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Original Article

Serum potassium as a predictor of adverse clinical outcomes in patients with increasing comorbidity burden

Eskinder Tafesse[1]*, Michael Hurst[2], Daniel Sugrue[2], Louise Hoskin[2], Karolina Badora[2], Lei Qin[1], Glen James[3], and Phil McEwan[2]

[1]Global Health Economics, AstraZeneca, 101 Orchard Ridge Drive, Gaithersburg, MD, USA, 20878; [2]Health Economics and Outcomes Research Ltd, Rhymney House, Unit A Copse Walk, Cardiff Gate Business Park, Cardiff, UK, CF23 8RB; and [3]Global Medical Affairs, AstraZeneca, Academy House, 136 Hills Road, Cambridge, UK, CB2 8PA

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Aims The aim of this study was to establish whether patients with multiple comorbidities may be at elevated risk of hyperkalaemia (HK), a potentially life-threatening electrolyte imbalance, and the associated adverse clinical outcomes.

Methods and results This was a retrospective, observational cohort study using UK primary and secondary care data. Adult patients with at least one of: resistant hypertension, chronic kidney disease stage 3+, dialysis, heart failure (HF), and diabetes, were eligible for inclusion. According to their diagnoses, patients were grouped into overlapping cohorts that were updated as multimorbidity progressed. Outcomes of interest were incident HK, all-cause mortality (ACM), and major adverse cardiovascular events (MACE). A total of 673 686 patients met the eligibility criteria, 36.3% of whom developed multimorbidity during the study period. A consistent U-shaped association was observed between serum K^+ level and adjusted incidence of ACM and MACE. Hyperkalaemia was progressively more common with increasing Charlson Comorbidity Index (CCI). Relative to a CCI <3, scores of ≥3 to <6, and ≥6 were associated with 2.9- and 6.2-fold increases, respectively, in crude HK (serum K^+ ≥5.0 mmol/L) incidence rate. In all condition-based cohorts except for HF, there was a clear correlation between increasing CCI and the risk of ACM and MACE associated with hypokalaemia and HK.

Conclusion Patients with a higher CCI are at an increased risk of developing HK and appear more prone to adverse clinical outcomes associated with abnormal serum K^+ levels, warranting additional routine clinical monitoring.

Keywords Hyperkalaemia • Comorbidity • Major adverse cardiovascular events • Mortality

Introduction

Multimorbidity, defined as the coexistence of several chronic diseases or conditions, is the most common condition among adults.[1] Multimorbid patients require substantial healthcare resources and account for over two-thirds of healthcare spending.[1] Recent estimates suggest that multimorbidity affects a third of the world population[2] and 27% of adults in England.[3]

Cardiovascular disease and diabetes are among the four major causes of mortality from non-communicable diseases worldwide, accounting for 31% and 3% of all global deaths, respectively.[4] Diabetes, cardiovascular, and renal conditions often present concomitantly, and the common pathophysiology of these conditions is well described. Risk factors, such as diabetes, elevated low-density lipoprotein-cholesterol levels, hypertension, and smoking stimulate molecular and cellular processes that ultimately lead to target organ

* Corresponding author. Tel: +1 (301) 398-0713, Email: eskinder.tafesse@astrazeneca.com

damage which, at its final stage, manifests itself as heart failure (HF) or end-stage renal disease.[5] The aforementioned risk factors tend to cluster,[5] with metabolic syndrome (the combination of abdominal obesity, insulin resistance, hypertension, and hyperlipidaemia) being a well know example, estimated to affect over a billion people worldwide.[6]

Patients with multimorbidity are at higher risk of safety incidents, due to polypharmacy, extensive management regimens, complex patient needs and increased vulnerability, amongst other factors.[7] Hyperkalaemia (HK), defined as a serum/plasma potassium (K^+) level exceeding the physiological range of 3.5–5.0 mmol/L,[8] is a potentially life-threatening electrolyte imbalance, which may result in electrophysiological disturbances causing cardiac arrhythmias, cardiac arrest, and sudden death.[9–11] Both hypokalaemia and HK are associated with an increased risk of mortality in patients with HF[12] and chronic kidney disease (CKD).[13]

Risk factors for HK were recently reviewed in detail.[14] Briefly, several drug classes used in the management of cardiovascular, metabolic, and renal conditions could cause HK, for example renin–angiotensin–aldosterone system inhibitors (RAASi, i.e. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists), beta-blockers and K^+-sparing diuretics.[15] A range of other risk factors for the development of HK exist, including CKD, HF, and diabetes.[16] Reducing dietary K^+ intake may help to prevent or treat HK,[16] but the low-K^+ diet can prove difficult to adhere to. Emergency treatment may be needed if HK is severe or associated with electrocardiogram changes.[16]

As described above, the risk of HK can be affected by both the conditions patients may have and the treatments used to manage them. We therefore speculated that patients with multiple comorbidities may be at a particularly high risk of HK. To address this hypothesis, the present study investigated the influence of comorbidity burden on the association between serum K^+ and adverse clinical outcomes, including all-cause mortality (ACM) and major adverse cardiovascular events (MACE). This relationship was explored in a large, contemporary, real-world cohort of UK patients with cardiovascular, renal, and metabolic conditions, using previously published risk equations.[12,13]

Methods

Study design

This was a retrospective, observational cohort study using pre-existing patient data from the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) databases, including data from primary and secondary care settings, respectively.[17,18] Data were collected from 01 January 2003 to 30 June 2018, encompassing the study period (01 January 2008 to 30 June 2018) and a 5-year look-back period (01 January 2003 to 31 December 2007). The protocol for this study (18_213) was approved by the Independent Scientific Advisory Committee (ISAC) on 30 October 2018, with a minor amendment subsequently approved on 7 February 2019.

Eligibility criteria

The study population comprised of all eligible patients in the CPRD and linked HES databases between 01 January 2008 and 30 June 2018. Included patients were aged ≥18 years and had a record of at least one of the following conditions (see Supplementary material online, *Table S1* for criteria used to identify these) during the study period (incident patients) or the 5-year look-back period (prevalent patients): resistant hypertension (RHTN), CKD stage 3+ (on or off dialysis), dialysis, HF, and diabetes.

Patients were excluded if they died or were lost to follow-up prior to the beginning of the study period (i.e. had no index date), were aged <18 years at index date, had <5 years of CPRD records available (in order to gain the 5-year lookback period) or if they had a history of renal transplant.

Data preparation and structuring

Structuring of patient data

Patients were grouped into cohorts according to their diagnoses and could accumulate into additional cohorts over time based on subsequent diagnoses. Where two or more conditions coexisted (e.g. CKD and dialysis, RHTN and HF), the patient was included in all relevant cohorts reflecting multimorbidity progression, so that the cohorts were overlapping. Two of the cohorts described herein (CKD and HF cohorts) were partly included in previous studies.[12,13] Specifically, these prior studies[12,13] included only incident patients, while the current study included both prevalent and incident patients.

The index date was set to 01 January 2008 for prevalent patients or to the date the condition of interest was first recorded in the CPRD during the study period for incident patients. The look-back period, which served to collect clinical histories, spanned 5 years prior to the index date. When a patient entered a new cohort, a new index date and look-back period were defined, so that different index dates and look-back periods were applied for the same patient across different cohorts. Within each cohort, a patient's follow-up time was divided into a series of non-overlapping intervals, with a new interval starting each time a serum K^+ measurement was recorded. The length of each interval was the time between successive K^+ measurements or condition-related events prompting cohort change. An example of structuring patient follow-up into cohorts is presented in *Figure 1*. In this example, the patient's first three K^+ measurements contributed to the diabetes cohort, while the fourth measurement to both the diabetes and HF cohorts.

All patients were followed up and their records extracted for all observations up to and including the first occurrence of any of the following: death; loss to follow-up defined as the date a patient was transferred out of the practice, the date that the practice left the database, or the last date of any measurements/event; end of the study period (30 June 2018).

Covariates of interest

The following covariates were extracted for all eligible patients at their index date and, for time-dependent covariates, updated at K^+ measurement intervals over the follow-up period. Time-independent covariates included gender (male/female) and Index of Multiple Deprivation (IMD, a measure of relative socioeconomic deprivation of a neighbourhood) ranging from 1 (least deprived) to 5 (most deprived). Time-dependent covariates were age, disease duration or time since dialysis initiation, smoking status, medication usage, clinical history, body mass index, systolic blood pressure, diastolic blood pressure, serum K^+ (categorized as <3.5 mmol/L, 3.5 to <4.0 mmol/L, 4.0 to <4.5 mmol/L, 4.5 to <5.0 mmol/L, 5.0 to <5.5 mmol/L, 5.5 to <6.0 mmol/L, and ≥6.0 mmol/L), serum creatinine, estimated glomerular filtration rate, cholesterol levels, white blood cell count, haemoglobin level, serum phosphorus level, and Charlson's Comorbidity Index (CCI).[19,20] See the Supplementary material online for further details on collecting covariate information.

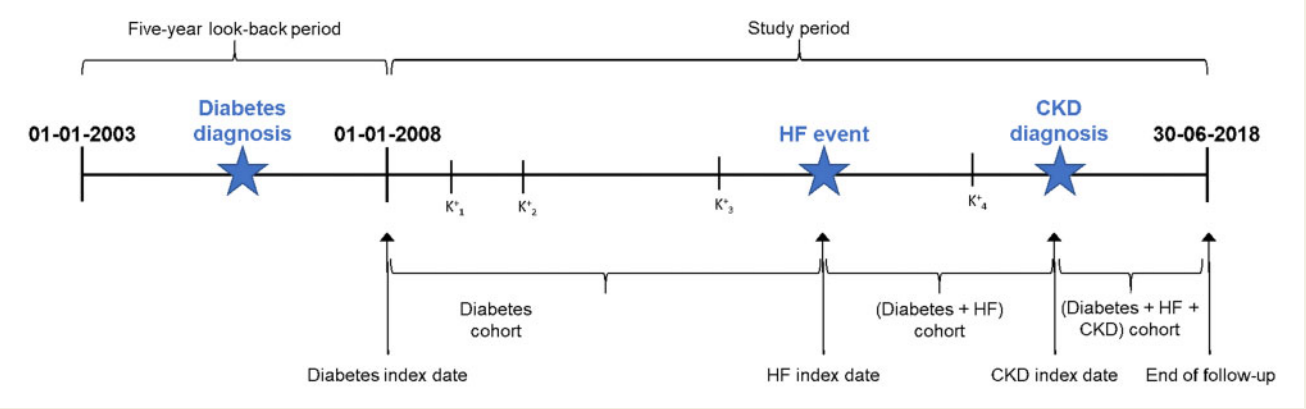

Figure 1 Illustrative example of assigning follow-up time to cohorts. CKD, chronic kidney disease; HF, heart failure; K^+_n denotes patient's *n*th potassium measurement over the study period.

Outcomes analysed

The key outcomes of interest collected in this study were incident HK, defined at three alternative serum K^+ measurement thresholds (≥5.0 mmol/L, ≥5.5 mmol/L, and ≥6.0 mmol/L); ACM, defined as death from any cause; MACE, defined as a composite of any of arrhythmia (including tachycardia, irregularity of heart beats/pulse, atrial/ventricular fibrillation/flutter), HF, myocardial infarction (MI), or stroke. Note that for patients with HF at baseline, a second HF record was classified as a MACE.

Data analysis

Data loading and structuring were undertaken using Structured Query Language (SQL) server 2016. Statistical analyses were performed using R version 3.5.2.[21] Prior to data analysis, data cleaning was conducted to remove from the dataset clearly implausible values, assumed to result from an administrative error.

Patient demographics were described using means and standard deviations (SDs) for continuous variables, while medians, counts, and proportions were used to describe categorical variables, along with associated measures of variability for both types of variables. Due to the way data were structured into cohorts, patients could fall into multiple cohorts which they entered at different time points. Baseline characteristics for the same patient could therefore be updated during the study at the point of entry into each new cohort. Each time, the most recent values recorded within 1 year prior to new index date were used, except for clinical histories and medication use, where 5-year and 3-month periods, respectively, were applied as described above. Missing clinical measurements at baseline were imputed using single stochastic regression imputation, followed by last-observation-carried-forward between time intervals across the follow-up period.

Unadjusted crude rates and 95% confidence intervals of mortality and MACE were estimated in each population over the study period. Kaplan–Meier curves for time to mortality and time to a patient's first MACE event were also fitted, stratified by time-updated serum K^+ category. The performance of the previously published equations for estimating the risk of death and MACE in CKD[13] and HF[12] patients were validated in the populations defined in this study. The risk equations[12,13] were created using the Generalized Estimating Equations (GEE) approach assuming a Poisson error distribution and an exchangeable working correlation structure. The same approach was used when assessing the generalizability of these equations to the current study population. All models presented in the main body of the manuscript were fitted using the CKD equation covariates[13]; the corresponding fits using HF covariates[12] are presented in the Supplementary material online. The equations were refitted to the current study population using the same covariates and model forms but allowing the values of the coefficients to change, adapting to the new dataset. Individual equations were fitted to each cohort. Incidence rate ratios (IRRs) of ACM and MACE were calculated for each serum K^+ category relative to serum K^+ level between 4.5 and <5.0 mmol/L (reference category).

Results

Population characteristics

A total of 673 686 patients met the eligibility criteria. Resistant hypertension (*n* = 317 135, 47.1%), diabetes (*n* = 288 871 42.9%), and CKD (*n* = 297 702 44.2%) were the most common cardiometabolic conditions identified. HF was substantially less common (*n* = 84 210, 12.5%) and very few patients received dialysis (*n* = 4415, 0.7%). Approximately a third of the included patients developed multimorbidity during the study period, with 179 259 (26.6%) patients having two conditions, 55 086 (8.2%) having three conditions, 9284 (1.4%) having four conditions, and 341 patients (0.1%) developing all five conditions of interest. The most common co-occurring conditions, assessed at the end of patient follow-up, were RHTN with CKD (*n* = 57 277, 8.50%) and RHTN with diabetes (*n* = 56 957, 8.45%). Details of comorbidities observed in the study population are presented in Supplementary material online, *Table S2* and progression of comorbidity burden over time is illustrated in Supplementary material online, *Figure S1*. While diabetes was the largest initial cohort, CKD was the most common second and third condition developed. The majority of patients experienced an HF as their fourth condition, while dialysis was mostly initiated in patients who had previously developed the other conditions of interest.

The mean age of patients ranged from 64.30 years in the diabetes cohort to 77.34 years in the HF cohort (*Table 1*). The CKD cohort included the highest proportion of females and the dialysis cohort the lowest (58.6% vs. 38.0%, respectively). IMD distribution was similar across cohorts. Cancer was the most common

Table 1 Baseline patient demographics, clinical histories, and medication usage, by condition-based cohort

Variables	Overall (*N* = 673 686)	RHTN (*N* = 317 135)	Diabetes (*N* = 288 871)	CKD (*N* = 297 702)	HF (*N* = 84 210)	Dialysis (*N* = 4415)
Follow-up time (years)	5.68 (3.22)	6.37 (3.06)	5.87 (3.23)	5.58 (3.20)	5.01 (3.20)	5.57 (3.19)
Patient demographics						
Age (years)	68.21 (13.64)	68.76 (12.08)	64.30 (13.87)	74.72 (11.25)	77.34 (11.59)	66.51 (14.36)
Female	350 568 (52.04%)	171 681 (54.13%)	129 883 (44.96%)	174 559 (58.64%)	39 542 (46.96%)	1678 (38.01%)
Current smoker	135 626 (20.13%)	58 664 (18.50%)	67 399 (23.33%)	46 375 (15.58%)	14 906 (17.70%)	925 (20.95%)
IMD						
1 (least deprived)	84 462 (12.54%)	40 510 (12.77%)	32 417 (11.22%)	38 095 (12.80%)	10 828 (12.86%)	570 (12.91%)
2	87 111 (12.93%)	42 055 (13.26%)	35 591 (12.32%)	39 035 (13.11%)	11 890 (14.12%)	648 (14.68%)
3	82 793 (12.29%)	38 724 (12.21%)	35 339 (12.23%)	37 248 (12.51%)	11 924 (14.16%)	697 (15.79%)
4	74 206 (11.01%)	34 038 (10.73%)	33 891 (11.73%)	33 015 (11.09%)	10 693 (12.70%)	603 (13.66%)
5 (most deprived)	62 986 (9.35%)	28 160 (8.88%)	30 818 (10.67%)	27 404 (9.21%)	9482 (11.26%)	576 (13.05%)
Serum K^+ (mmol/L)	4.42 (0.47)	4.38 (0.48)	4.44 (0.47)	4.51 (0.50)	4.47 (0.52)	4.77 (0.68)
BMI (kg/m^2)	29.53 (6.42)	29.79 (6.23)	31.32 (6.78)	28.30 (5.86)	28.45 (6.63)	28.67 (6.69)
SBP (mmHg)	139.16 (17.99)	146.58 (17.50)	136.28 (16.50)	135.86 (17.69)	131.92 (19.40)	137.30 (21.79)
DBP (mmHg)	78.62 (10.96)	80.84 (11.49)	77.77 (10.36)	75.28 (10.38)	73.99 (11.45)	74.56 (12.69)
CCI	3.89 (2.01)	3.63 (2.03)	3.89 (2.12)	5.53 (1.77)	5.72 (2.13)	5.35 (2.32)
Clinical histories						
Cancer	38 622 (5.73%)	15 779 (4.98%)	14 678 (5.08%)	23 346 (7.84%)	8200 (9.74%)	585 (13.25%)
Chronic liver disease	10 978 (1.63%)	4520 (1.43%)	6354 (2.20%)	3752 (1.26%)	1383 (1.64%)	109 (2.47%)
MI	25 742 (3.82%)	10 846 (3.42%)	9587 (3.32%)	14 268 (4.79%)	13 174 (15.64%)	369 (8.36%)
PVD	17 034 (2.53%)	9530 (3.01%)	8225 (2.85%)	9749 (3.27%)	3917 (4.65%)	246 (5.57%)
Stroke	20 244 (3.00%)	10 368 (3.27%)	7408 (2.56%)	11 707 (3.93%)	4778 (5.67%)	227 (5.14%)
Baseline medication usage						
Beta blockers	183 865 (27.29%)	92 338 (29.12%)	72 074 (24.95%)	96 729 (32.49%)	47 028 (55.85%)	1846 (41.81%)
Bronchodilators	106 482 (15.81%)	53 909 (17.00%)	43 632 (15.10%)	47 872 (16.08%)	23 526 (27.94%)	752 (17.03%)
Calcium channel blockers	253 401 (37.61%)	210 295 (66.31%)	84 930 (29.40%)	95 237 (31.99%)	23 336 (27.71%)	2226 (50.42%)
Diuretics	299 410 (44.44%)	187 388 (59.09%)	97 779 (33.85%)	146 487 (49.21%)	67 854 (80.58%)	2301 (52.12%)
Insulin	38 557 (5.72%)	15 153 (4.78%)	39 109 (13.54%)	15 124 (5.08%)	5806 (6.89%)	897 (20.32%)
RAASi	360 525 (53.52%)	251 692 (79.36%)	134 926 (46.71%)	152 026 (51.07%)	45 681 (54.25%)	1413 (32.00%)

BMI, body-mass index; CCI, Charlson's Comorbidity Index; CKD, chronic kidney disease; DBP, diastolic blood pressure; HF, heart failure; IMD, index of multiple deprivation; MI, myocardial infarction; PVD, peripheral vascular disease; RAASi, renin–angiotensin–aldosterone system inhibitors; RHTN, resistant hypertension; SBP, systolic blood pressure; SD, standard deviation.
Please note that the number of patients in individual cohorts exceeds the number of patients included in the study, as the cohorts were overlapping.

medical history in all cohorts except the HF cohort, which had a higher proportion of patients with a history of MI. Chronic liver disease was the least common history for all cohorts. The dialysis cohort had the highest proportion of patients with cancer, chronic liver disease and peripheral vascular disease, while the HF cohort had the highest proportion of patients with a history of MI and stroke.

Out of the 673 686 patients included in the study, 386 982 patients had at least one event prior to 01 January 2008 (i.e. prevalent patients). The largest prevalent cohort included patients with RHTN (n = 191 210, 49.4% of prevalent patients), while the most common incident event was CKD (n = 152 794, 22.7% of incident patients). Heart failure (n = 57 818 incident cases vs. 26 392 prevalent cases), CKD (n = 152 794 vs. 144 908) and dialysis (n = 3099 vs. 1316) were first recorded during the study period (incident events) more frequently than in the look-back period (prevalent events), while the reverse was observed for RHTN (n = 125 925 vs. 191 210) and diabetes (n = 126 687 vs. 162 184) (*Table 2*). This is likely to reflect multimorbidity progression, e.g. from

Table 2 Prevalent and incident comorbidities

Comorbidity	Prevalent CM (pre 01 January 2008) (*N* = 386 982)	Incident CM (post 01 January 2008) (*N* = 673 686[a])	Total (*N* = 673 686)
RHTN	191 210 (49.41%)	125 925 (18.69%)	317 135 (47.07%)
Diabetes	162 184 (41.91%)	126 687 (18.81%)	288 871 (42.88%)
CKD	144 908 (37.45%)	152 794 (22.68%)	297 702 (44.19%)
HF	26 392 (6.82%)	57 818 (8.58%)	84 210 (12.50%)
Dialysis	1316 (0.34%)	3099 (0.46%)	4415 (0.66%)

CKD, chronic kidney disease; CM, comorbidity; HF, heart failure; RHTN, resistant hypertension.
[a]The number of patients eligible for an event post 01 January 2008.

Table 3 Crude rates of adverse outcomes

Cohort	Crude rate per 1000 PYs (95% CI)	
	ACM	MACE
Overall	40.42 (40.21–40.63)	111.99 (111.51–112.46)
RHTN	34.42 (34.15–34.69)	113.40 (112.73–114.08)
Diabetes	34.56 (34.26–34.86)	93.87 (93.21–94.54)
CKD	64.89 (64.47–65.32)	151.73 (150.85–152.62)
HF	159.46 (157.91–161.03)	570.72 (566.9–574.57)
Dialysis	146.14 (139.88–152.61)	280.08 (269.46–291.01)

Unadjusted survival curves for mortality and MACE are shown in Supplementary material online, *Figures S2* and *S3*, respectively. Low and high serum K^+ levels were associated with lower probability of survival/survival without a MACE, and therefore a greater risk of mortality of MACE.
ACM, all-cause mortality; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; MACE, major adverse cardiovascular events; PYs, patient-years; RHTN, resistant hypertension.

RHTN or diabetes to CKD, from RHTN to HF, and from stage 3+ CKD to dialysis.

Incidence of adverse clinical outcomes—unadjusted

Mortality rate was 40.4 events per 1000 patient-years (PYs) in the overall population, while the rate of MACE was almost thrice as high at 112.0 events per 1000 PYs. The highest rates of mortality and MACE were observed in the HF cohort (159.5 and 570.7 events per 1000 PYs, respectively). *Table 3* presents crude incidence rates of ACM and MACE in the overall study population and in individual condition-based patient cohorts.

Incidence of adverse clinical outcomes—adjusted

Figure 2 illustrates the relationship between mortality (*A*) or MACE (*B*) and serum K^+ level, expressed as IRR relative to serum K^+ within the normal range. Mortality and MACE displayed a prominent U-shaped association with serum K^+ level that was consistently observed across all conditions of interest, although the relationship was least pronounced for the dialysis cohort, for which added uncertainty existed due to a reduction in patient numbers. Overall, both hypokalaemia and HK were universally associated with an increased incidence of MACE and mortality in patients with the five chronic conditions studied.

Comorbidity burden and hyperkalaemia

Charlson Comorbidity Index for patients in the overall population ranged from 0 to 21 points, with a mean index of 4.8 (SD = 2.3). Crude incidence of HK by cohort and stratified by CCI category (CCI of <3, ≥3 to <6, and ≥6) is presented in *Table 4*.

Hyperkalaemia was progressively more common with increasing CCI. At the serum K^+ threshold of ≥5.0 mmol/L, crude HK incidence rate increased from 73.5 per 1000 PYs in patients with a CCI <3 to 210.1 per 1000 PYs in patients with a CCI ≥3 to <6 and 457.7 per 1000 PYs in those with a CCI ≥6; 2.9- and 6.2-fold increases, respectively. While more severe HK, defined by the ≥5.5 mmol/L and ≥6.0 mmol/L thresholds was less common, the increase in incidence rates with increasing comorbidity burden was even more substantial (*Table 4*). At the HK threshold of ≥5.5 mmol/L, the rate of HK increased 3.5-fold in patients with a CCI ≥3 to <6 and 9.8-fold in patients with a CCI ≥6, relative to a CCI <3. The corresponding increases at the HK threshold of ≥6.0 mmol/L were 3.9- and 13.2-fold, respectively.

The association between comorbidity burden, serum K^+ and adverse clinical outcomes

Figures 3 and *4* show adjusted IRRs of ACM and MACE, respectively, for the different serum K^+ categories and stratified by patients' CCI category at the start of each interval. There was a clear correlation between increasing CCI and an increase in the risk of death and MACE associated with hypokalaemia and HK. In patients with a CCI score ≥6, this was especially prominent, suggesting that patients with a high comorbidity burden may be particularly susceptible to experiencing adverse clinical outcomes associated with abnormal serum K^+ levels. This pattern was observed across all condition-based cohorts; the only exception being the HF cohort, where CCI appeared to have no substantial effect on the association between the risk of MACE and serum K^+.

Very similar results were obtained when fitting the HF rather than CKD equations to the data (Supplementary material online, *Figures S4–S6*).

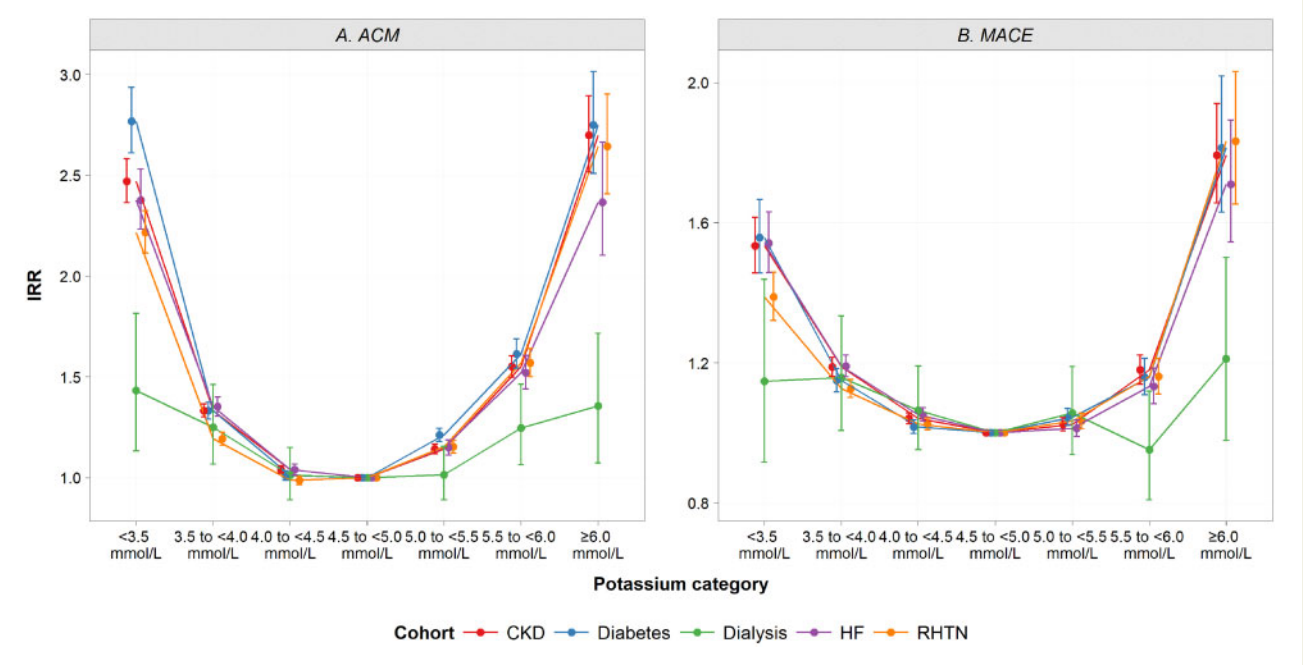

Figure 2 IRRs of ACM and MACE for different serum K^+ levels, stratified by condition-based cohort. ACM, all-cause mortality; CKD, chronic kidney disease; HF, heart failure; IRRs, incidence rate ratios; MACE, major adverse cardiovascular events; RHTN, resistant hypertension. Serum K^+ level between 4.5 and <5.0 mmol/L was defined as the reference category.

Table 4 Incidence of HK by comorbidity burden, for HK defined at K^+ thresholds of ≥5.0 mmol/L, ≥5.5 mmol/L, and ≥6.0 mmol/L

CCI category	Crude HK rate per 1000 PYs (95% CI)		
	K^+ ≥5.0 mmol/L	K^+ ≥5.5 mmol/L	K^+ ≥6.0 mmol/L
<3	73.52 (73.09–73.96)	11.62 (11.45–11.80)	1.47 (1.41–1.53)
≥3 to <6	210.10 (209.48–210.72)	40.56 (40.29–40.84)	5.85 (5.75–5.96)
≥6	457.70 (456.44–458.97)	113.23 (112.60–113.86)	19.83 (19.57–20.09)

CCI, Charlson's Comorbidity Index; CI, confidence interval; HK, hyperkalaemia; PYs, patient-years.

Discussion

The current study examined the influence of comorbidity burden on the association between serum K^+ and adverse clinical outcomes in a large, contemporary, real-world cohort of UK patients with cardiovascular, renal, and metabolic conditions. Previously published risk equations[12,13] used to assess these relationships were found to perform well in the diverse patient population investigated in the present study. Clear U-shaped relationships were identified between ACM and serum K^+ level and between MACE and serum K^+ level, consistent with the original studies describing these equations[12,13]; however, the magnitude of the relationships differed between individual cohorts and was weakest in the dialysis cohort, potentially due to its small size and the increased tolerance for HK in advanced CKD. Building upon the existing body of evidence, this study explored the associations between HK and adverse clinical outcomes in patients with a wide range of conditions, often presenting concomitantly.

The relationship between ACM, or MACE, and serum K^+ level became more prominent in patients with a higher comorbidity burden (defined based on increasing CCI[19,20]) The increased risk of ACM in patients with higher CCI is consistent with the long-established use of the CCI as a prognostic marker for mortality.[20,22,23] However, the associations between adverse clinical outcomes and serum K^+ levels also became more prominent with increasing CCI, suggesting that patients with a higher comorbidity burden are more sensitive to abnormal K^+ levels. Further studies may be warranted to examine if tight control of serum K^+ to prevent hypokalaemia or HK in highly comorbid patients could improve clinical outcomes. Patients with a higher comorbidity burden were not only at increased risk of mortality or MACE associated with abnormal serum K^+ levels; they also experienced a higher rate of HK, which increased progressively with increasing CCI. Therefore, increased comorbidity burden is associated with both higher risk of HK and increased risk of adverse clinical outcomes once HK occurs.

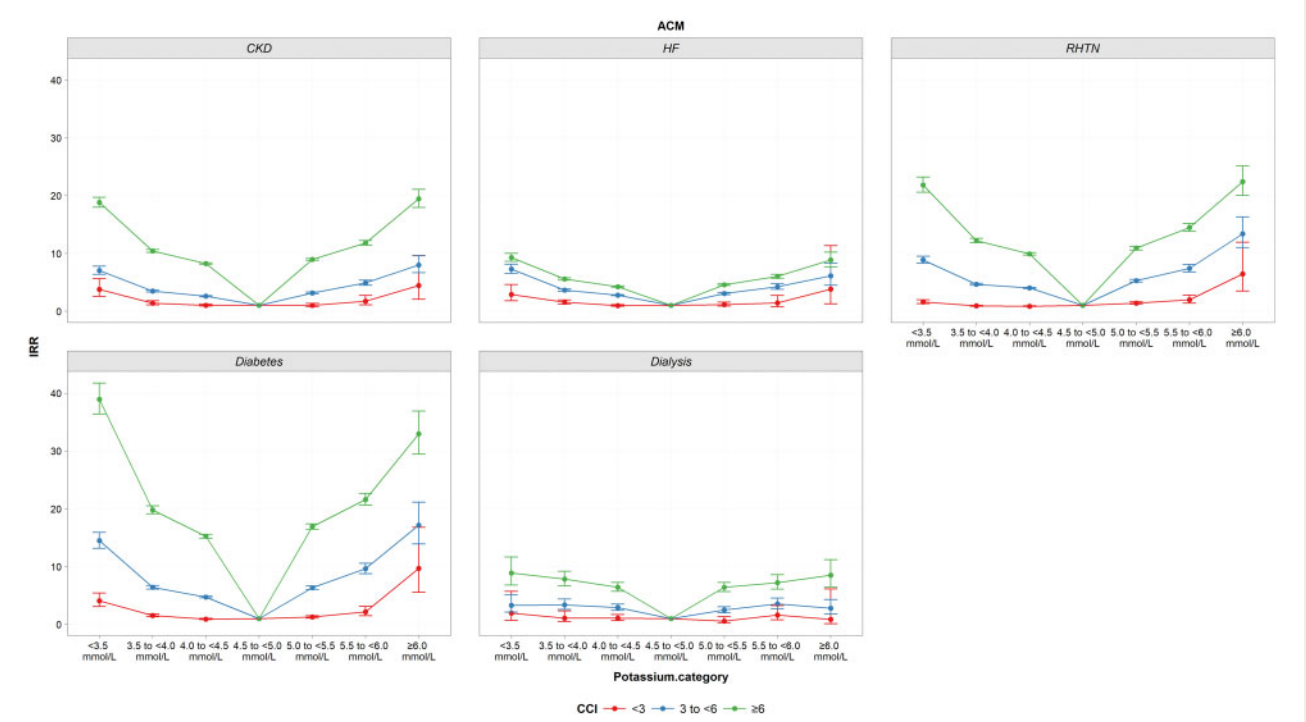

Figure 3 IRRs of ACM for different serum K^+ levels, stratified by condition-based cohort and CCI. ACM, all-cause mortality; CCI, Charlson's Comorbidity Index; CKD, chronic kidney disease; HF, heart failure; IRRs, incidence rate ratios; RHTN, resistant hypertension. Serum K^+ level between 4.5 and <5.0 mmol/L defined as the reference category.

The risk of ACM associated with hypokalaemia and HK increased with increasing comorbidity burden in all cohorts studied. The results were similar for MACE; except for the HF cohort where the risk of MACE was comparable across all CCI categories. This suggests that MACE risk in HF patients may be driven by other factors, including possible under-utilization of RAASi, since only 54% of HF patients received RAASi at baseline, and the presence of established cardiovascular disease (nearly 16% of HF patients had a history of MI at baseline).

The current analysis enrolled a large and diverse cohort of real-world patients, approximately a third of whom experienced multimorbidity, defined as the presence of two or more chronic conditions. Patients with significant comorbidities are often ineligible for inclusion in clinical studies but frequently encountered in routine practice, to which the results of the present study should be readily generalizable. Comorbidity was quantified using a well-known and established index, the CCI,[19,20] which has been in use for over 30 years. Furthermore, both incident and prevalent patients were captured in the analysis, well reflecting the varying duration of chronic disease among patients routinely encountered in clinical practice.[19,20]Another substantial strength of this study was the long follow-up period, allowing outcomes such as mortality and MACE to be adequately captured.

Nonetheless, the study was not free of limitations, which arise mainly from its retrospective design and from the real-world nature of the data source. The study was only able to determine associations, rather than causality between ACM or MACE and serum K^+ levels. Despite the employment of statistical measures to control for clinically relevant covariates, it is possible that additional factors that were not assessed in this study could have contributed to the observed associations. The CPRD provides a large and diverse sample of patients treated in the primary care setting, however, its use as the sole data source renders the study reliant on the accuracy and completeness of data entered into this database and restricts the population to the UK setting. Furthermore, linked HES data is not available for all practices participating in the CPRD, so that it is possible that some relevant diagnoses and/or outcomes were not captured in the present study due to the absence of secondary care data for some patients. Whereas for the majority of comorbidities, the linkage of primary and secondary care data will be sufficient, for the dialysis cohort, there may be a degree of misreporting due to patients receiving dialysis in tertiary care centres. The dialysis cohort may also be subject to variability in serum K^+ caused by differences in timing of the K^+ measurement relative to last dialysis session. The prevalence of HK in haemodialysis patients has been reported to vary depending on the length of the interdialytic interval,[24] and we did not account for dialysis schedule in our analyses. Finally, while the previously developed risk equations[12,13] appear to be readily generalizable to a broader patient population, these equations have, so far, only been applied to CPRD-derived UK data. The use of a different database or registry to validate these equations could increase the confidence in their predictions.

This large, real-world study of a diverse patient cohort adds to the expanding repertoire of evidence on the relationship between serum K^+ level and the incidence of adverse clinical outcomes. Patients with a higher comorbidity burden are at an increased risk of developing

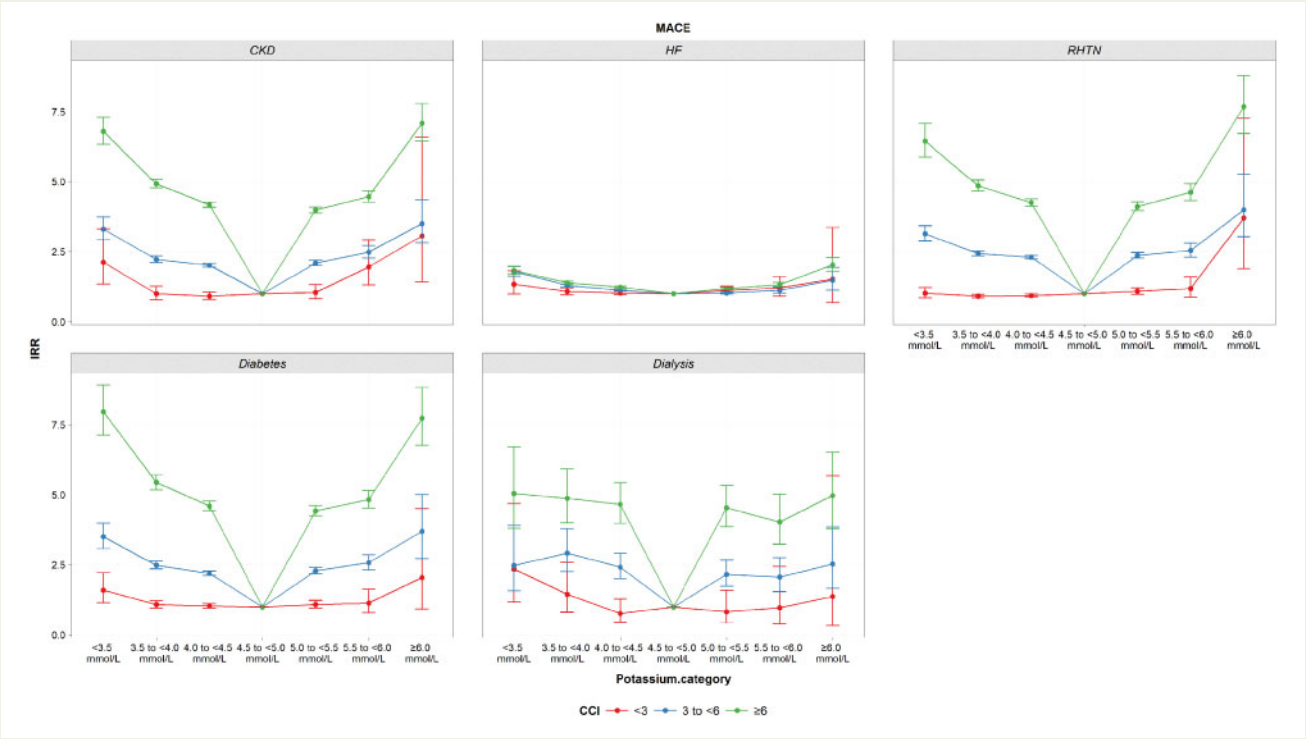

Figure 4 IRRs of MACE for different serum K^+ levels, stratified by condition-based cohort and CCI. CCI, Charlson's Comorbidity Index; CKD, chronic kidney disease; HF, heart failure; IRRs, incidence rate ratios; MACE, major adverse cardiovascular events; RHTN, resistant hypertension. Serum K^+ level between 4.5 and <5.0 mmol/L defined as the reference category.

HK and appear more prone to adverse clinical outcomes associated with abnormal serum K^+ levels. Since the incidence of mortality and MACE was generally lowest in normokalaemia, effective measures to monitor serum K^+ and maintain it within the normal range could potentially improve clinical outcomes in these patients. Future studies are warranted to determine whether incorporating more effective serum K^+ management strategies into the everyday care of highly comorbid patients reduces the risk of adverse outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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Data availability statement

The anonymized patient data underlying this manuscript are derived from the CPRD and linked HES databases and cannot be made available by the authors. An application to the Independent Scientific Advisory Committee (ISAC) should be made to obtain access to the data.

Conflict of interest: E.T. and G.J. are employees of AstraZeneca. D.S., L.H., M.H., and P.M.E. are employees, and K.B. is a contractor, of Health Economics and Outcomes Research Ltd, a consultancy that received grant funding from AstraZeneca to conduct this work. L.Q. has nothing to disclose.

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