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ORIGINAL RESEARCH

Impact of Plasma Potassium Normalization on Short-Term Mortality in Patients With Hypertension and Hyperkalemia

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BACKGROUND: Hyperkalemia can be harmful, but the effect of correcting hyperkalemia is sparsely studied. We used nationwide data to examine hyperkalemia follow-up in patients with hypertension.

METHODS AND RESULTS: We identified 7620 patients with hypertension, who had the first plasma potassium measurement ≥4.7 mmol/L (hyperkalemia) within 100 days of combination antihypertensive therapy initiation. A second potassium was measured 6 to 100 days after the episode of hyperkalemia. All-cause mortality within 90 days of the second potassium measurement was assessed using Cox regression. Mortality was examined for 8 predefined potassium intervals derived from the second measurement: 2.2 to 2.9 mmol/L (n=37), 3.0 to 3.4 mmol/L (n=184), 3.5 to 3.7 mmol/L (n=325), 3.8 to 4.0 mmol/L (n=791), 4.1 to 4.6 mmol/L (n=3533, reference), 4.7 to 5.0 mmol/L (n=1786), 5.1 to 5.5 mmol/L (n=720), and 5.6 to 7.8 mmol/L (n=244). Ninety-day mortality in the 8 strata was 37.8%, 21.2%, 14.5%, 9.6%, 6.3%, 6.2%, 10.0%, and 16.4%, respectively. The multivariable analysis showed that patients with concentrations >5.5 mmol/L after an episode of hyperkalemia had increased mortality risk compared with the reference (hazard ratio [HR], 2.27; 95% CI, 1.60–3.20; P<0.001). Potassium intervals 3.5 to 3.7 mmol/L and 3.8 to 4.0 mmol/L were also associated with increased risk of death (HR, 1.71; 95% CI, 1.23–2.37; P<0.001; HR, 1.36; 95% CI, 1.04–1.76; P<0.001, respectively) compared with the reference group. We observed a trend toward increased risk of death within the interval 5.1 to 5.5 mmol/L (HR, 1.29; 95% CI, 0.98–1.69). Potassium concentrations <4.1 mmol/L and >5.0 mmol/L were associated with increased risk of cardiovascular death.

CONCLUSIONS: Overcorrection of hyperkalemia to levels <4.1 mmol/L was frequent and associated with increased all-cause and cardiovascular mortality. Potassium concentrations >5.5 mmol/L were also associated with an increased all-cause and cardiovascular mortality.

Key Words: hyperkalemia ■ hyperkalemia correction ■ hypertension ■ potassium normalization

Potassium plays a key role in maintaining normal myocardial electrical activity. A shift in potassium balance or persistent potassium disturbances can have a negative effect on the heart, regardless of the direction.[1] Patients with persistent cardiovascular diseases, such as hypertension, are especially exposed to potassium disturbances attributable to treatment side effects.[2]

We recently demonstrated a U-shaped relationship between potassium and mortality among patients with hypertension. Mortality risk was higher even for low and high normal potassium ranges, suggesting a more strict normal interval of 4.1 to 4.7 mmol/L.[3] However, there are currently no data on the impact of plasma potassium normalization on short-term mortality in patients with hypertension and hyperkalemia. Therefore,

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CLINICAL PERSPECTIVE

What Is New?

- In this register study comprising 7620 patients with hyperkalemia, we observed that balancing hyperkalemia to levels between 4.1 and 5.5 mmol/L was associated with better short-term prognosis compared with patients with concentrations outside the interval.
- Patients treated with combination antihypertensive therapy, who had hyperkalemia (≥4.7 mmol/L) at the first potassium measurement within 100 days of treatment initiation had increased 90-day mortality risk if potassium levels were higher than 5.0 mmol/L or lower than 4.1 mmol/L at the second measurement (within 6–100 days).
- Hyperkalemia is a common side effect of antihypertensive treatment and is associated with arrhythmogenesis and increased mortality risk in patients with hypertension.

What Are the Clinical Implications?

- This study suggests that correction of hyperkalemia to a level in the high end of the normal reference interval is associated with improved prognosis.

it is important to investigate how correction and even overcorrection of hyperkalemia changes short-term prognosis in patients with hypertension.

Using Danish national registers, we investigated the 90-day mortality for patients with hypertension and an initial high potassium measurement, according to their subsequent plasma potassium concentrations measured within 6 to 100 days following the episode of elevated potassium.

METHODS

Availability of Data and Materials

Because of restrictions related to Danish law and protecting patient privacy, the combined set of data and analyses used in this study can be made available only through a trusted third party, Statistics Denmark. This state organization holds the data used for this study. University-based Danish scientific organizations can be authorized to work with data within Statistics Denmark and such organization can provide access to individual scientists inside and outside of Denmark. Data are available upon request to authorized scientists by contacting Statistics Denmark (http://www.dst.dk/en/OmDS/organisation/TelefonbogOrg.aspx?kontor=13&tlfbogsort=sektion) or the Danish Data Protection Agency (https://www.datatilsynet.dk/english/the-danish-data-protection-agency/contact/). More information regarding data access is available at https://www.dst.dk/en/TilSalg/Forskningsservice. Being register based, no institutional review board approval or subject informed consent is needed. Statistics Denmark deidentified each citizen before making the data sets available for research.

Databases

Residents in Denmark have a personal, unique, and permanent civil registration number that enables linkage of data from all nationwide administrative registries.

The Danish Civil Registration System was used to collect data regarding age and sex.[4] From the Danish National Patient Registry, we obtained information about hospital admission dates, hospital discharge dates, discharge diagnoses, dates of procedure, and procedure codes.[5] Discharge diagnoses are coded according to the World Health Organization *International Classification of Diseases (ICD)*. From 1994 and onwards the *Tenth Revision* (*ICD-10*) was in use. The Danish National Patient Registry covers information from 1978 until the present time.

Information on each resident's redeemed prescription was collected from the Danish National Prescription Registry.[6] This register includes all dispensed prescriptions from all Danish pharmacies since 1995 based on the Anatomical Therapeutic Chemical System. The Danish healthcare system is state financed and partly reimburses drug costs. For this reason, all Danish pharmacies are compelled by law to register all dispensed drug prescriptions, providing a complete overview of all prescriptions.

The electronic registers of laboratory data contain blood test results from 3 of the 5 regions in Denmark, covering ≈4 058 000 inhabitants. Blood samples originated from either primary care, outpatient visits, or hospitalizations.

Study Population

Hypertension was defined as first-time redemption of at least 2 antihypertensive drugs in 2 consecutive quarters, and this definition has been validated previously.[7] Patients entered the study in the second quarter, and this time was referred to as hypertension date. Patients entered the study regardless of being prescribed antihypertensives as a single pill combination or as multiple pills. In this study, we define "combination antihypertensive therapy" as redemption of minimum 2 antihypertensive drug classes as a single pill or as multiple pills. We applied this definition of hypertension for 2 reasons. First, the great majority of the patients treated for high blood pressure are monitored by the general practitioner and are not

registered with a hypertension *ICD-10* code during hospitalization or outpatient clinic visit. Second, most of the drugs used for management of hypertension can also be used to treat other cardiovascular diseases. Therefore, a monotherapy approach would be less specific. Olesen et al[7] demonstrated that treatment with 2 classes of antihypertensive agents has a positive predictive value of 80% and a specificity of 94.7% to identify patients with hypertension. Table S1 contains Anatomical Therapeutic Chemical System codes used to identify patients with hypertension. A plasma potassium measurement >4.6 mmol/L (hyperkalemia) within 100 days of the date of hypertension was required to be included in the study. The first measurement within this time frame was retained and referred to as the first potassium measurement. As the aim of the study was to investigate the impact of changes in potassium concentrations on mortality in patients with hypertension and hyperkalemia, we required a subsequent potassium measurement within 6 to 100 days following the first potassium measurement. The first measurement within this time frame was retained. This plasma potassium measurement was referred to as the second potassium measurement and represents the start of follow-up in this study. We considered this time frame appropriate, as in most of the cases potassium imbalances are corrected within a few days, regardless of the pharmacological or dietary strategies applied. Patients <18 years of age were excluded from the study. Figure S1 illustrates the population flowchart.

Comorbidities and Medication

Comorbidities and medication that clinically and theoretically could be regarded as confounding factors in relation to studying the association between changes in potassium and short-term mortality were identified. We considered patients as having a previous history with a specific comorbidity if the hospital discharge diagnosis was registered before the index date. The following comorbidities were identified: heart failure, chronic obstructive pulmonary disease, ischemic heart disease, chronic liver disease, stroke, diabetes mellitus, inflammatory bowel disease, and malignancy. Moreover, we excluded patients with a past history of primary adrenal insufficiency, primary hyperaldosteronism, and diabetes insipidus. The *ICD-10* codes used to identify these comorbidities can be seen in Table S2. The renal function of the patients was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula[8] and an estimated glomerular filtration rate <30 mL/min per 1.73 m^2 was used to define renal dysfunction. We registered creatinine measurements available the same day as the index date or within a week from the index date in case of missing values. Patients were excluded if no creatinine concentrations were available in this time limit. Additionally, patients with missing sodium measurements the same day as the index date were also excluded.

We identified prescriptions dated up to 90 days before the index date for the following drugs: laxatives, xantines, nonsteroidal anti-inflammatory drugs, corticoids, potassium supplement, and antimicrobials. See Table S2 for relevant Anatomical Therapeutic Chemical System codes.

Exposure Variable

Normal plasma potassium interval varies within populations. Therefore, different reference intervals are used worldwide.[9–11] The Nordic Reference Interval Project defines hypokalemia as plasma potassium concentrations <3.5 mmol/L and hyperkalemia and potassium levels >4.6 mmol/L.[10]

As potassium does not have a linear relationship with mortality, the second potassium measurement was divided into 8 intervals: 2.2 to 2.9 mmol/L, 3.0 to 3.4 mmol/L, 3.5 to 3.7 mmol/L, 3.8 to 4.0 mmol/L, 4.1 to 4.6 mmol/L, 4.7 to 5.0 mmol/L, 5.1 to 5.5 mmol/L, and 5.6 to 7.8 mmol/L. Plasma potassium interval 4.1 to 4.6 mmol/L was used as the reference for statistical analyses. We chose this interval as the reference group on the basis of the study of Krogager et al[3] and the lowest mortality risk observed in a restricted cubic spline curve (Figure 1).

Outcome

The primary outcome of the study was all-cause mortality within 90 days of the second plasma potassium measurement occurring 6 to 100 days after the first plasma potassium measurement indicating hyperkalemia. The secondary outcome was cardiovascular death within 90 days of the second potassium measurement.

Statistical Analysis

Categorical variables were presented as counts and percentages, and continuous variables as median and 25th and 75th percentiles. To evaluate differences for nonnormally distributed continuous variables we used the Kruskal–Wallis test, and for differences across categorical variables, we used the chi-squared test.

To illustrate survival, Kaplan–Meier curves were plotted for the 8 potassium intervals. The Cox proportional regression model was used to investigate the association between the 8 potassium groups and mortality. The multivariable model was adjusted for age, sex, plasma sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive

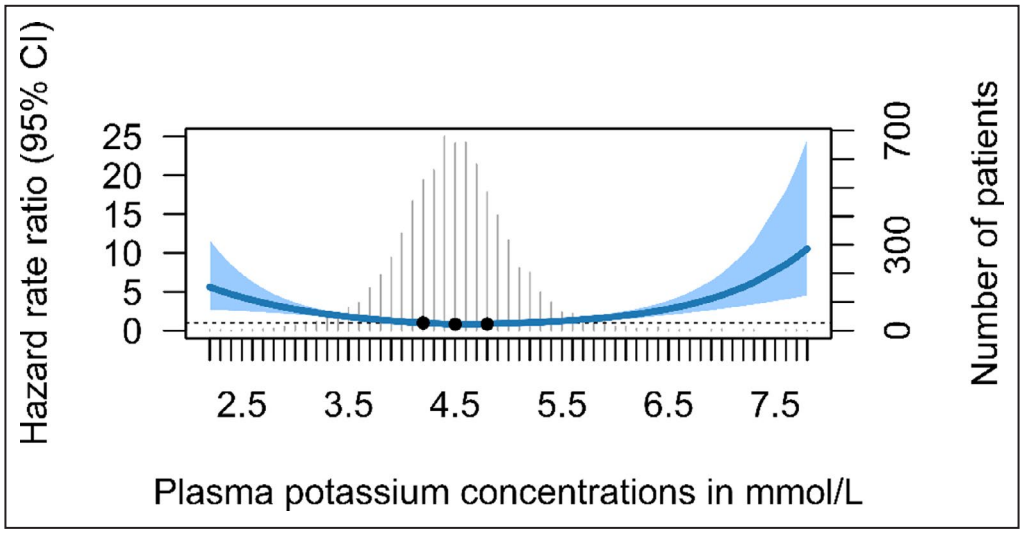

Figure 1. Restricted cubic spline curve showing the adjusted hazard ratios for all-cause mortality as a function of second plasma potassium measurement.
Knots at the 25th, 50th, and 75th percentiles of plasma potassium. The model is adjusted for age, sex, plasma sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease, inflammatory bowel disease, antihypertensive therapy, corticosteroids, antimicrobials, nonsteroidal anti-inflammatory drugs, xanthines, laxatives, digoxin, and potassium supplements.

pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, nonsteroidal anti-inflammatory drugs, xanthines, laxatives, digoxin, and potassium supplements. Hazard ratios (HRs) were estimated with 95% CIs.

To test the robustness of the main results, 9 sensitivity analyses were constructed: (1) subgroup of patients with normal kidney function; (2) patients without past history of any malignancy; (3) patients without past history of heart failure or loop diuretic prescriptions; (4) patients without past history of ischemic heart disease; (5) patients with available *ICD-10* hypertension diagnosis; (6) analyses investigating risk of cardiovascular death in relation to the 8 potassium intervals; (7) analyses using last instead of first available potassium concentrations within 6 to 100 days of first measurement; (8) multivariable model adjusted for the first potassium measurement; and (9) multivariable model adjusted for time between first and second potassium measurement. In the survival analyses, $P<0.05$ was considered statistically significant. All data management and analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).[12]

RESULTS

Model Construction

The assumption of proportional hazards was tested using Schoenfeld residuals, log-minus-log plots and log-rank tests. The proportionality assumption was not violated in any of the tests above. The following variables were tested for interaction with plasma potassium on mortality: age, sex, diabetes mellitus, and renal dysfunction. A likelihood ratio test comparing the model with and without the interaction term was performed. A P value <0.01 was considered as a statistically significant interaction. We observed no interaction between potassium and age, sex, diabetes mellitus, or renal dysfunction on mortality. The same approach was used to assess whether age had a linear relationship on mortality. As the linearity assumption was not fulfilled for age as a continuous variable, age was included in the regression models as a categorical variable with 5 levels, using cutoff values from 20th percentiles: 18 to 58, 59 to 67, 68 to 73, 74 to 81, and 82 to 102.

To examine model fit and performance, we calculated the Akaike Information Criterion and the area under the receiver operating characteristic curve (Table S3).

Demographics

A total of 7620 patients were included in the study in the period 1995 to 2017, and the characteristics stratified according to the second potassium measurement are shown in Table 1. Median time from first to second potassium measurement was 24 days (range, 6–100). Of the total population with hyperkalemia at the first potassium measurement, 61.01% of the patients had normokalemia at the second

Table 1. Demographics Stratified According to the 8 Predefined Plasma Potassium Intervals

		2.2–2.9 mmol/L (n=37)	3.0–3.4 mmol/L (n=184)	3.5–3.7 mmol/L (n=325)	3.8–4.0 mmol/L (n=791)	4.1–4.6 mmol/L (n=3533)	4.7–5.0 mmol/L (n=1786)	5.1–5.5 mmol/L (n=720)	5.6–7.8 mmol/L (n=244)	Total (n=7620)	*P* Value
Age	Median (range)	73.8 (28.4–94.5)	70.9 (26.2–95.9)	70.4 (20.1–98.7)	70.2 (18.6–97.9)	69.7 (18.2–102.3)	71 (18.3–98.7)	70.5 (19.2–99.0)	71 (21.3–101.8)	70.3 (18.2–102.3)	0.010
Sex	Male	19 (51.4)	79 (42.9)	166 (51.1)	428 (54.1)	2120 (60.0)	1150 (64.4)	453 (62.9)	144 (59.0)	4559 (59.8)	<0.0001
Renal insufficiency (second measuremt)		10 (27.0)	41 (22.3)	47 (14.5)	102 (12.9)	344 (9.7)	279 (15.6)	189 (26.2)	103 (42.2)	1115 (14.6)	<0.0001
Plasma sodium (second measurement)	Median (range)	138 (123–169)	138 (108–151)	138 (112–159)	139 (110–164)	139 (112–160)	139 (112–166)	138 (112–151)	137 (114–147)	139 (108–169)	<0.0001
Plasma potassium (first measurement)	4.7–5.5 mmol/L	30 (81.1)	163 (88.6)	310 (95.4)	755 (95.4)	3422 (96.9)	1690 (94.6)	661 (91.8)	196 (80.3)	7227 (94.8)	
	>5.5 mmol/L	7 (18.9)	21 (11.4)	15 (4.6)	36 (4.6)	111 (3.1)	96 (5.4)	59 (8.2)	48 (19.7)	393 (5.2)	<0.0001
Renal insufficiency (first measuremt)		12 (35.3)	40 (22.2)	49 (16.4)	92 (12.9)	357 (10.8)	251 (14.7)	163 (23.6)	83 (35.0)	1047 (14.6)	<0.0001
	Missing									446	
Time from first to second potassium measurement	Median (range)	9 (6–81)	7 (6–99)	11 (6–99)	19 (6–100)	27 (6–100)	27 (6–100)	26 (6–100)	21 (6–98)	24 (6–100)	<0.0001
Hospitalization at the time of second potassium measurement		36 (97.3)	171 (92.9)	313 (96.3)	712 (90.0)	2977 (84.3)	1457 (81.6)	581 (80.7)	205 (84.0)	6452 (84.7)	<0.0001
Time from the second potassium measurement to death	Mean (SD)	68.5 (32.5)	78.1 (25.2)	80.7 (24)	84.3 (18.9)	86.4 (15.1)	86.5 (15)	84.7 (18.1)	79.4 (25.6)	85.3 (17.3)	<0.0001
Death 90-d		14 (37.8)	39 (21.2)	47 (14.5)	76 (9.6)	224 (6.3)	110 (6.2)	72 (10.0)	40 (16.4)	622 (8.2)	<0.0001
	Cardiovascular death	5 (13.5)	14 (7.6)	26 (8.0)	38 (4.8)	125 (3.5)	59 (3.3)	29 (4.0)	22 (9.0)	318 (4.2)	<0.0001
Comorbidities											
Malignancy		10 (27.0)	42 (22.8)	59 (18.2)	125 (15.8)	580 (16.4)	253 (14.2)	130 (18.1)	38 (15.6)	1237 (16.2)	0.014
Chronic obstructive pulmonary disease		7 (18.9)	44 (23.9)	72 (22.2)	136 (17.2)	467 (13.2)	237 (13.3)	89 (12.4)	30 (12.3)	1082 (14.2)	<0.0001
Chronic kidney disease		≤3	38 (20.7)	38 (11.7)	81 (10.2)	344 (9.7)	244 (13.7)	139 (19.3)	66 (27.0)	≤953	<0.0001
Chronic liver disease		4 (10.8)	14 (7.6)	15 (4.6)	55 (7.0)	152 (4.3)	65 (3.6)	36 (5.0)	13 (5.3)	354 (4.6)	0.003
Stroke		≤3	24 (13.0)	33 (10.2)	79 (10.0)	354 (10.0)	155 (8.7)	72 (10.0)	21 (8.6)	≤741	0.594
Hypertension (*ICD-10*)		13 (35.1)	75 (40.8)	122 (37.5)	270 (34.1)	1084 (30.7)	544 (30.5)	233 (32.4)	69 (28.3)	2410 (31.6)	0.008
Atrial fibrillation/atrial flutter		9 (24.3)	45 (24.5)	82 (25.2)	179 (22.6)	849 (24.0)	385 (21.6)	136 (18.9)	49 (20.1)	1734 (22.8)	0.064
Ischemic heart disease		13 (35.1)	49 (26.6)	112 (34.5)	253 (32.0)	1216 (34.4)	585 (32.8)	200 (27.8)	71 (29.1)	2499 (32.8)	0.012
Heart failure		12 (32.4)	57 (31.0)	91 (28.0)	233 (29.5)	1189 (33.7)	644 (36.1)	219 (30.4)	84 (34.4)	2529 (33.2)	0.008

(*Continued*)

Table 1. Continued

		2.2–2.9 mmol/L (n=37)	3.0–3.4 mmol/L (n=184)	3.5–3.7 mmol/L (n=325)	3.8–4.0 mmol/L (n=791)	4.1–4.6 mmol/L (n=3533)	4.7–5.0 mmol/L (n=1786)	5.1–5.5 mmol/L (n=720)	5.6–7.8 mmol/L (n=244)	Total (n=7620)	*P* Value
Diabetes mellitus		6 (16.2)	38 (20.7)	71 (21.8)	156 (19.7)	865 (24.5)	478 (26.8)	222 (30.8)	79 (32.4)	1915 (25.1)	<0.0001
Pharmacotherapy											
Digoxin		7 (18.9)	32 (17.4)	64 (19.7)	140 (17.7)	655 (18.5)	325 (18.2)	113 (15.7)	53 (21.7)	1389 (18.2)	0.534
Potassium supplement	ATC: A12B	26 (70.3)	112 (60.9)	194 (59.7)	378 (47.8)	1629 (46.1)	773 (43.3)	306 (42.5)	124 (50.8)	3542 (46.5)	<0.0001
	ATC: C03	≤3	34 (18.5)	57 (17.5)	135 (17.1)	499 (14.1)	235 (13.2)	100 (13.9)	27 (11.1)	≤1090	0.028
Beta-blockers		22 (59.5)	90 (48.9)	155 (47.7)	398 (50.3)	1983 (56.1)	1012 (56.7)	372 (51.7)	124 (50.8)	4156 (54.5)	0.001
Calcium channel blockers		12 (32.4)	50 (27.2)	76 (23.4)	207 (26.2)	914 (25.9)	432 (24.2)	204 (28.3)	59 (24.2)	1954 (25.6)	0.409
Renin angiotensin system inhibitors		20 (54.1)	90 (48.9)	175 (53.8)	486 (61.4)	2496 (70.6)	1315 (73.6)	485 (67.4)	176 (72.1)	5243 (68.8)	<0.0001
Loop diuretics		20 (54.1)	114 (62.0)	186 (57.2)	384 (48.5)	1570 (44.4)	827 (46.3)	355 (49.3)	139 (57.0)	3595 (47.2)	<0.0001
Thiazides		7 (18.9)	52 (28.3)	97 (29.8)	226 (28.6)	819 (23.2)	376 (21.1)	179 (24.9)	43 (17.6)	1799 (23.6)	<0.0001
Thiazide-like diuretics										73 (1.0)	0.273
Potassium sparing diuretics		≤3	7 (3.8)	11 (3.4)	10 (1.3)	45 (1.3)	27 (1.5)	10 (1.4)	6 (2.5)	≤119	0.004
Mineral receptor antagonists		12 (32.4)	46 (25.0)	74 (22.8)	161 (20.4)	730 (20.7)	421 (23.6)	181 (25.1)	66 (27.0)	1691 (22.2)	0.010
Vaso		0 (0.0)	0 (0.0)	0 (0.0)	≤3	≤3	0 (0.0)	0 (0.0)	0 (0.0)	≤6	0.791
AntiAdrenerg		0 (0.0)	4 (2.2)	7 (2.2)	9 (1.1)	35 (1.0)	23 (1.3)	13 (1.8)	≤3	≤94	0.313
Antimicrobials		21 (56.8)	111 (60.3)	220 (67.7)	446 (56.4)	2044 (57.9)	1009 (56.5)	391 (54.3)	137 (56.1)	4379 (57.5)	0.008
Beta-2 agonists		6 (16.2)	61 (33.2)	100 (30.8)	225 (28.4)	858 (24.3)	418 (23.4)	162 (22.5)	54 (22.1)	1884 (24.7)	0.001
Corticoids		6 (16.2)	35 (19.0)	76 (23.4)	166 (21.0)	717 (20.3)	385 (21.6)	138 (19.2)	41 (16.8)	1564 (20.5)	0.474
Laxatives		≤3	8 (4.3)	12 (3.7)	32 (4.0)	105 (3.0)	61 (3.4)	26 (3.6)	13 (5.3)	≤260	0.482
Xantines		≤3	8 (4.3)	17 (5.2)	25 (3.2)	93 (2.6)	46 (2.6)	26 (3.6)	5 (2.0)	≤223	0.125
NSAIDs		23 (62.2)	103 (56.0)	210 (64.6)	430 (54.4)	1995 (56.5)	1032 (57.8)	403 (56.0)	142 (58.2)	4338 (56.9)	0.110

ICD-10 indicates *International Classification of Diseases, Tenth Revision*.

potassium measurement. We observed that 36.1% of the patients with hyperkalemia at the first potassium measurement had elevated potassium concentrations at the second measurement as well. Of the total patients, 2.9% were overcorrected to hypokalemia. As for patients with potassium levels 4.7 to 5.5 mmol/L at the first measurement, 3.4% developed higher (5.6–7.8 mmol/L) concentrations at the second measurement. Overall, 39% of the patients with hyperkalemia at the first potassium measurement had abnormal concentrations at the second measurement. The majority of the patients (84.7%) had their second potassium draw taken during hospitalization, and nearly 15% had an estimated glomerular filtration rate <30 mL/min per 1.73 m^2. Of the primary diagnoses assessed at each hospitalization, 9.7% were related to heart disease and 4.9% attributable to kidney disease (Table S4).

See Figure S2 displaying the distribution of the first potassium measurement, average of potassium measurements drawn within 1 to 5 days of the first potassium measurement (n=2161), and second potassium measurement. Of the patients with available potassium measurements within 1 to 5 days of the first potassium measurement indicating hyperkalemia, 7.4% developed hypokalemia, and 27.9% persisted with hyperkalemia. Of the 2161 patients, 1429 had normokalemia at the last potassium measurement within 1 to 5 days from the first potassium measurement. Of the 1429 patients who achieved normokalemia within 1 to 5 days of hyperkalemia, 1043 (81.1%) had persistent normokalemia at the first measurement within 6 to 100 days from hyperkalemia (otherwise known as "second potassium measurement"). Of the deceased within 90 days from the second potassium measurement, 374 (60.1%) had available potassium measurements within 1 to 5 days of the first potassium measurement (Table S5).

Predominant comorbidities were ischemic heart disease, heart failure, and diabetes mellitus.

Survival Analysis

During 90 days' follow-up after the second plasma potassium measurement, 633 (8.3 %) patients died, of which 318 had an underlying cardiovascular cause. The absolute mortality proportion in the 8 strata was 37.8%, 21.2%, 14.5%, 9.6%, 6.3%, 6.2%, 10.0%, and 16.4%, respectively. Survival curves are illustrated in Figure 2, and causes of death are shown in Table S6. Patients who died were older, with higher kidney insufficiency burden at the time of potassium measurement, higher hospitalization rate at the time of potassium measurement, and more likely with a previous history of malignancy, stroke, chronic obstructive pulmonary disease, atrial fibrillation, and chronic liver disease within the past 5 years (Table S7).

The results of the univariable and multivariable Cox proportional regression, with plasma potassium 4.1 to 4.6 mmol/L as the reference group, are shown in Figure 3. The univariable analysis showed that potassium concentrations outside the interval 4.1 to 5.0 mmol/L were associated with increased all-cause mortality, in patients with hypertension and initial hyperkalemia. Highest mortality was observed in patients with potassium levels 2.2 to 2.9 mmol/L (HR, 7.18; 95% CI, 4.18–12.32; P<0.001), 3.0 to 3.4 mmol/L (HR, 3.61; 95% CI, 2.57–5.08; P<0.001), 3.5 to 3.7 mmol/L (HR, 2.41; 95% CI, 1.76–3.30; P<0.001), and 5.6 to 7.8 mmol/L (HR, 2.77; 95% CI, 1.98–3.88; P<0.001). The multivariable analysis showed similar results, but the interval 5.1 to 5.5 mmol/L was no longer associated with increased mortality (HR, 1.29; 95% CI, 0.98–1.69; P=0.073).

Sensitivity Analyses

We performed 9 sensitivity analyses to test the robustness of our main results. The findings are shown in Table 2.

First, a subgroup analysis on patients with normal kidney function was performed (n=6505). The results were similar with the main analysis.

Second, a subgroup analysis on patients without past history of malignancy (n=6383) also showed similar results with the main analysis.

Third, we performed a subgroup analysis on population without heart failure or loop diuretic prescription (n=3149). Plasma potassium intervals 2.2 to 2.9 mmol/L and 3.0 to 3.4 mmol/L were associated with increased all-cause mortality (HR, 7.79; 95% CI, 2.54–23.90; P<0.001; and HR, 2.79; 95% CI, 1.35–5.78; P=0.006, respectively) compared with the reference. We also noted a trend toward increased risk of death in patients with potassium concentrations above 5.5 mmol/L (HR, 1.88; 95% CI, 0.90–3.91; P=0.091).

Fourth, we performed an analysis where patients with a past history of ischemic heart disease were excluded (n=5121). The results were similar to the main analysis, except lack of statistically significant association between potassium interval 3.8 to 4.0 mmol/L and 90-day mortality.

Fifth, we analyzed only patients with available *ICD-10* hypertension diagnosis (n=2410). The results were similar to the main analysis.

Sixth, we analyzed the risk of 90-day cardiovascular death with all-cause mortality as competing risk. We observed that potassium concentrations outside the interval 4.1 to 5.0 mmol/L were associated with increased

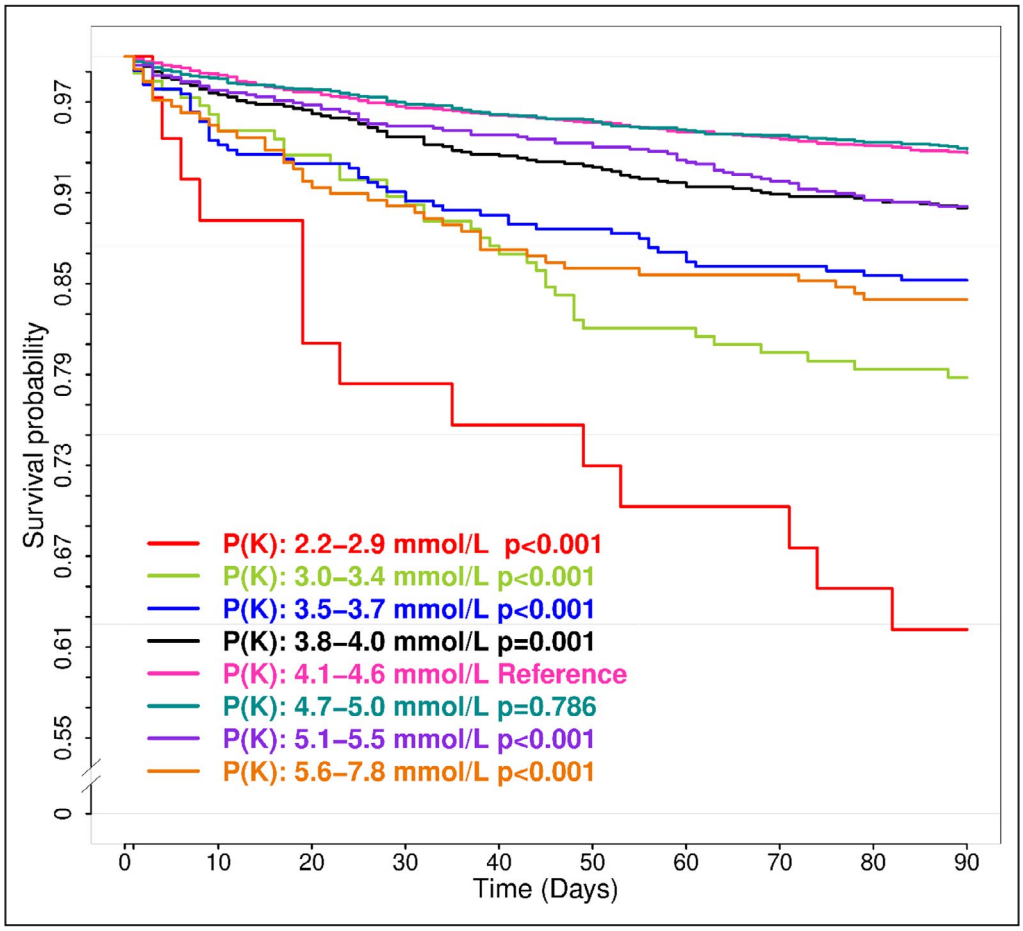

Figure 2. Kaplan–Meier survival curves across the 8 plasma potassium intervals.
The *P* values indicate the difference among plasma potassium groups compared with the reference group based on log-rank test.

risk of cardiovascular mortality after an episode of hyperkalemia (2.2–2.9 mmol/L: HR, 6.86; 95% CI, 3.40–13.85; *P*<0.001; 3.0–3.4 mmol/L: HR, 3.21; 95% CI, 2.05–5.04; *P*<0.001; 3.5–3.7 mmol/L: HR, 1.85; 95% CI, 1.15–2.96; *P*=0.010; 3.8–4.0 mmol/L: HR, 1.56; 95% CI, 1.09–2.25; *P*=0.022; 5.1–5.5 mmol/L: HR, 1.80; 95%

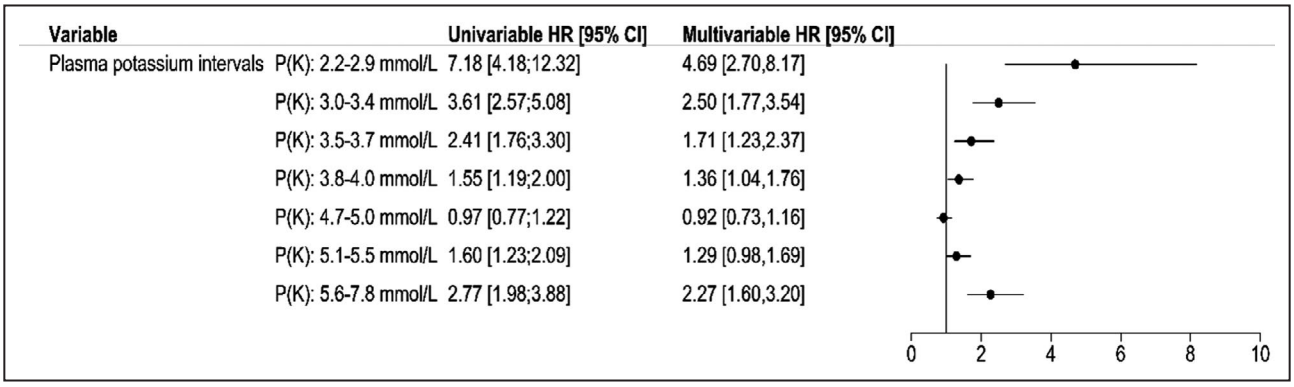

Figure 3. All-cause mortality after hyperkalemia according to subsequent potassium measurements in patients treated with combination antihypertensive therapy (90 days' follow-up, n=7620).
Potassium interval K: 4.1 to 4.6 mmol/L represented the reference range. Adjusted for age, sex, plasma sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, nonsteroidal anti-inflammatory drugs, xanthines, laxatives, digoxin, and potassium supplements. HR indicates hazard ratio.

Table 2. Sensitivity Analyses

	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
1. Patients with normal kidney function (N=6505)						
2.2–2.9 mmol/L	6.55	(3.35–12.78)	<0.001	5.36	(2.71–10.62)	<0.001
3.0–3.4 mmol/L	4.17	(2.87–6.08)	<0.001	2.90	(1.98–4.25)	<0.001
3.5–3.7 mmol/L	2.63	(1.87–3.70)	<0.001	1.81	(1.27–2.59)	0.001
3.8–4.0 mmol/L	1.52	(1.14–2.03)	0.005	1.39	(1.04–1.87)	0.03
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	0.90	(0.69–1.17)	0.421	0.87	(0.66–1.13)	0.293
5.1–5.5 mmol/L	1.58	(1.15–2.17)	0.005	1.28	(0.93–1.76)	0.132
5.6–7.8 mmol/L	3.43	(2.28–5.17)	<0.001	2.73	(1.80–4.14)	<0.001
2. Patients without past history of malignancy (N=6383)						
2.2–2.9 mmol/L	7.15	(3.51–14.57)	<0.001	4.21	(2.00–8.86)	<0.001
3.0–3.4 mmol/L	4.15	(2.73–6.30)	<0.001	2.91	(1.90–4.44)	<0.001
3.5–3.7 mmol/L	2.47	(1.67–3.67)	<0.001	1.89	(1.27–2.82)	0.002
3.8–4.0 mmol/L	1.57	(1.13–2.17)	0.007	1.40	(1.02–1.93)	0.039
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	1.00	(0.75–1.32)	0.991	0.92	(0.69–1.23)	0.591
5.1–5.5 mmol/L	1.51	(1.07–2.13)	0.021	1.16	(0.81–1.64)	0.443
5.6–7.8 mmol/L	3.01	(2.01–4.52)	<0.001	2.35	(1.54–3.57)	<0.001
3. Patients without past history of heart failure or loop diuretic prescriptions (N=3149)						
2.2–2.9 mmol/L	11.31	(4.55–28.13)	<0.001	7.79	(2.54–23.90)	<0.001
3.0–3.4 mmol/L	3.80	(1.89–7.64)	<0.001	2.79	(1.35–5.78)	0.006
3.5–3.7 mmol/L	1.75	(0.84–3.66)	0.135	1.54	(0.72–3.28)	0.279
3.8–4.0 mmol/L	1.33	(0.79–2.25)	0.282	1.28	(0.75–2.18)	0.374
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	0.85	(0.54–1.36)	0.501	0.82	(0.51–1.31)	0.403
5.1–5.5 mmol/L	1.39	(0.82–2.39)	0.224	1.26	(0.73–2.19)	0.418
5.6–7.8 mmol/L	2.58	(1.28–5.18)	0.008	1.88	(0.90–3.91)	0.091
4. Patients without past history of ischemic heart disease (N=5121)						
2.2–2.9 mmol/L	8.30	(4.51–15.29)	<0.001	6.35	(3.39–11.89)	<0.001
3.0–3.4 mmol/L	3.64	(2.49–5.31)	<0.001	2.66	(1.80–3.92)	<0.001
3.5–3.7 mmol/L	2.87	(2.03–4.06)	<0.001	2.53	(1.78–3.60)	<0.001
3.8–4.0 mmol/L	1.41	(1.03–1.92)	0.032	1.30	(0.95–1.77)	0.101
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	0.91	(0.70–1.19)	0.493	0.87	(0.66–1.14)	0.313
5.1–5.5 mmol/L	1.63	(1.21–2.20)	0.001	1.51	(1.11–2.04)	0.008
5.6–7.8 mmol/L	2.35	(1.56–3.52)	<0.001	2.34	(1.55–3.55)	<0.001
5. Patients with an *ICD-10* hypertension diagnosis (N=2410)						
2.2–2.9 mmol/L	10.89	(4.68–25.32)	<0.001	5.15	(2.09–12.69)	<0.001
3.0–3.4 mmol/L	3.66	(2.00–6.71)	<0.001	2.84	(1.52–5.29)	0.001
3.5–3.7 mmol/L	1.53	(0.75–3.09)	0.242	1.04	(0.49–2.18)	0.923
3.8–4.0 mmol/L	1.67	(1.02–2.75)	0.041	1.75	(1.05–2.89)	0.032
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	1.08	(0.69–1.69)	0.754	1.07	(0.68–1.69)	0.773
5.1–5.5 mmol/L	2.22	(1.38–3.57)	<0.001	2.31	(1.43–3.75)	<0.001
5.6–7.8 mmol/L	2.82	(1.39–5.71)	0.004	2.54	(1.22–5.29)	0.012

(*Continued*)

Table 2. Continued

	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
6. Cardiovascular death (all-cause mortality as competing risk, N=7620)						
2.2–2.9 mmol/L	10.02	(5.07–19.80)	<0.001	6.86	(3.40–13.85)	<0.001
3.0–3.4 mmol/L	5.01	(3.24–7.75)	<0.001	3.21	(2.05–5.04)	<0.001
3.5–3.7 mmol/L	2.44	(1.54–3.86)	<0.001	1.85	(1.15–2.96)	0.010
3.8–4.0 mmol/L	1.80	(1.25–2.58)	0.001	1.56	(1.09–2.25)	0.022
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	0.99	(0.71–1.38)	0.953	0.97	(0.70–1.37)	0.880
5.1–5.5 mmol/L	2.11	(1.48–3.00)	<0.001	1.80	(1.26–2.57)	0.001
5.6–7.8 mmol/L	2.70	(1.63–4.45)	<0.001	2.61	(1.56–4.35)	<0.001
7. Last potassium measurement available within 6–100 d from the first potassium measurement (N=7620)						
2.2–2.9 mmol/L	10.54	(6.02–18.47)	<0.001	8.00	(4.53–14.13)	<0.001
3.0–3.4 mmol/L	4.44	(3.17–6.23)	<0.001	3.29	(2.33–4.64)	<0.001
3.5–3.7 mmol/L	3.17	(2.40–4.18)	<0.001	2.55	(1.92–3.38)	<0.001
3.8–4.0 mmol/L	1.43	(1.09–1.87)	0.011	1.28	(0.97–1.68)	0.082
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L	1.18	(0.94–1.49)	0.164	1.16	(0.92–1.47)	0.213
5.1–5.5 mmol/L	1.93	(1.45–2.55)	<0.001	1.59	(1.19–2.13)	0.002
5.6–7.8 mmol/L	7.04	(5.22–9.51)	<0.001	3.73	(2.70–5.15)	<0.001
8. Multivariable analyses adjusted for potassium concentrations obtained at the first measurement as well						
2.2–2.9 mmol/L				4.63	(2.66–8.06)	<0.001
3.0–3.4 mmol/L				2.39	(1.69–3.40)	<0.001
3.5–3.7 mmol/L				1.74	(1.26–2.39)	<0.001
3.8–4.0 mmol/L				1.38	(1.06–1.78)	0.013
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L				0.90	(0.72–1.14)	0.391
5.1–5.5 mmol/L				1.27	(0.97–1.66)	0.080
5.6–7.8 mmol/L				2.17	(1.53–3.07)	<0.001
9. Multivariable analysis adjusted for time between first and second potassium measurement as well						
2.2–2.9 mmol/L				3.74	(2.15–6.51)	<0.001
3.0–3.4 mmol/L				1.95	(1.38–2.76)	<0.001
3.5–3.7 mmol/L				1.55	(1.13–2.14)	0.007
3.8–4.0 mmol/L				1.24	(0.96–1.61)	0.103
4.1–4.6 mmol/L	REF.					
4.7–5.0 mmol/L				0.92	(0.73–1.16)	0.502
5.1–5.5 mmol/L				1.32	(1.01–1.73)	0.043
5.6–7.8 mmol/L				2.25	(1.60–3.18)	<0.001

Adjusted for age, sex, plasma sodium, renal insufficiency (÷1), malignancy (÷2), heart failure (÷3), chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease (÷4), inflammatory bowel disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, xanthines, laxatives, digoxin and potassium supplement. HR indicates hazard ratio; and *ICD-10*, *International Classification of Diseases, Tenth Revision*.

CI, 1.26–2.57; *P*=0.001; 5.6–7.8 mmol/L: HR, 2.61; 95% CI, 1.56–4.35; *P*<0.001).

Seventh, by retaining the last available plasma potassium measurement within 6 to 100 days of the first potassium measurement (instead of the first available measurement) we observed similar results with the main analysis.

Eighth, multivariable analyses adjusted for potassium concentrations obtained at the first measurement showed similar results to the main analysis: Potassium levels outside the interval 4.6 to 5.5 mmol/L after a recent episode of hyperkalemia were associated with increased short-term mortality risk.

Ninth, analyses including time between first and second potassium draw as a covariate showed similar results to the main analysis.

DISCUSSION

This Danish register-based cohort study investigated the 90-day mortality among 7620 patients with hypertension and hyperkalemia in relation to the subsequent plasma potassium measurement. The major findings were: (1) More than one-third of the patients with initial hyperkalemia persisted with hyperkalemia at a subsequent measurement; (2) potassium concentrations >5.5 mmol/L were associated with increased all-cause and cardiovascular mortality; (3) decrease in potassium to levels <4.1 mmol/L in patients with initial hyperkalemia was associated with increased mortality risk (all-cause and cardiovascular) compared with the reference (4.1–4.6 mmol/L); (4) aiming for potassium concentrations between 4.1 and 5.5 mmol/L, after an episode of hyperkalemia, was associated with increased survival.

Numerous studies have previously shown the importance of potassium on mortality in different populations with or without cardiovascular disease.[3,13–17] However, no prior studies have examined the risk of mortality in patients who persisted with hyperkalemia or who had hypokalemia at the second measurement compared with patients with normal plasma potassium concentrations.

We observed a significantly increased mortality risk among patients who, following an episode of hyperkalemia, had their potassium downregulated to levels <4.1 mmol/L within 6 to 100 days. This finding was expected considering our previous findings,[3] where we observed an apparent optimal potassium range within 4.1 to 4.7 mmol/L in a similar population. We also observed significant associations with presumed cardiovascular death. Potassium concentrations <4.1 and >5.5 mmol/L are associated with both all-cause and cardiovascular mortality, which might suggest that potassium has 2 roles: risk factor and risk marker. In other words, potassium in itself could be responsible for mortality, and potassium abnormalities could identify sicker patients with increased risk of mortality or patients physiologically or genetically "unable" to maintain potassium homeostasis when having concurrent heart disease.

A retrospective register-based study, using records of 114 977 emergency department patients hospitalized from October 2016 to October 2017, showed that potassium normalization within the first 8 hours after hyperkalemia (≥5.5 mmol/L) at admission was associated with 50% mortality reduction.[18] Distribution of comorbidities was not described by the authors; therefore, we cannot compare the burden of cardiovascular diseases. However, the findings of Singer et al[18] are a wake-up call. In our study, we also observed that plasma potassium >5.5 mmol/L (after an episode of hyperkalemia) was associated with higher mortality compared with concentrations between 4.1 and 4.6 mmol/L.

McMahon et al[19] examined the association between the highest potassium concentration on the admission day and 30-, 90- and 365-day mortality in >39 000 intensive care unit–treated patients. The authors found significantly higher mortality in patients with potassium levels >4.5 mmol/L. Moreover, the study showed a better prognosis in patients who had a decline in potassium concentration >1 mmol/L within 48 hours following critical care initiation. Our study suggested that lowering potassium levels in patients who originally had concentrations >4.6 mmol/L was beneficial. However, the survival benefit was lost when potassium was corrected to levels <4.1 mmol/L. Another study by Khanagavi et al[20] including hospitalized patients with potassium levels >5.1 mmol/L reported that the duration of hyperkalemia was associated with increased risk of death. Unfortunately, we do not have information about the duration of hyperkalemia. However, according to good clinical practice, most clinicians in Denmark do not initiate or change antihypertensive treatment unless blood tests are available within a short period of time. Data from the studies mentioned above suggested that not only the absolute value of potassium was important in relation to mortality, but also duration of hyperkalemia, the severity of disease, and velocity and magnitude of potassium correction.

We noted that kidney insufficiency, age, history of malignancy, stroke, chronic obstructive pulmonary disease, atrial fibrillation, and chronic liver disease and hospitalization at the time of potassium measurement were significant predictors of mortality. An et al[21] found similar predictors of mortality in patients with severe hyperkalemia requiring hospitalization.

Limitations

Because of the observational design, we cannot exclude residual confounding such as vomiting, diarrhea, or diet, as this information was not available.

At the first potassium measurement, all patients had a plasma potassium level >4.6 mmol/L, and it is expected that treatment for potassium normalization is initiated immediately afterwards, at least in patients with concentrations >5.0 mmol/L. However, it was not possible in this register-based study to explore the effect of any potential effectuated treatment or drug adjustment. The Danish National Prescription Registry registers filled prescriptions; thus, a decrease or an increase in dosage could not be traced. In addition, the majority of the patients were hospitalized at the time of potassium measurement, and any treatment under hospitalization is not registered in the Danish National Prescription Registry.

There is a possibility that potassium normalization (at the second potassium measurement) can be explained by regression toward the mean and not by any active pharmacological or nonpharmacological intervention. Regression toward the mean implies that some of the extreme values at the first measurements should be results of random error and therefore be closer to the mean at the second measurement. This would lead to more people having normalized their potassium in addition to those who had it corrected. This would result in a biased conclusion/observation of the group that had potassium corrected, but not for the group in which dyskalemia persisted.

We cannot exclude the possibility of hemolyzed blood specimens. However, in case of significant hemolysis with high hemolytic index, laboratories frequently reject plasma samples submitted for potassium measurement and mark these with no values.

Information on comorbidities and risk factors from the primary sector was not available. Therefore, patients who were not prescribed any of the medications of interest or were not registered an *ICD* code from the secondary sector might have been misclassifies as "healthy." Patients with complications related to hypertension are more likely to be referred to the secondary sector and therefore have a higher probability for being diagnosed with other conditions (compared with patients with uncomplicated hypertension), leading to an ascertainment/surveillance bias and nondifferential misclassification bias. To reduce this bias, we defined hypertension as use of at least 2 antihypertensive drugs in 2 concomitant quarters. Whether hypertension was resistant, controlled, or uncontrolled was unknown, and data about ejection fraction and etiology of heart failure were not available.

Because of multiple comparisons, we cannot exclude the possibility of inflated type I error. In this study we have 21 comparisons, and the critical *P* value of <0.05 in a worst-case scenario should be ≤0.002, correcting for the comparisons. This correction holds for all comparisons except potassium group 3.8 to 4.0 mmol/L, where the *P* value was 0.01.

Because of the great burden of comorbidities and administration of combination antihypertensive therapy, the results of this paper are not generalizable to the entire population with high blood pressure.

Finally, our results can be interpreted only as associations, and no causal relations can be drawn from this study.

CONCLUSIONS

Overcorrection of hyperkalemia to levels <4.1 mmol/L was frequent and associated with increased all-cause and cardiovascular mortality. Potassium concentrations >5.5 mmol/L were also associated with increased all-cause and cardiovascular mortality.

PERSPECTIVES

Although we may not be able to report the mechanism through which potassium was lowered, our results emphasized the importance of potassium normalization after an episode of hyperkalemia and nonradical correction of hyperkalemia in patients with hypertension treated with combination antihypertensive therapy.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S7
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. List of antihypertensive drugs and corresponding ATC codes used to define hypertension.

ATC codes	Name of drug
C02A	Antiadrenergic agents, centrally acting
C02B	Antiadrenergic agents, ganglion blocking
C02C	Antiadrenergic agents, peripherally acting
C02DA	Thiazide-derivatives
C02DB	Hydrazynophthalazin-derivatives
C02DD	Nitroferricyanide-derivatives
C02DG	Guanidin-derivatives
C02L	Antihypertensives and diuretics in combination
C03AA	Thiazides
C03AB	Thiazides and potassium in combination
C03BA	Sulfonamides
C03BB	Sulfonamides and potassium in combination
C03C	Loop diuretics
C03DA	Aldosteron antagonists
C03DB	Other potassium sparing agents

C03EA	Low-ceiling diuretics and potassium sparing agents
C03EB	High-ceiling diuretics and potassium sparing agents
C03X	Other diuretics
C07A	Beta-blockers
C07B	Beta-blockers and thiazides
C07C	Beta-blockers and other diuretics
C07D	Beta-blockers, thiazides and other diuretics
C07FB	Beta-blockers and calcium antagonists
C07FX	Beta-blockers and other combinations
C08C	Selective calcium antagonists primarily with vascular effect
C08D	Selective calcium antagonists with direct cardiac effect
C08E	Non-selective calcium antagonists
C08G	Calcium antagonists and diuretics
C09AA	Angiotensin converting enzyme inhibitors
C09BA	Angiotensin converting enzyme inhibitors and diuretics

C09BB	Angiotensin converting enzyme inhibitors and calcium antagonists
C09CA	Angiotensin II antagonists
C09DA	Angiotensin II antagonists and diuretics
C09DB	Angiotensin II antagonists and calcium antagonists
C09XA	Renin-inhibitors

Table S2. Definitions of comorbidities, procedures and concomitant medications based on different ICD-10, Nordic Classification of Surgical Procedures (NCSP), and ATC codes identified prior to index date.

	ICD-10 codes	Time prior to index date	NCSP codes	Time prior to index date	ATC codes	Time prior to index date
Comorbidities and procedures						
Ischemic heart disease including myocardial infarction[1]	I20-25	5 years	KFNG, KFNA-E	5 years	–	–
Atrial flutter or fibrillation	I48	5 years	–	–	–	–
Chronic obstructive pulmonary disease	J40-44	5 years	–	–	–	–
Chronic liver disease	B18, C22, K71-77	5 years	–	–	–	–
Syndrome of inappropriate antidiuretic hormone secretion	E22.2	5 years	–	–	–	–
Diabetes insipidus	E23.2, N25.1	5 years	–	–	–	–
Addison disease	E27.1	5 years	–	–	–	–
Primary hyperaldosteronism	E26.0	5 years	–	–	–	–
Diabetes	E10-14	5 years	–	–	–	–
Cancer	C00-99	5 years	–	–	–	–
Hypertension	DI11-15	5 years	–	–	–	–
Heart failure	I110, I130,	5 years	–	–	–	–

	I132, I42, I50, J81					
Stroke	DI61, DI62, DI63, DI64, DG458-459, DG433-438	5 years	–	–	–	–
Inflammatory bowel disease (IBD)	DK50-51	5 years	–	–	–	–
Concomitant medications						
Potassium supplements	–	–	–	–	A12B C03AB C03BB C03CB	90 days
Loop diuretics	–	–	–	–	C03C	90 days
Non-steroidal anti-inflammatory drugs	–	–	–	–	M01A	180 days
Antimicrobials	–	–	–	–	J01CF06, J01CA01, J01CE, J01G, J02AA01, J05AD01, J01CF05	30 days
β2-agonists	–	–	–	–	R03AC02, C01CA2, C01CA24, R03AC13 C01CA02, R03AB02 R03CB01,	90 days

					R01BA02, R03AC03, R03AC12	
Mineralo- and glucocorticoids	–	–	–	–	A01AC03, A07EA02, C05AA01, D07AA02, H02AB09, S01BA02, S02BA01, H02AA02, A07EA03, H02AB07	90 days
Laxatives	–	–	–	–	V03AE01, A06AB04, A06AG10	30 days
Xantines	–	–	–	–	R03DA04, N06BC01	30 days
Macrolides	–	–	–	–	J01FA	30 days

Table S3. Aikaike Information Criterion and area under the ROC curve for the main model and sensitivity analyses.

	Univariable analysis		Multivariable analysis	
	AIC	**AUC**	**AIC**	**AUC**
Main model	11156	0.60	10605	0.74
Sensitivity analyses				
1. Patients with normal kidney function (N= 6505)	8435	0.61	7992	0.73
2. Patients without past history with malignancy (N= 6383)	6949	0.60	6636	0.73
3. Patients without past history with heart failure or loop diuretic prescriptions (N= 3149)	2486	0.56	2287	0.79
4. Patients without past history with ischemic heart disease (N= 5121)	7949	0.60	7567	0.77
5. Patients with and ICD-10 hypertension diagnosis (N= 2410)	2639	0.61	2505	0.79
6. Cardiovascular death (all cause mortality as competing risk, N= 7620)	5631	0.88	5354	0.78
7. Last potassium measurement available within 7-100 days from the first potassium measurement (N= 7620)	10840	0.60	10137	0.75
8. Main model adjusted for the first potassium measurement as well	11156	0.60	10606	0.74
9. Main model adjusted for the time from first to second potassium measurement as well	11156	0.60	10500	0.76

Table S4. Hospitalization diagnoses at the time of second potassium measurement.

Primary and secondary diagnoses	Frequency	
DA00-DB99 Certain infectious and parasitic diseases	60	
DC00-DD48 Neoplasm	61	
DD50-DD89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	50	
DE00-DE90 Endocrine, nutritional and metabolic disorders	118	
DG00-DG99 Diseases of the nervous system	43	
DI00-DI99 Diseases of the circulatory system	558	
Heart disease		449
DJ00-DJ99 Diseases of the respiratory system	494	
DK00-DK93 Diseases of the digestive system	301	
DL00-DL99 Diseases of the skin and subcutaneous tissue	47	
DM00-DM99 Diseases of the muculoskeletal system and connective tissue	154	
DN00-DN99 Diseases of the genitourinary system	365	
Glomerular diseases, Renal tubulo-interstitial diseases or Renal failure		227
DR00-DR99 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	694	
DS00-DT98 Injury, poisoning and certain other consequences of external causes	301	
DZ00-DZ99 Factors influencing health status and contact with health services	1277	
Others	106	
Total:	4629	
Others include:		
DF00-DF99 Mental and behavioural disorders		
DH00-DH59 Diseases of the eye and adnexa		
DQ00-DQ99 Congenital malformations, deformations and chromosomal abnormalities		
DV01-DY98 External causes of morbidity and mortality		

Table S5. Distribution of the first potassium measurement and potassium draws within 1-5 days from the first potassium measurement (stratified by the second potassium measurement groups)

		2.2-2.9 mmol/L (n=29)	**3.0-3.4 mmol/L (n=130)**	**3.5-3.7 mmol/L (n=164)**	**3.8-4.0 mmol/L (n=336)**	**4.1-4.6 mmol/L (n=898)**	**4.7-5.0 mmol/L (n=361)**	**5.1-5.5 mmol/L (n=181)**	**5.6-7.8 mmol/L (n=62)**	**Total (n=2161)**	**p-value**
First potassium measurement	median(range)	4.9(4.7, 6.6)	4.8(4.7, 8.9)	4.9(4.7, 7.5)	4.9(4.7, 8.2)	4.9(4.7, 9.1)	4.9(4.7, 8.0)	5(4.7, 7.7)	5.1(4.7, 7.3)	4.9(4.7, 9.1)	<0.001
First potassium measurement (groups)	4.7-5.5 mmol/L	22 (75.9)	112 (86.2)	150 (91.5)	308 (91.7)	818 (91.1)	323 (89.5)	156 (86.2)	48 (77.4)	1,937 (89.6)	
	>5.5 mmol/L	7 (24.1)	18 (13.8)	14 (8.5)	28 (8.3)	80 (8.9)	38 (10.5)	25 (13.8)	14 (22.6)	224 (10.4)	<0.001
Average of potassium drawn between 1-5 days from the first potassium measurement	mean (sd)	3.8 (0.6)	4 (0.5)	4.1 (0.5)	4.3 (0.4)	4.4 (0.4)	4.6 (0.4)	4.8 (0.5)	4.9 (0.6)	4.4 (0.5)	<0.001
Death-90 days		14 (48.3)	32 (24.6)	35 (21.3)	52 (15.5)	125 (13.9)	53 (14.7)	43 (23.8)	20 (32.3)	374 (17.3)	<0.001

Table S6. Causes of death.

Causes of death	Frequency
Cardiovascular	318
Certain infectious and parasitic disease	14
Neoplasm	116
Mental and behavioural disorders	8
Diseases of the nervous system	4
Diseases of the respiratory system	35
Diseases of the digestive system	46
Diseases of the genitourinary system	6
Others	25
missing	61

Table S7. Demographics by survival status.

		Alive (n=6998)	Deceased (n=622)	Total (n=7620)	p-value
Second potassium measurement	median(range)	4.5(2.3, 7.8)	4.4(2.2, 7.6)	4.5(2.2, 7.8)	0.001
First potassium measurement	median(range)	4.8(4.7, 9.1)	4.9(4.7, 7.4)	4.8(4.7, 9.1)	< 0.0001
Age	median(range)	69.8(18.2, 102.3)	75.1(19.5, 101.8)	70.3(18.2, 102.3)	< 0.0001
Sex	Female	2,769 (39.6)	292 (46.9)	3,061 (40.2)	
	Male	4229 (60.4)	330 (53.1)	4,559 (59.8)	0.0004
Renal insufficiency (second measuremt)		973 (13.9)	142 (22.8)	1,115 (14.6)	< 0.0001
Serum sodium (second measurement)	median(range)	139(108, 166)	135(112, 169)	139(108, 169)	< 0.0001
Renal insufficiency (first measuremt)		924 (14.1)	123 (20.5)	1,047 (14.6)	< 0.0001
	missing			446	
Hospitalization at the time of first potassium measurement		1992 (28.6)	400 (64.3)	2,392 (31.5)	< 0.0001
Hospitalization at the time of second potassium measurement		5876 (84.0)	576 (92.6)	6,452 (84.7)	< 0.0001
Malignancy		1012 (14.5)	225 (36.2)	1,237 (16.2)	< 0.0001
Chronic obstructive pulmonary disease		938 (13.4)	144 (23.2)	1,082 (14.2)	< 0.0001
Atrial fibrillation/Atrial flutter		1569 (22.4)	165 (26.5)	1,734 (22.8)	0.023
Chronic kidney disease		881 (12.6)	72 (11.6)	953 (12.5)	0.501
Chronic liver disease		276 (3.9)	78 (12.5)	354 (4.6)	< 0.0001
Hypertension (ICD-10)		2243 (32.1)	167 (26.8)	2,410 (31.6)	0.01
Ischemic heart disease		2342 (33.5)	157 (25.2)	2,499 (32.8)	< 0.0001
Diabetes		1798 (25.7)	117 (18.8)	1,915 (25.1)	0.0002
Heart failure		2315 (33.1)	214 (34.4)	2,529 (33.2)	0.532
Stroke		653 (9.3)	88 (14.1)	741 (9.7)	0.0001

Figure S1. Population flowchart.

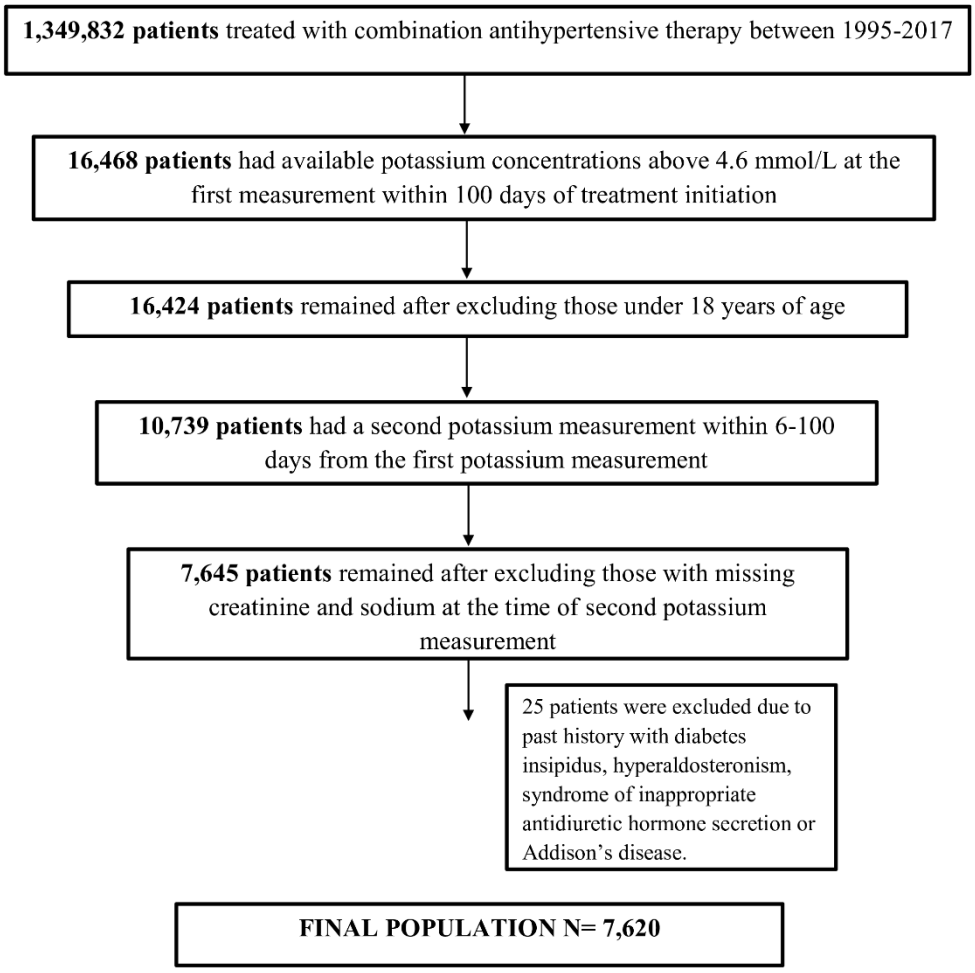

Figure S2. Distribution of the first potassium measurement (1, n= 7620), average potassium measurements drawn within 1-5 days from the first potassium measurement (2, n= 2161) and distribution of the second potassium measurement (3, n= 7620).