CLINICAL KIDNEY JOURNAL

ORIGINAL ARTICLE

Serum potassium variability as a predictor of clinical outcomes in patients with cardiorenal disease or diabetes: a retrospective UK database study

Glen James[1], Jennifer Kim[2], Carl Mellström[3], Kerrie L. Ford[4], Nia C. Jenkins[4], Carmen Tsang[4], Marc Evans[5] and Phil McEwan [ID][4]

[1]Biopharmaceuticals Business Unit, AstraZeneca, Cambridge, UK, [2]Biopharmaceuticals Business Unit, AstraZeneca, Gaithersburg, MD, USA, [3]Biopharmaceuticals Business Unit, AstraZeneca, Gothenburg, Sweden, [4]Health Economics and Outcomes Research Ltd, Cardiff, UK and [5]Department of Diabetes and Endocrinology, University Hospital Llandough, Cardiff, UK

Correspondence to: Phil McEwan; E-mail: phil.mcewan@heor.co.uk

ABSTRACT

Background. Hyperkalaemia is an electrolyte abnormality associated with adverse clinical outcomes; however, few studies have investigated the relationship with patterns of hyperkalaemia over time. This study explored the impact of time spent in a hyperkalaemic state and variability of serum potassium (sK^+) on major adverse cardiovascular events (MACE) and all-cause mortality in patients with chronic kidney disease (CKD), resistant hypertension, heart failure and diabetes.

Methods. Cohorts comprised adult patients diagnosed with CKD stage 3+, resistant hypertension, heart failure or diabetes, and/or renin–angiotensin–aldosterone system inhibitor prescription, between 1 January 2003 and 30 June 2018, from the UK Clinical Practice Research Datalink. Associations between percentage of follow-up spent in a hyperkalaemic state ($sK^+ \geq 5.0$ mmol/L, ≥ 5.5 mmol/L, ≥ 6.0 mmol/L) or sK^+ variability (standard deviation above or below median standard deviation) and all-cause mortality or MACE were investigated.

Results. For $sK^+ \geq 5.0$ mmol/L, time spent in a hyperkalaemic state was associated with reduced risk of all-cause mortality across all cohorts. For higher sK^+ thresholds, this trend was attenuated or reversed; for time spent in a hyperkalaemic state at $sK^+ \geq 6.0$ mmol/L, an increased risk of mortality was seen in the overall cohort and for patients with diabetes, resistant hypertension or prescribed renin–angiotensin–aldosterone system inhibitors, with no consistent association seen for patients with CKD or heart failure. Risk of MACE in the overall cohort and in patients with CKD, diabetes or resistant hypertension increased with time spent in a hyperkalaemic state at all sK^+ thresholds; however, no correlation was seen in patients with heart failure or those receiving dialysis. High sK^+ variability was associated with a higher risk of MACE compared with low sK^+ variability across most sK^+ categories in the overall population and in all disease cohorts, except patients on dialysis; however, no association between sK^+ variability and all-cause mortality was observed.

Conclusions. Patterns of hyperkalaemia, including time spent in hyperkalaemia and sK^+ variability, are associated with adverse clinical outcomes. Regular monitoring of sK^+ in high-risk populations in broader community, primary care and outpatient settings may enable guideline-recommended management of hyperkalaemia and help avoid adverse events.

INTRODUCTION

Hyperkalaemia (HK) is commonly defined as serum potassium (sK$^+$) >5.0 mmol/L [1–3]. Major risk factors include chronic kidney disease (CKD), resistant hypertension (RHTN), diabetes mellitus and cardiovascular diseases, particularly heart failure (HF) [2, 4, 5]. These diseases are frequently comorbid, reflecting both common risk factors, such as smoking, dyslipidaemia and obesity, as well as the interdependence of renal and cardiac function and the systemic damage caused by metabolic dysfunction including diabetes [6]. Consequently, many patients have more than one risk factor for developing HK and the incidence rate of HK events has been shown to increase with higher comorbidity burden [7].

The cardiorenal protective benefits of renin–angiotensin–aldosterone system inhibitors (RAASis) are well documented, and patients with one or more of these conditions are often managed with these agents. However, treatment with RAASi increases the risk of developing HK because these drugs decrease renal K$^+$ excretion [1, 4, 5, 8–10]. Consequently, downtitration and discontinuation of RAASi are frequently used to manage HK, leaving patients unable to benefit from the disease-modifying effects of RAASi [8, 11, 12]. Discontinuation from RAASi therapy or failure to achieve guideline-recommended RAASi dosing have been associated with adverse clinical outcomes, including major adverse cardiovascular events (MACE) and all-cause mortality (ACM) [11, 13–15].

HK is associated with adverse clinical outcomes including MACE [composite of arrhythmia, HF, myocardial infarction (MI) and stroke], hospitalization and ACM [8]. A 'U-shaped' association between sK$^+$ and adverse clinical outcomes has been described in several studies, including in patients with CKD, HF or diabetes [8, 16–21]. However, the majority of studies were not designed to capture associations between transient, recurrent or variable sK$^+$ and adverse clinical outcomes. One recent study showed that a proportion of patients suffer frequently recurrent HK events [22], potentially leading to patients spending a high proportion of their time in an HK state. Other previous studies of patients in the intensive care unit (ICU) or receiving dialysis have demonstrated that increased sK$^+$ variability is associated with increased mortality [23–25], while another study in patients receiving haemodialysis demonstrated an association between HK excursions and adverse clinical outcomes [26]. This study aimed to explore the impact of length of time spent in an HK state, defined by thresholds of sK$^+$ 5.0, ≥5.5 or 6.0 mmol/L, on adverse clinical outcomes and to investigate sK$^+$ variability as a risk factor for adverse clinical outcomes independent of mean sK$^+$ in real-world cohorts of patients with cardiorenal conditions and diabetes.

MATERIALS AND METHODS

Study design and patient population

This was a retrospective cohort study using electronic health record data from the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) databases [27, 28]. The study period was 1 January 2008 to 30 June 2018, with data also extracted for a 5-year look-back period (1 January 2003 to 31 December 2007). Eligible patients were ≥18 years of age and had a record of at least one of CKD stage 3+, dialysis, RHTN, diabetes or HF during the study period or look-back period, and/or RAASi prescription, defined as angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists or renin inhibitors, during the study period. Figure 1 shows the patient flow chart representing selection of the study population and Figure 2 shows the time-independent overlap of the study cohorts. Full definitions of inclusion criteria are in the Supplementary material.

The study protocol (18_213) was approved by the Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency on 30 October 2018 and further amendments approved between 2019 and 2021 (final protocol reference 18_213R2MnA3).

Data structuring and covariates

Cohorts were defined according to the first recorded incidence of CKD stage 3+, dialysis, RHTN, diabetes, HF or RAASi prescription. Within each cohort, the index date was the start of the study period or the date the condition or RAASi prescription was first recorded during the study period. Patients were followed up until the end of the study period, loss to follow-up (defined as the date a patient transferred out of the practice, the date the practice left CPRD or the last date of any record) or death, whichever occurred earliest. Clinical history data were extracted for 5 years prior to the first index date per patient. For further details on study methodology, see the Supplementary material.

Outcomes and data analysis

HK was defined using sK$^+$ thresholds (sK$^+$ ≥5.0, ≥5.5 and ≥6.0 mmol/L), ACM defined as death from any cause and MACE defined as a composite of arrhythmia, HF, MI and stroke. Time in an HK state was expressed as the percentage of total follow-up spent with sK$^+$ ≥5.0, ≥5.5 or ≥6.0 mmol/L, subdivided into 1% intervals. The relationship between percentage of follow-up time spent in an HK state and the risk of ACM or MACE was calculated per patient and was expressed relative to the risk experienced by patients who spent no time in an HK state during their follow-up period; the logarithm of each relative risk was then calculated, allowing the baseline risk at 0% time spent in an HK state to be defined as 0. Thus, a log relative risk <0 indicates that the risk of adverse clinical outcomes for that 1% interval was lower than the risk associated with no follow-up time spent in an HK state.

Variability of sK$^+$ was defined as sK$^+$ standard deviation (SD) above (high variability) or below (low variability) the median SD, calculated over a patient's entire follow-up. Crude rates of ACM and MACE, stratified by sK$^+$ variability, were calculated for each cohort, then adjusted rates were calculated by fitting generalized linear models with an interaction term for mean and SD sK$^+$ using published coefficients (see Supplementary methods) [20].

Statistical analyses were performed using R version 3.5.2 or later [29].

RESULTS

Summary and baseline characteristics

In total, 931 460 patients met the eligibility criteria (Figures 1 and 2): 317 135 RHTN, 288 871 diabetes, 297 702 CKD, 84 210 HF,
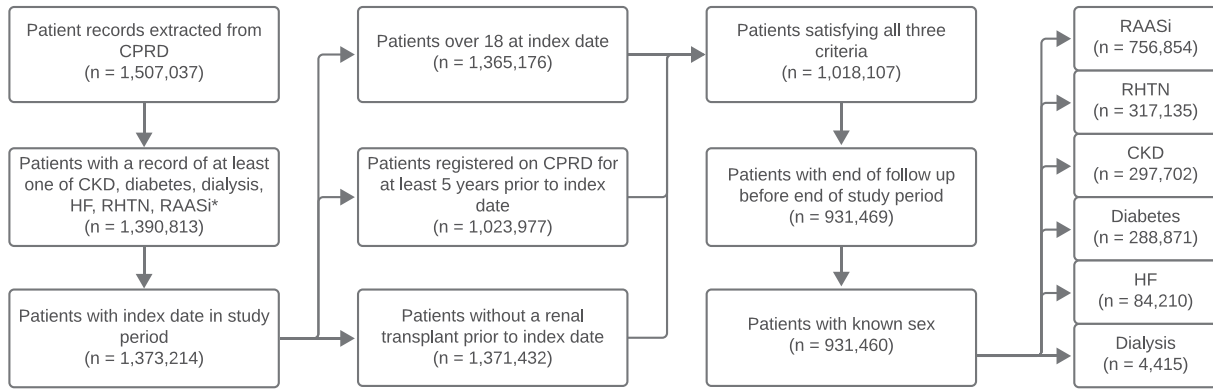
FIGURE 1: Patient flow chart. *Details of how each cohort was defined can be found in Supplementary data, Table S1.
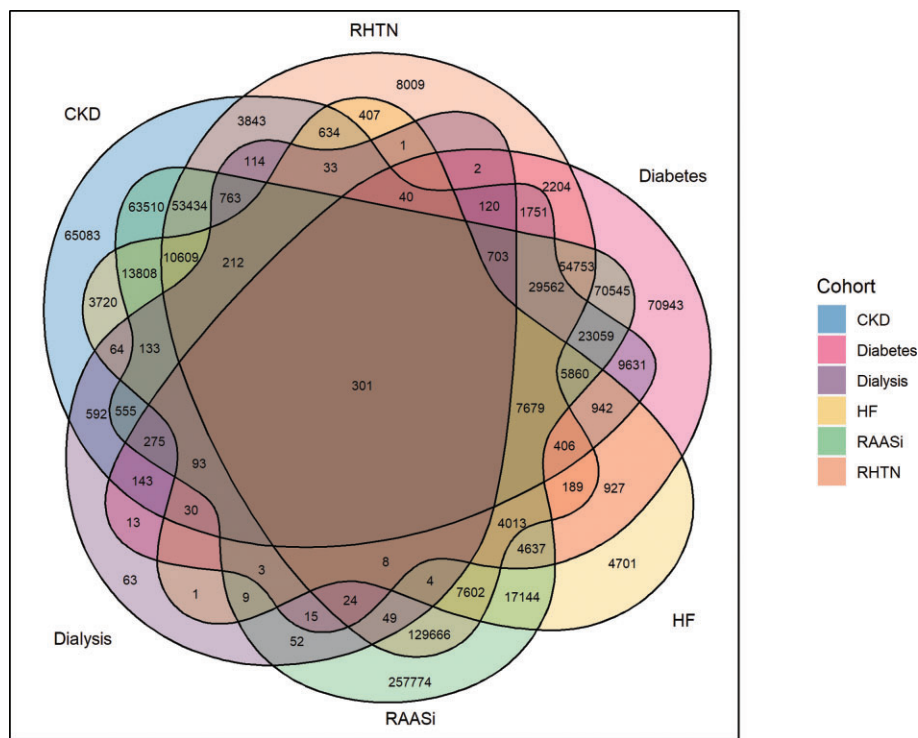

FIGURE 2: Venn diagram showing overlap of study cohorts. This figure represents time-independent cohorts, i.e. each cohort comprises all patients who have ever been a member of that cohort.

756 854 RAASi prescription. A total of 257 774 (27.7%) patients were in the RAASi cohort and were not entered into any other cohorts. There were 4415 patients with end-stage renal disease receiving dialysis. Baseline characteristics for these cohorts can be found in the Supplementary results, Table S11.

Frequency of HK and time spent in HK

Patients with HF had the highest crude rate of HK events [490.6 (487.8–493.3), 125.6 (124.21–127.0) and 23.4 (22.8–24.0) per 1000 patient-years at sK^+ $\geq$5.0, $\geq$5.5 and $\geq$6.0 mmol/L, respectively], but patients with CKD and those with diabetes cohort typically spent longer in an HK state at both sK^+ $\geq$5.0 mmol/L (0.72 and 0.73 mean years spent in HK) and $\geq$5.5 mmol/L (0.12 and 0.11

mean years spent in HK) (Table 1). The cohort of patients receiving RAASi had the lowest rate of HK events and time spent in an HK state (Table 1).

Relationship between time spent in HK and risk of adverse clinical outcomes

The risks of ACM (Figure 3) or MACE (Figure 4) relative to time spent in an HK state were calculated for the overall population and each cohort. Time spent in an HK state was defined as the percentage of follow-up time spent with sK^+ $\geq$5.0 mmol/L, $\geq$5.5 mmol/L or $\geq$6.0 mmol/L. The histograms highlight that the majority of patients did not experience HK during the follow-up period; data presented were capped at 20% follow-up time spent

Table 1. Rate of HK and time spent in HK

	Overall (N = 931 460)	CKD (N = 297 702)	RHTN (N = 317 135)	Diabetes (N = 288 871)	HF (N = 84 210)	RAASi (N = 756 854)	Dialysis (N = 4415)
HK events (HK defined as sK$^+$ ≥5.0 mmol/L)							
Total number of events	1 057 762	558 806	466 660	534 609	123 809	681 732	7028
Mean no. HK events per patient (SD)	1.14 (2.83)	1.88 (3.69)	1.47 (3.26)	1.85 (3.65)	1.47 (3.13)	0.9 (2.36)	1.59 (3.52)
Crude rate of HK events per 1000 PYs (95% CI)	223.53 (223.10–223.96)	410.93 (409.85–412.01)	261.35 (260.60–262.10)	354.96 (354.01–355.91)	490.55 (487.82–493.29)	211.04 (210.54–211.55)	501.01 (489.36–512.86)
Total time spent in HK, years	445 623.28	213 488.73	186 482.54	211 016.88	34 892.54	284 116.09	2803.05
Mean time spent in HK per patient, years (SD)	0.48 (1.09)	0.72 (1.28)	0.59 (1.17)	0.73 (1.31)	0.41 (0.89)	0.38 (0.96)	0.63 (1.21)
Percentage of follow-up time spent in a hyperkalaemic state	8.51	15.04	10.24	13.04	11.68	8.04	17.33
HK events (HK defined as sK$^+$ ≥5.5 mmol/L)							
Total number of events	227 543	138 273	106 073	120 916	31 698	148 149	2632
Mean no. HK events per patient (SD)	0.24 (1.05)	0.46 (1.50)	0.33 (1.27)	0.42 (1.44)	0.38 (1.23)	0.2 (0.87)	0.60 (1.75)
Crude rate of HK events per 1000 PYs (95% CI)	48.08 (47.89–48.28)	101.68 (101.15–102.22)	59.41 (59.05–59.76)	80.28 (79.83–80.74)	125.59 (124.21–126.98)	45.86 (45.63–46.1)	187.63 (180.53–194.94)
Total time spent in HK, years	65 210.48	36 634.20	28 106.51	33 116.79	5979.20	41 395.65	1056.76
Mean time spent in HK per patient, years (SD)	0.07 (0.34)	0.12 (0.45)	0.09 (0.38)	0.11 (0.43)	0.07 (0.30)	0.05 (0.29)	0.24 (0.71)
Percentage of follow-up time spent in a hyperkalaemic state	1.30	2.71	1.61	2.08	2.18	1.29	6.51
HK events (HK defined as sK$^+$ ≥6.0 mmol/L)							
Total number of events	36 333	24 220	17 905	19 640	5895	23 413	716
Mean no. HK events per patient (SD)	0.04 (0.30)	0.08 (0.44)	0.06 (0.37)	0.07 (0.41)	0.07 (0.37)	0.03 (0.25)	0.16 (0.69)
Crude rate of HK events per 1000 PYs (95% CI)	7.68 (7.60–7.76)	17.81 (17.59–18.04)	10.03 (9.88–10.18)	13.04 (12.86–13.22)	23.36 (22.76–23.96)	7.25 (7.16–7.34)	51.04 (47.37–54.92)
Total time spent in HK, years	5754.05	3625.01	2555.75	2918.02	634.97	3384.14	300.29
Mean time spent in HK per patient, years (SD)	0.01 (0.09)	0.01 (0.12)	0.01 (0.10)	0.01 (0.11)	0.01 (0.08)	0 (0.07)	0.07 (0.40)
Percentage of follow-up time spent in a hyperkalaemic state	0.13	0.30	0.16	0.20	0.27	0.13	1.80

FIGURE 3: Relative risk of ACM according to time spent in an HK state. Lines represent the log relative risk, bars represent the number of patients ('000 000s') at risk for each time interval. Time is represented as % follow-up time spent in an HK state at the given sK$^+$ threshold, in non-overlapping 1% windows, and is capped at 20%. DM: diabetes mellitus.

FIGURE 4: Relative risk of MACE according to time spent in an HK state. Lines represent the log relative risk, bars represent the number of patients ('000 000s') at risk for each time interval. Time is represented as % follow-up time spent in an HK state at the given sK$^+$ threshold, in non-overlapping 1% windows, and is capped at 20%. DM: diabetes mellitus.
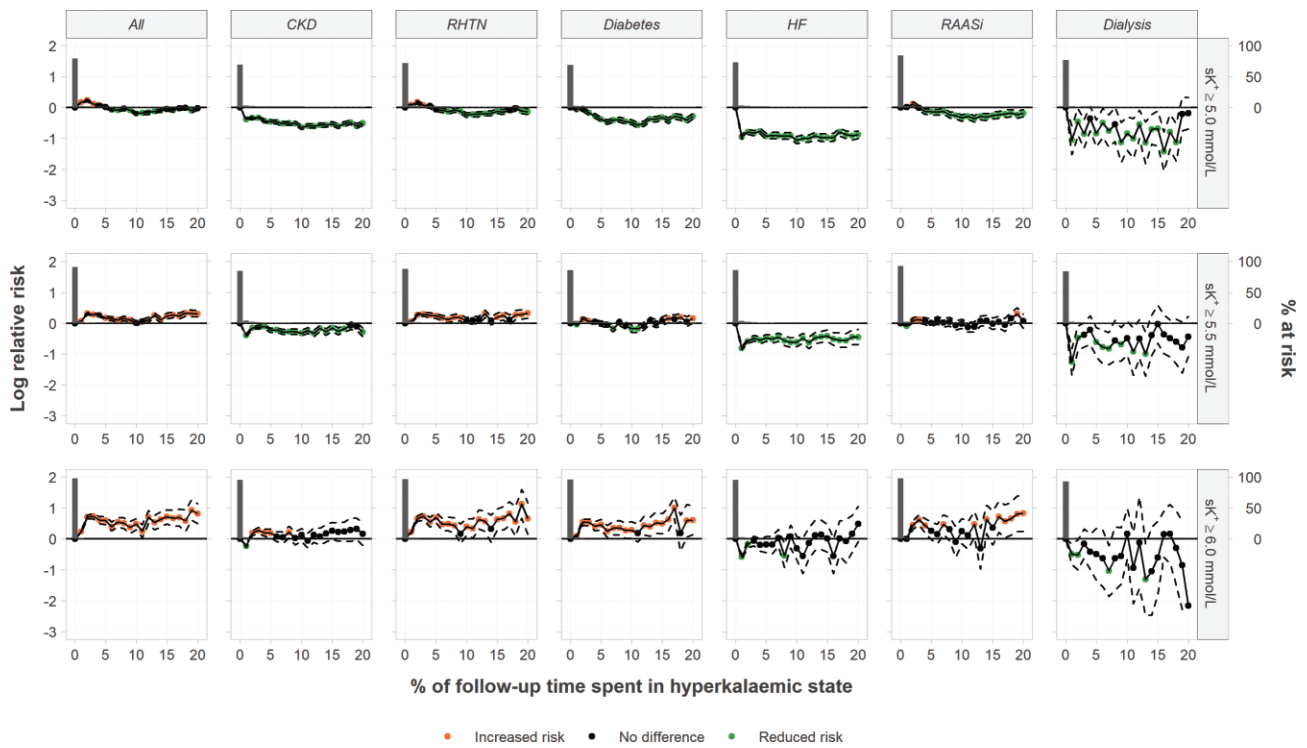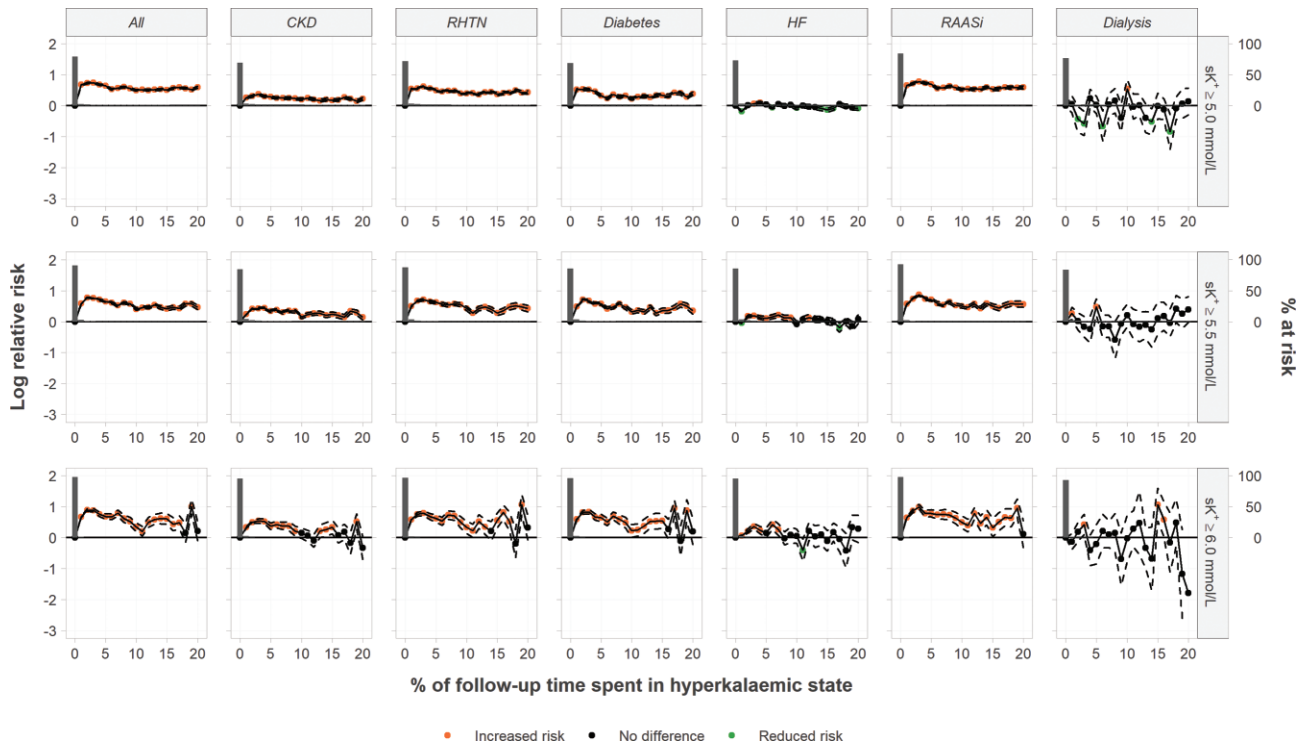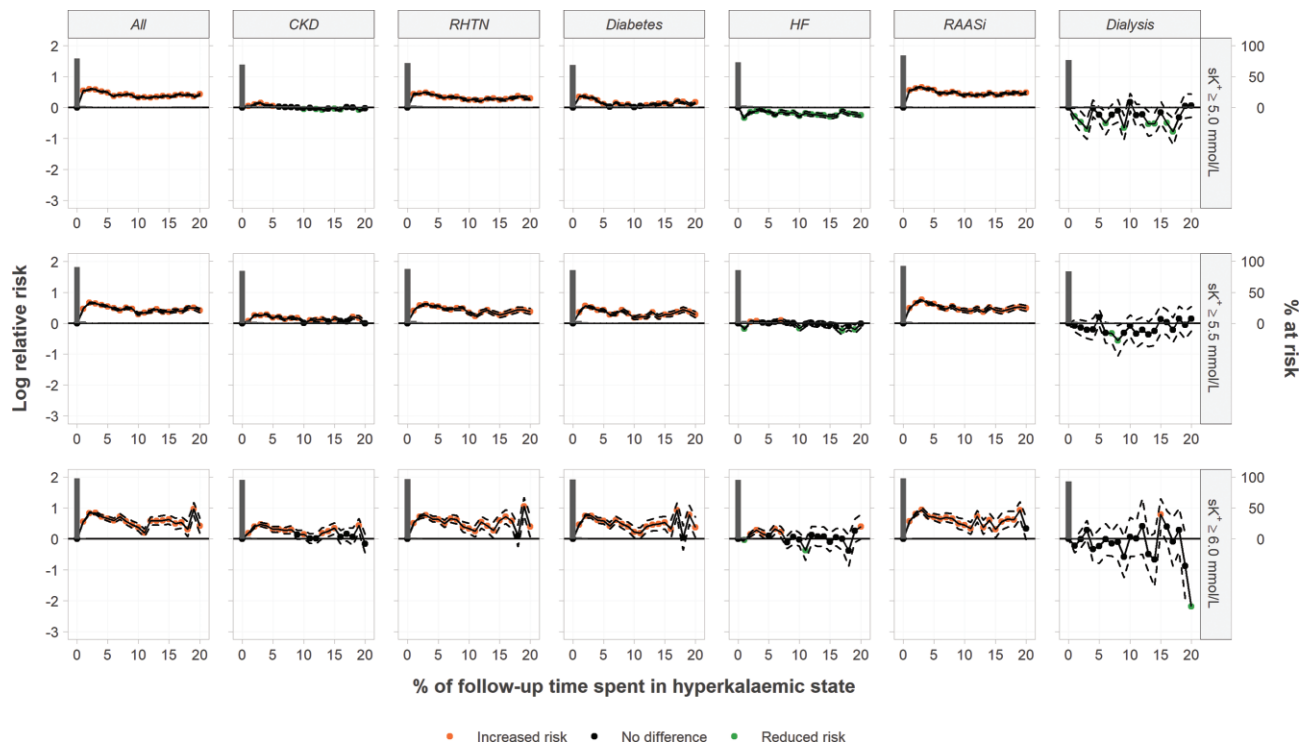
FIGURE 5: Relative risk of ACM or MACE according to time spent in an HK state. Lines represent the log relative risk, bars represent the number of patients ('000 000s') at risk for each time interval. Time is represented as % follow-up time spent in an HK state at the given sK⁺ threshold, in non-overlapping 1% windows, and is capped at 20%. DM: diabetes mellitus.

in an HK state due to small patient numbers above this range leading to large uncertainties.

At an HK threshold of ≥5.0 mmol/L, time spent in an HK state was associated with a reduced relative risk of mortality, particularly in patients with CKD, diabetes, HF or receiving dialysis, and to a lesser extent in the overall cohort and in patients with RHTN or prescribed RAASi (Figure 3). At an HK threshold of ≥5.5 mmol/L, this trend started to reverse in the overall cohort and for patients with diabetes or RHTN, with longer time spent in an HK state associated with increased risk, while a reduction in risk was still seen in patients with CKD, HF or on dialysis. At an HK threshold of ≥6.0 mmol/L, an association between time spent in HK and increased risk of mortality was seen most strongly in the overall cohort and in patients with RHTN, diabetes and those on RAASi. For patients with HF or CKD, the association between time spent in an HK state and reduced risk of mortality remained but became weaker as the threshold increased to 5.5 or 6.0 mmol/L. Patient numbers were too small in the dialysis cohort for time spent with HK at a threshold ≥6.0 mmol/L to draw conclusions about any relationship with mortality.

At all HK thresholds, the risk of MACE for the overall cohort and patients with CKD, diabetes or RHTN or prescribed RAASi initially increased rapidly with time spent in an HK state, then plateaued at an increased relative risk across the range (Figure 4). The risk of MACE for patients with HF or those on dialysis did not show a clear relationship with time spent in a HK state at any threshold.

Given the generally opposing relationship between time spent in an HK state and ACM versus MACE, a combined outcome of 'ACM or MACE' was explored (Figure 5). Broadly, the associations observed were similar to those for the MACE outcome, with an increased risk associated with time spent in an HK state

for the overall cohort and patients with CKD, diabetes, RHTN or prescribed RAASi at all thresholds, although the relationship for patients with CKD was attenuated, particularly at an HK threshold of ≥5.0 mmol/L. Similarly, no clear relationship between time spent in an HK state and 'ACM or MACE' was observed for patients with HF or those on dialysis, except for a small but consistent decrease in risk for patients with HF at an HK threshold of ≥5.0 mmol/L.

Baseline characteristics associated with sK⁺ variability

All included patients were divided into patients with a mean sK⁺ in the normokalaemic range (3.5 to <5.0 mmol/L) and those with a mean sK⁺ in the HK range (≥5.0 mmol/L). Each group was stratified into high and low sK⁺ variability, defined as sK⁺ SD above (high variability) or below (low variability) the median SD. Baseline characteristics, stratified by sK⁺ variability, are presented in Table 2 (see Supplementary data, Table S12 for additional characteristics). Similar associations were seen between high sK⁺ variability and baseline characteristics in both normokalaemic and HK groups. In particular, clinical characteristics indicating reduced kidney function (lower estimated glomerular filtration rate, higher serum creatinine) and history of severe renal disease were associated with high sK⁺ variability regardless of mean sK⁺.

Relationship between sK⁺ variability and risk of adverse clinical outcomes

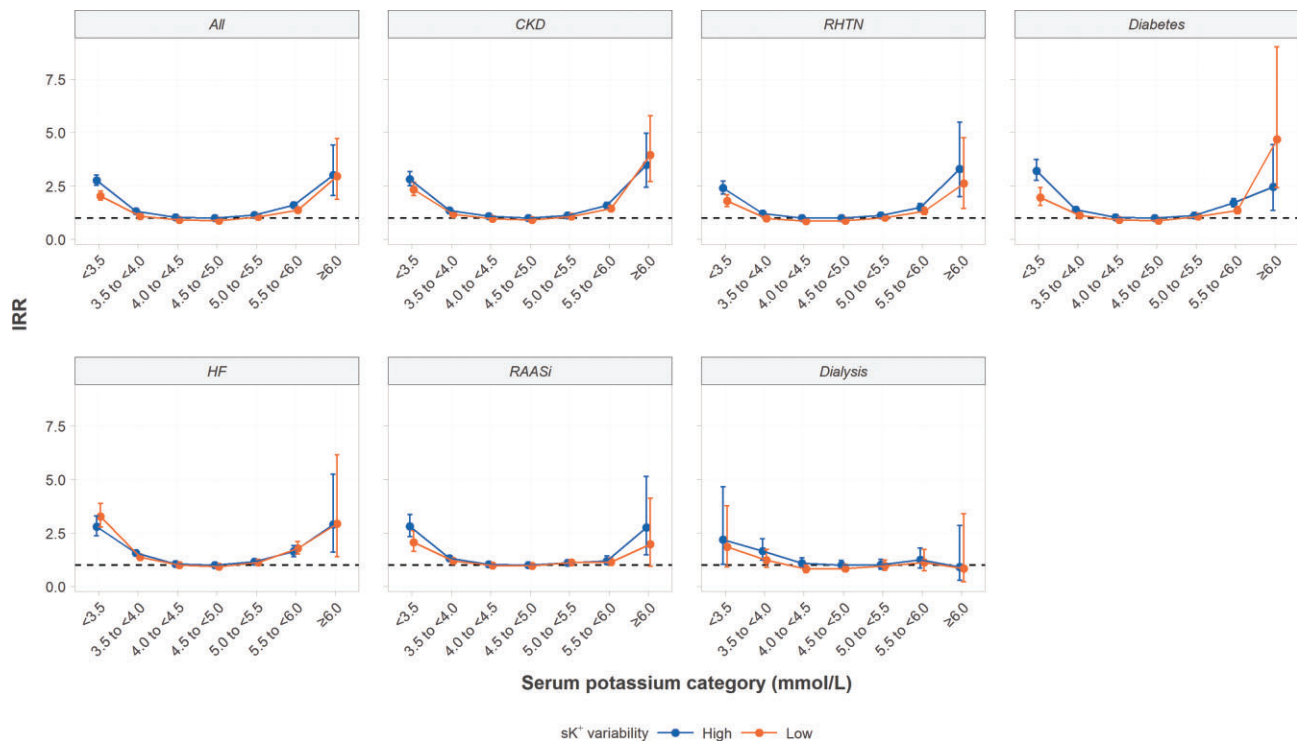Crude event rates for ACM and MACE were adjusted using published risk equations [20] and adjusted for sK⁺ 0.5 mmol/L

Table 2. Baseline characteristics associated with sK$^+$ variability for overall cohort

Variable	Mean sK$^+$: 3.5 to <5.0 mmol/L			Mean sK$^+$: ≥5.0 mmol/L		
	Low variability[a] (N = 278 445)	High variability[a] (N = 278 454)	P	Low variability[a] (N = 22 236)	High variability[a] (N = 22 237)	P
Baseline demographics						
Follow-up, mean years (SD)	5.82 (3.10)	6.30 (2.99)	<0.0001	5.40 (3.20)	5.80 (3.08)	<0.0001
Age, mean years (SD)	69.06 (13.55)	71.20 (13.30)	<0.0001	73.86 (12.08)	73.76 (12.37)	0.3765
Female, n (%)	145 214 (52.15)	145 678 (52.32)	0.2189	10 869 (48.88)	10 485 (47.15)	0.0003
Current smoker, n (%)	50 416 (18.11)	52 306 (18.78)	<0.0001	4464 (20.08)	4720 (21.23)	0.0028
CCI, mean (SD)	4.09 (2.14)	4.51 (2.25)	<0.0001	5.34 (2.18)	5.44 (2.25)	<0.0001
Baseline clinical characteristics, mean (SD)						
BMI (kg/m^2)	29.81 (6.48)	29.07 (6.37)	<0.0001	29.11 (6.48)	28.73 (6.57)	<0.0001
SBP (mmHg)	137.20 (17.51)	136.69 (18.37)	0.0180	136.26 (17.79)	135.85 (18.66)	<0.0001
DBP (mmHg)	77.52 (10.75)	76.74 (11.13)	0.2859	74.28 (10.78)	74.17 (10.99)	<0.0001
Serum creatinine (μmol/L)	89.46 (26.99)	95.27 (32.48)	<0.0001	114.55 (41.53)	120.33 (45.19)	<0.0001
eGFR (mL/min/1.73 m^2)	64.39 (17.51)	60.69 (18.75)	<0.0001	51.52 (18.80)	49.04 (19.74)	<0.0001
Haemoglobin (g/dL)	13.18 (2.02)	12.70 (2.42)	0.7409	11.84 (3.03)	12.05 (2.20)	0.0004
Serum lipids (mmol/L)	4.73 (1.14)	4.68 (1.15)	0.0367	4.53 (1.15)	4.50 (1.17)	<0.0001
Baseline clinical history, n (%)						
Acute kidney injury	6890 (2.47)	13 548 (4.87)	<0.0001	1509 (6.79)	2317 (10.42)	<0.0001
Renal disease[b]	75 034 (26.95)	88 631 (31.83)	<0.0001	10 996 (49.45)	11 467 (51.57)	<0.0001
Hypertension	163 461 (58.70)	174 435 (62.64)	<0.0001	12 840 (57.74)	13 331 (59.95)	<0.0001
Hyperlipidaemia	44 352 (15.93)	48 792 (17.52)	<0.0001	4026 (18.11)	4176 (18.78)	0.0688
T1DM	6129 (2.20)	7335 (2.63)	<0.0001	986 (4.43)	1163 (5.23)	0.0001
T2DM	83 794 (30.09)	75 741 (27.20)	<0.0001	7452 (33.51)	7163 (32.21)	0.0036
MI	9679 (3.48)	12 558 (4.51)	<0.0001	1155 (5.19)	1391 (6.26)	<0.0001
Atrial fibrillation	23 586 (8.47)	34 271 (12.31)	<0.0001	2381 (10.71)	2893 (13.01)	<0.0001
Cardiovascular disease	13 399 (4.81)	16 449 (5.91)	<0.0001	1332 (5.99)	1416 (6.37)	0.1024
Stroke	8048 (2.89)	10 077 (3.62)	<0.0001	774 (3.48)	884 (3.98)	0.0064
Peripheral vascular disease	5784 (2.08)	7462 (2.68)	<0.0001	906 (4.07)	1050 (4.72)	0.0009
Arrhythmia	27 866 (10.01)	39 274 (14.10)	<0.0001	2780 (12.50)	3284 (14.77)	<0.0001
Chronic liver disease	4817 (1.73)	5639 (2.03)	<0.0001	236 (1.06)	335 (1.51)	<0.0001
Baseline clinical medications, n (%)						
RAASi	188 289 (67.62)	197 598 (70.96)	<0.0001	16 443 (73.95)	16 312 (73.36)	0.1593
ACEi	136 090 (48.88)	140 116 (50.32)	<0.0001	12 355 (55.56)	12 078 (54.31)	0.0084
ARB	57 228 (20.55)	60 032 (21.56)	<0.0001	4512 (20.29)	4533 (20.38)	0.8156
MRA	7717 (2.77)	17 222 (6.18)	<0.0001	1146 (5.15)	1867 (8.40)	<0.0001
Renin inhibitors	203 (0.07)	241 (0.09)	0.0790	25 (0.11)	31 (0.14)	0.5039
Anti-diabetic	74 870 (26.89)	67 698 (24.31)	<0.0001	8343 (37.52)	7296 (32.81)	<0.0001
Diuretics	110 623 (39.73)	137 110 (49.24)	<0.0001	7570 (34.04)	9282 (41.74)	<0.0001
K$^+$-sparing diuretics	3218 (1.16)	4679 (1.68)	<0.0001	301 (1.35)	297 (1.34)	0.9013

BMI: body mass index; CCB: calcium channel blocker; CCI: Charlson's Comorbidity Index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; MRA: mineralocorticoid receptor antagonist; SBP: systolic blood pressure; T1DM: type I diabetes mellitus; T2DM: type II diabetes mellitus.

Subgroups do not sum to overall population due to either missing sK$^+$ values or open groupings.

[a]Low variability: patient sK$^+$ SD below median SD; high variability: patient sK$^+$ SD above median SD.

[b]Renal disease includes all Read codes related to both acute renal failure and CKD.

Note that these values include the dialysis cohort.

FIGURE 6: Adjusted rates of ACM with respect to sK⁺, stratified by sK⁺ variability. Adjusted for patient demographics and clinical characteristics using published risk equations [20]. Dotted line indicates IRR = 1.

increments. Adjusted rates stratified by sK⁺ variability are presented for ACM in Figure 6 and for MACE in Figure 7. 'U-shaped' relationships between sK⁺ and ACM, with an increased risk for sK⁺ <3.5 mmol/L, 5.5–6.0 mmol/L and ≥6.0 mmol/L, were observed for all cohorts except patients receiving dialysis (Figure 6). No increase in risk was seen for the sK⁺ categories between 4.0 and 5.5 mmol/L. No relationship between sK⁺ variability and adjusted rates of ACM was observed (Figure 6).

For MACE, there was no clear association between sK⁺ and the incidence rate ratio (IRR), although a trend to increased risk was seen at sK⁺ ≥6.0 mmol/L in the overall cohort and in patients with RHTN or CKD (Figure 7). However, increased sK⁺ variability was associated with a higher risk of MACE compared with low sK⁺ variability across most sK⁺ categories in the overall population and in all disease cohorts, except patients on dialysis (Figure 7). The separation in IRR between the high and low variability was most prominent in the overall cohort and in patients with CKD, RHTN and diabetes, and less clear in patients with HF, those receiving RAASi and in all cohorts at higher concentrations of sK⁺.

Serum K⁺ testing frequency

To understand real-world monitoring frequency and identify possible unmet need, the frequency of sK⁺ testing in each cohort was analysed. Although patients with HF had, on average, the lowest absolute number of sK⁺ tests (7.3), when adjusted for follow-up [per 1000 patient-years (PYs)] the crude testing rate was significantly higher than all the other cohorts {2429.3 per 1000 PYs [95% confidence interval (CI) 2423.2–2435.3]} (Table 3). Patients prescribed RAASi had the lowest testing rate [1216.19

per 1000 PYs (1214.99–1217.4)]. In light of the lower risk of ACM associated with time spent in an HK state described above, the relationship between the rate of sK⁺ testing, stratified by the number of HK episodes, and ACM was investigated (Figure 8). In the overall population and in all the cohorts, patients who had experienced two or more HK events had a higher rate of sK⁺ testing, but a lower rate of ACM, than patients who experienced only one HK event.

DISCUSSION

This study investigated the association between adverse clinical outcomes and sK⁺ dynamics, specifically time spent in an HK state and variability of sK⁺. The aim of the study was to understand whether these relationships would affect the risks of ACM or MACE in a large, real-world UK cohort of 931 460 patients with renal, cardiovascular and metabolic conditions.

An increased risk of MACE was associated with increased time spent in an HK state at all HK thresholds in patients with CKD, RHTN, diabetes or prescribed RAASi; however, this increased risk was not observed for patients with HF, which is consistent with previous analysis of incident HF patients within this cohort [20] and with a recent meta-analysis that showed no clear relationship between HK and MACE in HF patients [8]. It is worth noting that there is no standard definition of MACE, which may also contribute to the heterogeneity of results related to this endpoint.

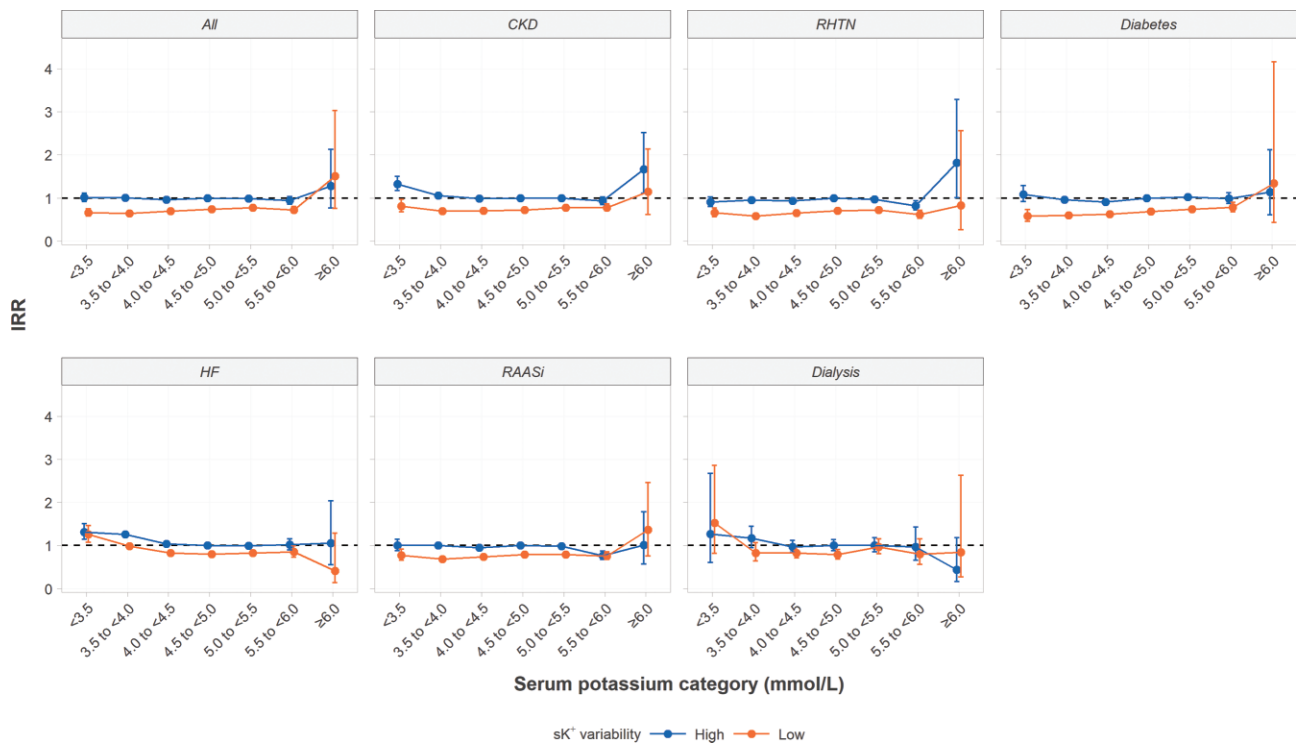Surprisingly, the relative risk of mortality was reduced over the range of time spent in an HK state at an HK threshold of ≥5.0 mmol/L, particularly in patients with CKD, diabetes, HF or receiving dialysis, with a small decrease in risk also seen across

FIGURE 7: Adjusted rates of MACE with respect to sK$^+$, stratified by sK$^+$ variability. Adjusted for patient demographics and clinical characteristics using published risk equations [20]. Dotted line indicates IRR = 1.

longer times spent in HK for the overall cohort and patients with RHTN or prescribed RAASi. As the HK threshold analysed was increased, the magnitude of the decrease in relative risk of mortality began to diminish, and a positive trend between the two was seen in the overall cohort and in patients with diabetes or RHTN or prescribed RAASi. This finding indicates that the severity of HK remains an important consideration and highlights the increase in risk associated with time spent in a relatively moderate HK state, although it should be noted that the decreased risk persisted for patients with CKD or HF for sK$^+$ ≥5.5 mmol/L and did not increase even at sK$^+$ ≥6.0 mmol/L for patients with HF. The analysis of sK$^+$ testing rates indicated that an increased rate of sK$^+$ monitoring in those with two or more HK events was associated with reduced ACM, suggesting that these patients may have benefitted from more proactive management, although ascertaining further details of treatment received was beyond the scope of this manuscript.

Although numerous studies have investigated the association between either single or time-averaged sK$^+$ measurements and adverse clinical outcomes in a range of patient populations, few analyses have considered sK$^+$ patterns over time, particularly in real-world clinical practice. Núñez *et al.* showed a U-shaped association between continuous, time-updated sK$^+$ and mortality in 2164 patients hospitalized for acute HF [30]. Although not directly comparable due to different analysis approaches, these results are broadly in agreement with those presented here, indicating that cumulative HK is associated with an increased risk of adverse clinical outcomes, and that the magnitude of the associated risk increases as sK$^+$ increases. However, in contrast to the patients with HF shown in Figure 3, Núñez *et al.* did not observe a decreased risk of ACM associated with longi-

tudinal sK$^+$ ≥5.0 mmol/L. This may be due to underlying differences in the study population—Núñez *et al.* considered patients hospitalised for acute HF only—or due to other methodological differences.

The current study also demonstrated that increased sK$^+$ variability may be a risk factor for MACE compared with low sK$^+$ variability, independent of the absolute sK$^+$ concentration; this is consistent with a recent study demonstrating that HK excursions are associated with mortality, hospitalizations and cardiovascular events in patients receiving haemodialysis [26]. It should be noted that no association between sK$^+$ variability and adverse outcomes was seen in patients on dialysis in the present study; however, the dialysis cohort was comparatively small, which led to wide CIs, limiting the conclusions that could be drawn. Furthermore, dialysis patients are typically managed in outpatient settings or dialysis centres that contribute little data to the CPRD; therefore, it is likely that this study did not capture the full extent of tests and events experienced by these patients.

It is plausible that patients who exhibit poor regulation of sK$^+$ might experience transient changes significant enough to affect cardiac electrophysiology, although without electrocardiogram data this remains speculative. Variability of sK$^+$ has previously been investigated in patients receiving peritoneal dialysis, with a higher risk of mortality seen in the two most variable quartiles (coefficient of variation of sK$^+$ 12.0 to <16.7% and ≥16.7%) [25]. Hessels *et al.* [24] and Engelhardt *et al.* [23] demonstrated that ICU patients with higher sK$^+$ variability had a higher adjusted risk of in-hospital mortality [adjusted odds ratio (OR) for potassium variability 5.61 (95% CI 3.64–8.66) and adjusted OR for potassium variability ≥3rd SD 1.74 (95% CI 1.44–2.11), respectively]. Furthermore, one consideration of the present analysis

Table 3. Frequency of sK+ testing

	Overall (N = 931 460)	CKD (N = 297 702)	RHTN (N = 317 135)	Diabetes (N = 288 871)	HF (N = 84 210)	RAASi (N = 756 854)	Dialysis (N = 4415)
Total number of sK+ tests	6448736	2599914	2959407	2821475	613120	3928638	23502
Mean no. sK+ tests per patient (SD)	6.92 (8.67)	8.73 (9.42)	9.33 (9.05)	9.77 (8.95)	7.28 (9.10)	5.19 (7.14)	5.32 (8.76)
Crude rate of sK+ tests per 1000	1362.76	1911.9	1657.42	1873.33	2429.25	1216.19	1675.39
PYs (95% CI)	1361.71–1363.82	1909.57–1914.22	1655.53–1659.31	1871.15–1875.52	2423.17–2435.34	1214.99–1217.4	1654.04–1696.95

is that, within the long time frame considered, sK+ can be affected by a range of unascertained and uncontrolled variables such as diet, additional comorbidities and medications. Hessels *et al.* implemented a computerized potassium regulation programme [24] but, despite the monitoring and sK+ regulation received by these patients, which would help mitigate these uncontrolled variables, higher sK+ variability remained associated with higher mortality. Notably, this relationship was seen in patients with a mean sK+ within the normokalaemic range.

No association between sK+ variability and ACM was seen in the current analyses (Figure 6), unlike in the prior studies discussed above [23, 24]. This could be due to the significant differences in patient populations studied; both Hessels *et al.* and Engelhardt *et al.* consider patients in the critical care setting [23, 24], whereas the data in the present study cover a patient population in routine, non-critical clinical practice. Nevertheless, the MACE results presented here contribute to a small but increasing body of evidence that sK+ variability is potentially a risk factor for adverse clinical outcomes, and this increased risk may be masked by assessment of competing biomarkers or analyses that only consider mean sK+ over time. For example, parallels can be drawn with the more established role of glucose variability as a risk factor and potential surrogate marker for cardiovascular and microvascular complications in patients with diabetes [31] and raises the possibility that sK+ variability could act as a similar surrogate for CV outcomes.

One implication of these findings for clinical practice is that a structured approach to regular monitoring of sK+ in high-risk patient populations in the broader community, primary care and outpatient settings may be desirable in order to manage sK+ and reduce risk of adverse clinical outcomes. Indeed, the UK Renal Association 2020 Clinical Practice Guidelines for Treatment of Acute Hyperkalaemia recommend that patients with CKD 1–3 require blood monitoring at least once or twice per year, patients with CKD 4–5 at least two to four per year, and patients who have experienced an HK episode should be monitored more frequently [32], while the 2021 KDIGO guidelines for the management of blood pressure in CKD recommend starting ACEi or ARB in patients with hypertension and CKD, with or without diabetes, but highlight the need for monitoring sK+ due to the risk of HK [33]. It is notable that the cohort of patients prescribed RAASi in this study had the lowest rate of HK events and sK+ tests, which may reflect discontinuation of RAASi following a first HK event to reduce the risk of recurrence, or may be a consequence of the proportion of patients who were prescribed RAASi but did not have any of the comorbidities evaluated, who may be at lower risk of developing HK and therefore require less frequent monitoring [34]. In general, proactive sK+ management may permit patients to remain on guideline-recommended doses of RAASi, which is significant in light of evidence suggesting that interruption, downtitration or cessation of RAASi therapy is independently associated with adverse clinical outcomes [11, 13–15]. Indeed, the 2021 ESC HF guidelines recognize that HK is a major contributor to RAASi underuse, and recommend consideration of novel K+ binders for treating HK. Interrogating this real-world dataset for sK+ testing frequency highlighted that HF patients had the highest rate of sK+ tests when adjusted for follow-up time, at nearly double the overall rate. This could indicate a heightened awareness of the risks of HK in this cohort; however, it could also be an incidental finding reflecting a general high rate of biochemical testing in these patients. This highlights one limitation of the current analysis, which is that findings of HK in a real-world cohort are subject to ascertainment bias, particularly

FIGURE 8: Rate of ACM with respect to rate of sK⁺ testing, stratified by number of HK episodes. ACM: all-cause mortality; CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; PYs: patient-years; RAASi: renin-angiotensin-aldosterone system inhibitors; RHTN: resistant hypertension; sK+ serum potassium.

confounding with repeated sK⁺ measures following an initial HK diagnosis.

Although there are many strengths of this study, which include the comprehensive analysis of a large, diverse, granular, real-world cohort of patients with renal, cardiovascular and metabolic conditions with long follow-up, there are some limitations. Firstly, this is a study using electronic health records from the UK; therefore, the findings may not be fully representative of other settings. As the data are collected under conditions of routine care, they are potentially subject to missingness and coding errors. Other limitations of the current study include its retrospective design, meaning that the relationships observed are associations, and conclusions cannot be drawn about causality; furthermore, data regarding treatment for HK episodes were not evaluated; therefore, any potential impact of treatment is not considered. The analysis also assumes that each elevated sK⁺ measurement represents an HK event, which does not take into account possible false positives due to, for example, haemolysis. Although the risk of adverse outcomes with respect to sK⁺ variability was adjusted for known relevant covariates, it is possible that additional, unascertained factors that were not adjusted for or residual confounding are contributing to the associations observed. For example, the risk equations used adjusted for time-updated RAASi usage and baseline status of selected other medications, but did not consider all medication prescriptions, nor was there any adjustment for dose. Furthermore, the risk equations used to calculate adjusted risks of MACE and ACM in the sK⁺ variability analysis were originally fitted using incident HF and CKD populations, whereas these data include both incident and prevalent patients. However, a previous analysis demonstrated that these published risk equations appear to be generalizable to broader populations [7].

In conclusion, this study adds to the increasing body of evidence supporting an association between sK⁺ variability, independent of the absolute sK⁺ level, and risk of adverse clinical outcomes in patients with a range of common renal, cardiovas-

cular and metabolic conditions. While a number of other studies have illustrated an association between sK⁺ variability and mortality, our study adds to this by showing an association between sK⁺ variability and morbidity, therefore providing further evidence in support of appropriate and timely management of HK in order to reduce the associated cardiovascular disease burden. A structured approach to routine sK⁺ monitoring in broader community, primary care and outpatient settings, proactive clinical awareness and chronic, guideline-recommended management of HK may improve outcomes for these patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

FUNDING

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part. G.J., J.K. and C.M. are employees of AstraZeneca and stock owners. K.L.F., C.T., N.C.J. and P.M. are or were employees of Health Economics and

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics databases. Access to these data are subject to approval of a research protocol via application to the CPRD Research Data Governance process (https://www.cprd.com/research-applications).

REFERENCES

1. Ben Salem C, Badreddine A, Fathallah N *et al*. Drug-induced hyperkalemia. *Drug Saf* 2014; 37: 677–692
2. Dunn JD, Benton WW, Orozco-Torrentera E *et al*. The burden of hyperkalemia in patients with cardiovascular and renal disease. *Am J Manag Care* 2015; 21 (15 Suppl): s307–s315
3. Sadjadi SA, McMillan JI, Jaipaul N *et al*. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Ther Clin Risk Manage* 2009; 5: 547–552
4. Michel A, Martín-Pérez M, Ruigómez A *et al*. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. *Eur J Heart Fail* 2015; 17: 205–213
5. Nilsson E, Gasparini A, Ärnlöv J *et al*. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017; 245: 277–284
6. Dzau VJ, Antman EM, Black HR *et al*. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes. *Circulation* 2006; 114: 2850–2870
7. Tafesse E, Hurst M, Sugrue D *et al*. Serum potassium as a predictor of adverse clinical outcomes in patients with increasing comorbidity burden. *Eur Heart J Qual Care Clin Outcomes* 2020
8. Palaka E, Grandy S, Darlington O *et al*. Associations between serum potassium and adverse clinical outcomes: a systematic literature review. *Int J Clin Pract* 2020; 74: e13421
9. Bandak G, Sang Y, Gasparini A *et al*. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc* 2017; 6: e005428
10. Tafesse E, Hurst M, Hoskin L *et al*. Risk factors associated with the incidence and recurrence of hyperkalaemia in patients with cardiorenal conditions. *Int J Clin Pract* 2021; 75: e13941
11. Epstein M. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. *Kidney Int Suppl* 2016; 6: 20–28
12. Linde C, Bakhai A, Furuland H *et al*. Real-World associations of renin-angiotensin-aldosterone system inhibitor dose, hyperkalemia, and adverse clinical outcomes in a cohort of patients with new-onset chronic kidney disease or heart failure in the United Kingdom. *J Am Heart Assoc* 2019; 8: e012655
13. Komajda M, Cowie MR, Tavazzi L *et al*. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUAL-IFY international registry. *Eur J Heart Fail* 2017; 19: 1414–1423
14. Ouwerkerk W, Voors AA, Anker SD *et al*. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017; 38: 1883–1890
15. Humphrey TJL, James G, Wittbrodt ET *et al*. Adverse clinical outcomes associated with RAAS inhibitor discontinuation: analysis of over 400 000 patients from the UK Clinical Practice Research Datalink (CPRD). *Clin Kidney J* 2021; 14: 2203–2212
16. Luo J, Brunelli SM, Jensen DE *et al*. Association between serum potassium and outcomes in patients with reduced kidney function. *Clin J Am Soc Nephrol* 2016; 11: 90–100
17. Collins AJ, Pitt B, Reaven N *et al*. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 2017; 46: 213–221
18. Kovesdy CP, Matsushita K, Sang Y *et al*. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. *Eur Heart J* 2018; 39: 1535–1542
19. Furuland H, McEwan P, Evans M *et al*. Serum potassium as a predictor of adverse clinical outcomes in patients with chronic kidney disease: new risk equations using the UK clinical practice research datalink. *BMC Nephrol* 2018; 19: 211
20. Linde C, Qin L, Bakhai A *et al*. Serum potassium and clinical outcomes in heart failure patients: results of risk calculations in 21 334 patients in the UK. *ESC Heart Fail* 2019; 6: 280–290
21. Kashihara N, Kohsaka S, Kanda E *et al*. Hyperkalemia in real-world patients under continuous medical care in Japan. *Kidney Int Rep* 2019; 4: 1248–1260
22. Tafesse E, Hurst M, Hoskin L *et al*. Risk factors associated with the incidence and recurrence of hyperkalaemia in patients with cardiorenal conditions. *Int J Clin Pract* 2020; 75: e13941
23. Engelhardt LJ, Balzer F, Müller MC *et al*. Association between potassium concentrations, variability and supplementation, and in-hospital mortality in ICU patients: a retrospective analysis. *Ann Intensive Care* 2019; 9: 100
24. Hessels L, Hoekstra M, Mijzen LJ *et al*. The relationship between serum potassium, potassium variability and in-hospital mortality in critically ill patients and a before-after analysis on the impact of computer-assisted potassium control. *Crit Care* 2015; 19: 4
25. Xu Q, Xu F, Fan L *et al*. Serum potassium levels and its variability in incident peritoneal dialysis patients: associations with mortality. *PLoS One* 2014; 9: e86750
26. Karaboyas A, Robinson BM, James G *et al*. Hyperkalemia excursions are associated with an increased risk of mortality and hospitalizations in hemodialysis patients. *Clin Kidney J* 2021; 14: 1760–1769
27. Medicines and Healthcare Products Regulatory Agency. *CPRD Linked Data*. 4 September 2019. https://cprd.com/linked-data (21 May 2021, date last accessed)

28. Medicines and Healthcare Products Regulatory Agency. *Primary Care Data for Public Health Research.* 4 September 2019. https://cprd.com/primary-care (21 May 2021, date last accessed)

29. R: A language and environment for statistical computing. *R Foundation for Statistical Computing, Vienna, Austria.* R Core Team, 2016. https://www.R-project.org (15 February 2021, date last accessed)

30. Núñez J, Bayés-Genís A, Zannad F *et al.* Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation* 2018; 137: 1320–1330

31. Ceriello A. Glucose variability and diabetic complications: is it time to treat? *Diabetes Care* 2020; 43: 1169–1171

32. The Renal Association .Alfonzo A, Harrison A *et al. Clinical Practice Guidelines: Treatment of Acute Hyperkalaemia in Adults.* 2020. https://renal.org/sites/renal.org/files/RENAL%20ASSOCIATION%20HYPERKALAEMIA%20GUIDELINE%202020.pdf (May 2021, date last accessed)

33. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021; 99: S1–S87

34. McDonagh TA, Metra M, Adamo M *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021; 42: 3599–3726