	25.3%	25.3%
Furosemide	2.2%	2.3%
Torsemide	0.1%	0.1%
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; NSAID: nonsteroidal anti-inflammatory drug.		
* <i>P</i> < 0.05.		

Significant predictors of HK (Fig. 2) as validated within this population are consistent with other bodies of evidence and include advancing age, male gender, comorbidities (eg, DM, HTN, HF, renal failure), and

medications associated with altered K⁺ homeostasis (eg, RAASi's, diuretics, beta-blockers, NSAIDs). Area under the curve c-statistics and 95% CIs for the derivation and validation cohorts were 0.850 (0.847, 0.853) and 0.853 (0.848, 0.858), respectively. ORs for incident HK in patients in the derivation cohort were evaluated in moderate- vs low-risk (OR = 2.64; *P* < 0.001) and high- vs low-risk (OR = 32.49; *P* < 0.001). In the validation cohort, OR for incident HK was evaluated in moderate- vs low-risk (OR = 2.81; *P* < 0.001) and high- vs low-risk (OR = 34.79; *P* < 0.001).

Discussion

Prior to this study, HK incidence and subsequent clinical and economic outcomes within a large healthcare system had not been fully described. Within Intermountain Healthcare, HK was associated with a large clinical burden, involving more than 1 in 10 patients.

In this analysis, compared to patients without HK, patients with HK were older (60 ± 18 vs 43 ± 18 years), more often male (51% vs 41%), and had a higher CCI (3.5 ± 2.8 vs 1.7 ± 1.4). Our findings are consistent with those in the medical literature, showing that HK is associated with multiple comorbidities. A retrospective analysis showed that the odds of HK were 57% higher in patients with ≥ 2 comorbid conditions (defined by the CCI criteria) compared with those without comorbidities [3]. Another study showed that in patients with HK, approximately 20.1% also had advanced CKD, 52.8% had DM, 53.3% had coronary artery disease, and 12.6% had peripheral vascular disease; furthermore, advanced CKD was a significant predictor of HK in patients with CVD, which was defined as the presence of HTN and HF [9]. In a retrospective claims analysis, Fitch et al found that the prevalence of several serious conditions (ie, CKD, HTN, and DM) was markedly higher in patients with HK than in the total Medicare and total commercially insured populations. In the total Medicare population and in Medicare patients with HK, the prevalences of CKD were 11.3% and 64.8%, respectively. In the total commercially insured population and in commercially insured patients with HK, the prevalences of CKD were 0.4% and 31.8%, respectively [10].

This analysis showed that HK was associated with higher yearly ED and inpatient costs than those without HK. These results are consistent with previous studies that evaluated resource utilization of HK [11]. In a study of patients with severe HK, the in-hospital mortality rate was 30.7%, which was strongly correlated with the difference between sK levels at admission and the level at its highest point (OR = 1.83; *P* < 0.001). In 2012, Fitch et al found that the average allowed per-patient per-month cost was 5 times higher in Medicare patients with HK than in the total Medicare population (\$5,645 vs \$1,035, respectively) and 15 times higher in commercially insured patients with HK than in the total commercially insured sample [10].

This study showed that HK was associated with a two-thirds increase in 3-year MACE, the composite of death, MI, stroke, and HF hospitalization. At 3 years, more HK patients experienced a MACE (19% vs 3%; *P* < 0.001), which persisted after adjustment (multivariable HR = 1.60; *P* < 0.001). Similarly, Luo et al showed that high sK levels are associated with a higher risk for hospitalization, MACE, and mortality. Compared with sK levels of 4.5–4.9 mmol/L, the adjusted MACE rate was nearly 2-fold higher for sK levels ≥ 6.0

mmol/L [12]. Jain et al showed that in patients with CVD who were taking antihypertensive drugs, HK was associated with increased all-cause mortality and an increased hospitalization rate [9]. In a retrospective observational study of 39,705 adults receiving inpatient critical care, HK was associated with higher all-cause mortality 30 days after the initiation of critical care [13]. Fitch et al found that the mortality rate in a Medicare sample with HK was 5.5 times higher than that in the total Medicare population (23.5% vs 4.3%, respectively) [10]. In a retrospective study of 1,924 patients diagnosed with acute MI, the mortality risk over a 3-year follow-up period was greater in those with HK than normokalaemia during hospitalization (HR = 4.78 for $sK \geq 5.0$ mmol/L) [14]. This information emphasizes that the incidence of HK, and its associated morbidity and mortality, is high enough that it justifies special consideration. Particularly among patients—and perhaps particularly older patient populations—who experience frequent recurrent episodes of HK, appropriate chronic preventative therapy may be considered.

The HyperK Score in this analysis was created and internally validated to have substantial ability to discriminate moderate vs severe HK. Use of the HyperK Score may assist in identifying patients needing careful monitoring and clinical management to prevent HK. This analysis showed that although risk worsens with the severity of HK, even mild HK was associated with a significant increase in medical costs and clinical risk.

Limitations

This is an observational study of usual care and did not guide treatment standardization, which could affect HK occurrence as well as its severity and frequency. Confounding was minimized through statistical modelling and appropriate adjustment. Nutritional intake was not assessed and may affect HK. The population was geographically concentrated in or near Utah and may not represent a general nationwide population. A direct association between the cause and effect of each HK episode cannot be determined from presently available data. In this study, overall rates of use of any K^+ binder were insufficiently low to analyse.

Conclusion

This analysis described HK incidence and subsequent clinical and economic outcomes within a large healthcare system. HK was shown to be associated with a large clinical and economic burden, involving more than 1 in 10 patients. HK was also associated with a marked increase in yearly ED and inpatient costs, and a two-thirds increase in 3-year MACEs. Risk, sequelae, and resource use worsened with either HK severity or HK frequency, with persistently recurring HK having perhaps the largest impact. Further, per investigator opinion, chronic management of HK is infrequently done, which was validated in this study. These findings justify a more careful look at mitigating the risks of and active management approaches to HK, including the role of recently approved K^+ binders approved for chronic HK management.

Abbreviations

ACEi: angiotensin-converting enzyme inhibitor

ARB: angiotensin-II receptor blockers

ASCVD: atherosclerotic cardiovascular disease

BMI: body mass index

CAD: coronary artery disease

CCB: calcium channel blocker

CCI: Charlson Comorbidity Index

CI: confidence interval

CKD: chronic kidney disease

CV: cardiovascular

CVD: cardiovascular disease

DM: diabetes mellitus

ED: emergency department

EF: ejection fraction

HF: heart failure

HFH: Heart failure hospitalization

HK: hyperkalaemia

HR: hazard ratio

HTN: hypertension

IQR: interquartile range

K⁺: potassium

MACE: major adverse cardiovascular event

MI: myocardial infarction

NSAID: nonsteroidal anti-inflammatory drug

OR: odds ratio

PVD: peripheral vascular disease

RAASi: renin-angiotensin-aldosterone system inhibitor

SBP: systolic blood pressure

SD: standard deviation

sK: serum potassium

SPS: sodium polystyrene sulfonate

TIA: transient ischaemic attack

Declarations

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Authors' contributions

JBM, HTM, JK designed the research; JBM and HTM conducted the research; HTM analysed the data; JBM and HTM wrote the paper and had primary responsibility for final content. All authors, JBM, JK, TLB, KUK, VTL, JLA, DLL, and HTM, have read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Intermountain Healthcare institutional review board and a waiver of informed consent was obtained prior to study initiation. Our investigation conforms with the principles outlined in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

Joseph B. Muhlestein, Tami L. Bair, Kirk K. Knowlton, Viet T. Le, Jeffrey L. Anderson, Donald L. Lappé, and Heidi T. May report employment by Intermountain Healthcare, which conducted research funded by Vifor Pharma, Inc.

Jennifer Kammerer reports employment by and stock in Vifor Pharma, Inc.

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Tables

Table 1. Overall Population - Baseline Characteristics and Post-Index Outcomes

	No-HK n=1,046,966	HK n=161,849
Mean age (years)*	43±18	60±18
<65 years	86%	56%
65-74 years	8%	20%
≥75 years	6%	24%
Sex (male)*	41%	51%
CCI*	1.7±1.4	3.5±2.8
Mean baseline sK (mmol/L)*,†	4.07±0.39	5.38±0.48
<i>Traditional CV Risk Factors</i>		
Hypertension*	20%	63%
Hyperlipidaemia*	17%	55%
Diabetes*	7%	33%
Smoking*	13%	26%
Renal insufficiency*	0.7%	16%
BMI, kg/m ² , n=662,888*	28.4±7.4	29.7±8.1
BMI ≥30	33%	40%
Maximum SBP (mm Hg)*	139.2±71.6	162.8±73.7
EF (%)*	60.9±10.2	58.0±12.9
<i>Prior Diagnoses</i>		
ASCVD*	4%	21%
CAD*	1%	7%
MI*	0.6%	4%
Stroke*	0.3%	2%
TIA*	0.7%	4%
PVD*	0.1%	1.0%
Heart failure*	2%	20%
Atrial fibrillation*	2%	14%
<i>Baseline Medications</i>		
Statin*	7%	39%
Other anti-diabetic*	1%	10%
Insulin*	2%	24%
Metformin*	3%	18%
Sulfonylurea*	1%	11%
NSAID*	39%	62%
ACEi*	8%	39%
ARB*	3%	16%
Aldosterone inhibitor*	0.6%	6%
Beta-blocker*	6%	32%
Diuretic*	9%	42%
CCB*	4%	22%
Furosemide*	3%	24%
Torsemide*	0.1%	1.2%
SPS*	0.04%	0.4%
Patiromer	0%	0%
<i>3-Year Post-Index Outcomes (n=1,128,582)</i>		
	n=983,409	n=145,173
MACE*	3.2%	18.8%
Death*	2.9%	16.7%

MI*	0.05%	0.2%
Stroke*	0.2%	0.9%
HFH*	0.2%	2.8%
<i>Multivariable Hazard Ratio (95% CI) for 3-Year MACE[‡]</i>		
No-HK vs HK*		1.60 (1.57, 1.63)
<i>Post-Index Average Costs/Year (n=1,208,815)</i>		
ED		
Cost±SD*	\$207±1,930	\$552±7,574
Median (IQR)	11 (0, 187)	56 (0, 408)
Inpatient		
Cost±SD*	\$1,477±21,423	\$10,956±93,026
Median (IQR)	0 (0, 740)	0 (0, 4585)
<i>Age ≥60 years Post-Index Average Costs/Year (n=290,972)</i>		
ED		
Cost±SD*	\$222±2,747	\$561±7,098
Median (IQR)	18 (0, 219)	72 (0, 444)
Inpatient		
Cost±SD*	\$3,765±35,137	\$13,844±109,257
Median (IQR)	0 (0, 2307)	1,277 (0, 6678)

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P < 0.001$.

[†]Taken within ± 1 month of index date (baseline sK level).

[‡]MACE is the composite of death, MI, stroke, and HFH.

Table 2. HK Frequency – Baseline Characteristics and Post-index Outcomes

	Transient n=82,307 (52%)	Intermittent n=72,382 (45%)	Persistent n=5,150 (3%)
Mean age (years)*	57±19	63±16	68±17
<65 years	64%	48%	40%
65-74 years	16%	24%	20%
≥75 years	20%	28%	40%
Sex (male)*	49%	53%	56%
CCI*	3.1±2.7	3.8±2.8	4.3±3.1
Mean baseline sK (mmol/L)*,†	5.3±0.5	5.4±0.5	5.6±0.6
<i>Traditional CV Risk Factors</i>			
Hypertension*	52%	74%	73%
Hyperlipidaemia*	49%	63%	55%
Diabetes*	23%	43%	43%
Smoking*	24%	29%	27%
Renal insufficiency*	10%	23%	30%
BMI ≥30	37%	43%	40%
Maximum SBP* (mm Hg)	158±82	168±64	168±49
EF (%)*	58±13	57±14	58±13
<i>Prior Diagnoses</i>			
ASCVD*	15%	26%	25%
CAD*	5%	10%	9%
MI*	3%	5%	4%
Stroke*	1%	2%	2%
TIA*	3%	4%	4%
PVD*	0.7%	1%	1%
Heart failure*	13%	27%	30%
Atrial fibrillation*	10%	17%	19%
<i>Baseline Medications</i>			
Statin*	33%	46%	41%
Other anti-diabetic*	6%	13%	14%
Insulin*	17%	32%	33%
Metformin*	13%	22%	23%
Sulfonylurea*	7%	16%	18%
NSAID*	61%	65%	59%
ACEi*	30%	47%	48%
ARB*	13%	20%	18%
Aldosterone inhibitor*	25%	39%	37%
Beta-blocker*	4%	9%	8%
Diuretic*	33%	52%	50%
CCB*	17%	27%	28%
Furosemide*	17%	32%	34%
Torsemide*	0.7%	2%	2%
SPS*	0.1%	0.7%	1%
Patiromer	0%	0%	0%
<i>3-Year Post-Index Outcomes (n=145,173)</i>			
	n=73,036	n=67,486	n=4,651
MACE*,‡	14.8%	21.3%	44.8%
Death*	14.1%	17.7%	44.2%

MI*	0.1%	0.3%	0.04%
Stroke*	0.6%	1.2%	0.5%
HFH*	0.9%	5%	1.8%
Multivariate Hazard Ratio (95% CI) for 3-Year MACE [‡]			
Persistent vs transient HK*	2.31 (2.20, 2.43)		
Intermittent vs transient HK	1.02 (0.99, 1.05)		
Post-Index Average Costs/Year			
ED			
Cost±SD*	\$422±4,221	\$620±2,305	\$1,737±37,846
Median (IQR)	0 (0, 274)	165 (0, 580)	0 (0, 70)
1-year visit* (primary diagnosis)	0.01%	0.3%	0.7%
Inpatient			
Cost±SD*	\$5,047±51,691	\$16,478±108,826	\$30,011±245,519
Median (IQR)	0 (0, 1347)	2681 (0, 9661)	0 (0, 1488)
1-year visit* (primary diagnosis)	0.004%	0.3%	0.9%

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P < 0.001$.

[†]Taken within ± 1 month of index date (baseline sK level).

[‡]MACE is the composite of death, MI, stroke, and HFH.

Table 3. HK Severity – Baseline Characteristics and Post-Index Outcomes

	Mild HK n=131,509 (81%)	Moderate HK n=25,380 (16%)	Severe HK n=4,960 (3%)
Mean age (years)*	60±18	60±19	58±19
<65 years	56%	55%	59%
65-74 years	20%	19%	18%
≥75 years	24%	26%	23%
Sex (male)*	51%	50%	48%
CCI*	3.2±2.7	3.9±2.9	4.1±3.0
Mean baseline sK (mmol/L)*,†	5.2±0.1	5.8±0.2	7.3±1.1
Traditional CV Risk Factors			
Hypertension*	62%	65%	65%
Hyperlipidaemia*	56%	51%	47%
Diabetes*	32%	36%	37%
Smoking*	25%	29%	33%
Renal insufficiency*	14%	24%	38%
BMI ≥30	40%	40%	40%
Maximum SBP (mm Hg)*	162±77	166±59	166±52
EF (%)*	38±13	57±14	58±13
Prior Diagnosis			
ASCVD*	20%	22%	19%
CAD*	7%	8%	7%
MI*	3%	4%	3%
Stroke*	1%	2%	2%
TIA*	4%	4%	3%
PVD*	1%	1%	0.9%
Heart failure*	18%	24%	26%
Atrial fibrillation*	13%	16%	17%
Baseline Medications			
Statin*	40%	37%	33%
Other anti-diabetic	10%	10%	9%
Insulin*	23%	29%	31%
Metformin [‡]	18%	17%	16%
Sulfonylurea*	11%	12%	10%
NSAID*	63%	61%	60%
ACEi*	38%	39%	36%
ARB	16%	16%	15%
Aldosterone inhibitor*	6%	8%	9%
Beta-blocker*	31%	34%	32%
Diuretic*	41%	46%	45%
CCB*	21%	24%	23%
Furosemide*	23%	29%	30%
Torsemide*	1%	2%	1%
SPS*	0.3%	0.8%	0.8%
Patiromer	0%	0%	0%
3-Year Post-Index Outcomes (n=145,173)			
	n=117,902	n=22,879	n=4392
MACE*,§	17.2%	25.1%	27.9%
Death*	15.2%	22.7%	25.9%

MI	0.2%	0.2%	0.2%
Stroke	0.9%	1%	0.7%
HFH*	2.6%	3.6%	3.3%
Multivariable Hazard Ratio (95% CI) for 3-Year MACE [§]			
Moderate vs mild HK*	1.29 (1.25, 1.33)		
Severe vs mild HK*	1.31 (1.23, 1.40)		
Post-Index Annualized Acute Care Trends			
ED			
Mean cost±SD*	\$519±7,819	\$701±6,936	\$668±2,100
Median (IQR)	54 (0, 391)	67 (0, 477)	68 (0, 554)
1-year visit* (primary diagnosis)	0.1%	0.4%	0.7%
Inpatient			
Mean cost±SD*	\$9,626±73,418	\$16,328±155,262	\$18,743±125,932
Median (IQR)	0 (0, 4235)	0 (0, 6222)	788 (0, 7332)
1-year visit* (primary diagnosis)	0.1%	0.4%	1.1%

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CCI: Charlson Comorbidity Index; CV: cardiovascular; ED: emergency department; EF: ejection fraction; HFH: heart failure hospitalization; HK: hyperkalaemia; IQR: interquartile range; MACE: major adverse CV event; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; sK: serum potassium; SPS: sodium polystyrene sulfonate; TIA: transient ischaemic attack.

Models adjusted by baseline characteristics, risk factors, and medications.

* $P \leq 0.001$.

[†]Taken within ± 1 month of index date (baseline sK level).

[‡] $P \leq 0.01$.

[§]MACE is the composite of death, MI, stroke, and HFH.

Table 4. HyperK – Baseline Characteristics

	Derivation n=754,109	Validation n=323,197
Mean age (years)	43.1±18.4	43.0±18.4
<65 years	85.1%	85.2%
65–74 years	8.4%	8.3%
≥75 years	6.5%	6.5%
Sex (male)*	41.7%	41.5%
Hypertension	21.5%	21.4%
Hyperlipidaemia	18.0%	17.9%
Diabetes	7.4%	7.3%
Smoking	13.0%	12.9%
ASCVD	4.2%	4.1%
Heart failure	2.6%	2.6%
Atrial fibrillation	2.5%	2.5%
Renal failure	1.5%	1.5%
Dialysis*	0.2%	0.2%
ACEi	5.6%	5.6%
ARB	2.2%	2.2%
Beta-blocker	4.5%	4.5%
Aldosterone	0.6%	0.6%
NSAID	25.3%	25.3%
Furosemide	2.2%	2.3%
Torsemide	0.1%	0.1%

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blockers; ASCVD: atherosclerotic cardiovascular disease; NSAID: nonsteroidal anti-inflammatory drug.

* $P<0.05$.

Figures

Figure 1

Percent of patients with MACE within 3 years stratified by A: HK vs No-HK; B: HK frequency; and C: HK severity. HK, hyperkalaemia; MACE, major adverse cardiovascular event. Figure 1A footnote: The number of patients with 3 years of follow-up was 1,128,582 (no-HK=983,409, HK=145,173). Figure 1B footnote:

The number of patients with 3 years of follow-up was 145,173 (transient HK=73,036, intermittent HK=67,486, persistent HK=4,651). Figure 1C footnote: The number of patients with 3 years of follow-up was 145,173 (mild HK=117,902, moderate HK=22,879, severe HK=4,392).

Figure 2

Significant predictors of incident HK (sK >5.5 mmol/L) compared to No-HK (sK ≤5.0 mmol/L). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CAD, coronary artery disease; HK, hyperkalaemia; NSAID, nonsteroidal anti-inflammatory drug; sK, serum potassium.