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Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data

Maria Lukács Krogager[1]*, Christian Torp-Pedersen[2,3], Rikke Nørmark Mortensen[3], Lars Køber[4], Gunnar Gislason[5,6], Peter Søgaard[7,8], and Kristian Aasbjerg[8]

[1]Faculty of Health Science, Aalborg University, Fredrik Bajers Vej 5, 9100 Aalborg, Denmark; [2]Department of Health Science and Technology, Aalborg University Hospital, Søndre Skovvej 15, 9000 Aalborg, Denmark; [3]Department of Clinical Epidemiology, Aalborg University Hospital, Søndre Skovvej 15, 9000 Aalborg, Denmark; [4]Department of Cardiology, The Heart Center, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; [5]Department of Cardiology, Copenhagen University Hospital Gentofte, Kildegårdsvej 28, 2900 Hellerup, Denmark; [6]Denmark and National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; [7]Heart Centre and Clinical Institute, Aalborg University Hospital, Aalborg, Denmark; and [8]Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark

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Aims Diuretics and renin–angiotensin–aldosterone system inhibitors are central in the treatment of hypertension, but may cause serum potassium abnormalities. We examined mortality in relation to serum potassium in hypertensive patients.

Methods and results From Danish National Registries, we identified 44 799 hypertensive patients, aged 30 years or older, who had a serum potassium measurement within 90 days from diagnosis between 1995 and 2012. All-cause mortality was analysed according to seven predefined potassium levels: <3.5 (hypokalaemia), 3.5–3.7, 3.8–4.0, 4.1–4.4, 4.5–4.7, 4.8–5.0, and >5.0 mmol/L (hyperkalaemia). Outcome was 90-day mortality, estimated with multivariable Cox proportional hazard model, with the potassium interval of 4.1–4.4 mmol/L as reference. During 90-day follow-up, mortalities in the seven strata were 4.5, 2.7, 1.8, 1.5, 1.7, 2.7, and 3.6%, respectively. Adjusted risk for death was statistically significant for patients with hypokalaemia [hazard ratio (HR): 2.80, 95% confidence interval (95% CI): 2.17–3.62], and hyperkalaemia (HR: 1.70, 95% CI: 1.36–2.13). Notably, normal potassium levels were also associated with increased mortality: K: 3.5–3.7 mmol/L (HR: 1.70, 95% CI: 1.36–2.13), K: 3.8–4.0 mmol/L (HR: 1.21, 95% CI: 1.00–1.47), and K: 4.8–5.0 mmol/L (HR: 1.48, 95% CI: 1.15–1.92). Thus, mortality in relation to the seven potassium ranges was U-shaped, with the lowest mortality in the interval of 4.1–4.4 mmol/L.

Conclusion Potassium levels outside the interval of 4.1–4.7 mmol/L were associated with increased mortality risk in patients with hypertension.

Keywords Serum potassium • Hypertension • Mortality

Introduction

The overall prevalence of hypertension in Europe is about 30–45% of the total population[1] with a treatment range from 11 to 66%.[2] Many antihypertensive agents including diuretics, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) can cause potassium disturbances[3,4] and influence survival.[5] Whereas the mechanisms that influence patient survival due to potassium disturbances are well known, little is known about the optimal range of serum potassium in disease and the levels associated with increased risk.[6,7] The normal potassium interval is defined based on apparently healthy individuals. The current guidelines provide normal lower potassium limit from 3.5 to 3.8 mmol/L, while the upper limit is between 5.0 and 5.5 mmol/L.[4,8,9]

Well-defined hyperkalaemia and hypokalaemia in patients with hypertension is known to increase the risk of death.[5] In patients with acute heart failure, potassium levels within the normal range are associated with increased risk of death, highlighting that the optimal level of potassium may differ from current definitions of the normal range.[10] Despite the widespread use of diuretics and other drugs that influence potassium levels in patients with hypertension, a search for optimal values of serum potassium has not

* Corresponding author. Tel: +45 53 14 88 24, Fax: +45 97 66 44 80, Email: lkcsmaria@yahoo.com; maria.krogager@rn.dk

been performed.[3,5,9] To address this issue, we used data from >40 000 individuals with hypertension to examine the relation between serum potassium and all-cause mortality.

Methods

Databases

All residents in Denmark have a personal, unique, and permanent civil registration number that enables individual linkage of administrative registries. The Danish National Patient Registry consists of information about all hospital admissions since 1978. At discharge, each hospitalization is registered with one primary and, if applicable, one or more secondary diagnoses according to the International Classification of Disease (ICD). Until 1994, the 8th revision (ICD-8) was in use and from 1994 onwards the 10th revision (ICD-10). The National Register for Medicinal Statistics includes all dispensed prescriptions from Danish pharmacies since 1995 based on the Anatomical Therapeutic Chemical System (ATC). As the healthcare system is state financed and partly reimburses drug costs, all Danish pharmacies are legally required to register all dispensed drug prescriptions, providing a valid and accurate register. Date of death, date of birth, and vital status were obtained from the Danish Register of Causes of Death and the Central Personal Registry. Blood test results were obtained from electronic registries of laboratory data, and we had access to data covering ~1.5 million individuals.

Study population

Hypertension was primarily defined by the use of at least two concomitant antihypertensive drugs in two concomitant quarters. Patients entered the study in the second quarter. This definition has previously been validated: positive predictive value 80% and specificity 94.7%.[1,11] We performed two sensitivity analyses where we selected the population based on ICD codes and where we excluded patients receiving loop diuretics. The first serum potassium measurement within 90 days of antihypertensive treatment was selected. To avoid extreme outliers, patients with potassium levels <2.9 mmol/L and >5.8 mmol/L were excluded. Patients under the age of 30 years were excluded because it is unlikely that this group would have essential hypertension. The patients were censored on 31 December 2012 or after 90-day follow-up. Patients with serum potassium measurements up to 90 days after dual single-pill antihypertensive drug treatment were included in the study. The outcome of the study was 90-day mortality from the date of serum potassium measurement.

Co-morbidities and drugs

The statistical analyses were performed on patients stratified in groups by the following potassium levels: <3.5, 3.5–3.7, 3.8–4.0, 4.1–4.4, 4.5–4.7, 4.8–5.0, and >5.0 mmol/L. Hypokalaemia was defined as potassium <3.5 mmol/L and hyperkalaemia as >5.0 mmol/L. Serum potassium interval of 4.1–4.4 mmol/L was used as reference for statistical analysis. The reference interval was chosen based on the restricted cubic splines results, and also other analysis, which confirmed that the lowest mortality risk was found in this range.

Besides age and gender, the following conditions present before the date of hypertension were assessed and used as covariates in the analysis: chronic obstructive pulmonary disease (ICD-8: 491, 492; ICD-10: J42–44), stroke (ICD-8: 433–438; ICD-10: I61, I62, I63, I64, DG458, DG459), acute myocardial infarction (ICD-10: I21), atrial fibrillation (ICD-10: I48), heart failure (ICD-10: I50), and diabetes.[12,13] Diabetes was defined as more than two dispensed prescriptions of glucose-lowering drugs (ATC code A10; insulin or oral hypoglycaemic agents), because patients with diabetes were not necessarily admitted to hospital with this specific diagnosis.[10,14–16] Serum creatinine was obtained within a week of serum potassium measurement. Patients with renal insufficiency and missing creatinine levels were excluded. Renal insufficiency was defined by a serum creatinine level: (i) >105 μmol/L for men <70 years, (ii) >125 μmol/L for men >70 years, (iii) >90 μmol/L for women <70 years, and (iv) >105 μmol/L for women >70 years.[17,18] A total of 1857 patients did not have a serum creatinine measurement. Serum sodium measured same day as serum potassium was also identified.

Patients who prior to the administration of two concomitant antihypertensives were diagnosed with acute (ICD-10: DN17, DN19, DR34) chronic kidney disease, including proteinuria (ICD-10: DN02–08, DN11–12, DN14, DN18–19, DN26, DN158–160, DN162–164, DN168, DN313, DQ612–613, DQ615, DQ619, DE102, DE112, DI120, DM300, DM319, DM321B) or primary hyperaldosteronism (ICD-10: DE260), were also excluded.

We included the five most prescribed antihypertensive single-pill drug combinations in the multivariable analysis: ACEIs/ARBs and thiazide diuretics; ACEIs/ARBs and β-blockers; ACEIs/ARBs and calcium channel blockers; ACEIs/ARBs, thiazide diuretics, and potassium supplements; and β-blockers, thiazide diuretics, and potassium supplements. The remaining possible combinations were categorized as other combinations of antihypertensive medication. The combination of ACEIs/ARBs with thiazide diuretics and potassium supplements was used as reference for statistical analysis. The following medications (ATC codes) were identified: renin–angiotensin system inhibitors C09; calcium channel blockers C08; β-blockers C07; diuretics C03; antiadrenergic drugs C02A, C02B, and C02C; and other antihypertensives C02DA, C02DB, C02DD, C02DG, and C02L. Apart from medication for hypertension, we have also included potassium supplements (ATC: A12B) in the multivariable statistical analysis.

Statistical analysis

Kaplan–Meier cumulative mortality curves were plotted for the seven preselected potassium intervals to illustrate trends in mortality. Cox proportional hazard regression models were used to determine the risk of death in hypertensive patients with different potassium intervals, adjusted for all covariates. To validate this statistical model, the three Cox proportional hazard model assumptions were assessed: proportionality, linearity, and interaction. As linearity assumption had not been fulfilled regarding the continuous variable age, we predefined four age intervals: 30–50 years, 51–70 years, 71–80 years, and >80 years. Age interval of 50–70 years was used as reference.

The association of potassium with mortality was also assessed using restricted cubic splines with knots at the 10th, 25th, 50th, 75th, and 90th percentiles of potassium.

Relative risks are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). *P*-values of <0.05 were considered significant. Analyses were performed with SAS (version 9·4, SAS Institute, Cary, NC, USA) and R statistical software (version 3.0.1, R development core team).

Results

Demographics

In the period 1995–2012, we identified 44 799 hypertensive patients that had a potassium measurement within 90 days from diagnosis. The average age in the population was 67.1 (±12.6)

Table I Demographics stratification according to potassium levels

	K: 2.9–3.4 mmol/L	K: 3.5–3.7 mmol/L	K: 3.8–4.0 mmol/L	K: 4.1–4.4 mmol/L	K: 4.5–4.7 mmol/L	K: 4.8–5.0 mmol/L	K: 5.1–5.8 mmol/L	Total
Gender								
Female	1095 (64.4%)	2401 (60.1%)	5176 (55.0%)	8908 (49.1%)	3521 (45.3%)	1203 (43.7%)	484 (47.2%)	22 788 (50.9%)
Male	604 (35.6%)	1593 (39.9%)	4236 (45.0%)	9242 (50.9%)	4247 (54.7%)	1548 (56.3%)	541 (52.8%)	22 011 (49.1%)
Age, mean/SD	67 (±13.8)	66.7 (±13.2)	66.4 (±12.8)	66.9 (±12.4)	67.7 (±12.3)	68.9 (±12.2)	70.7 (±12.3)	67.1 (±12.6)
No. of antihypertensive drug prescription, mean/SD	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.3 (±0.5)	2.2 (±0.5)
Thiazide diuretics	1168 (68.7%)	2633 (65.9%)	5866 (62.3%)	9474 (52.2%)	3359 (43.2%)	1027 (37.3%)	389 (38.0%)	23 916 (53.4%)
Loop diuretics	422 (24.8%)	875 (21.9%)	1857 (19.7%)	3484 (19.2%)	1696 (21.8%)	738 (26.8%)	334 (32.6%)	9406 (21.0%)
Potassium-sparing diuretics	71 (4.2%)	130 (3.3%)	265 (2.8%)	738 (4.1%)	467 (6.0%)	249 (9.1%)	142 (13.9%)	2062 (4.6%)
Aldosteron antagonist	71 (4.2%)	127 (3.2%)	260 (2.8%)	736 (4.1%)	463 (6.0%)	248 (9.0%)	141 (13.8%)	2046 (4.6%)
ACEIs/ARBs	878 (51.7%)	2343 (58.7%)	6215 (66.0%)	12 986 (71.5%)	5994 (77.2%)	2121 (77.1%)	816 (79.6%)	31 353 (70.0%)
β-blockers (BB)	618 (36.4%)	1505 (37.7%)	3810 (40.5%)	8209 (45.2%)	3822 (49.2%)	1445 (52.5%)	505 (49.3%)	19 914 (44.5%)
Calcium channel blockers (CCB)	763 (44.9%)	1553 (38.9%)	3100 (32.9%)	5768 (31.8%)	2219 (28.6%)	729 (26.5%)	272 (26.5%)	14 404 (32.2%)
Antihypertensive drugs that contain potassium	893 (52.6%)	1907 (47.7%)	3998 (42.5%)	6322 (34.8%)	2242 (28.9%)	706 (25.7%)	260 (25.4%)	16 328 (36.4%)
Potassium supplement	792 (46.6%)	1901 (47.6%)	4518 (48.0%)	8687 (47.9%)	3766 (48.5%)	1354 (49.2%)	476 (46.4%)	21 494 (48%)
Antiadrenergic drugs	32 (1.9%)	45 (1.1%)	113 (1.2%)	220 (1.2%)	83 (1.1%)	33 (1.2%)	8 (0.8%)	534 (1.2%)
Antihypertensive drug combinations								
ACEIs/ARBs + BB	50 (2.9%)	188 (4.7%)	695 (7.4%)	2393 (13.2%)	1371 (17.6%)	532 (19.3%)	148 (14.4%)	5377 (12.0%)
ACEIs/ARBs + CCB	57 (3.4%)	167 (4.2%)	500 (5.3%)	1398 (7.7%)	679 (8.7%)	245 (8.9%)	84 (8.2%)	3130 (7.0%)
ACEIs/ARBs + thiazides	138 (8.1%)	437 (10.9%)	1259 (13.4%)	2179 (12.0%)	784 (10.1%)	213 (7.7%)	77 (7.5%)	5087 (11.4%)
ACEIs/ARBs + thiazides + potassium supplement	190 (11.2%)	558 (14.0%)	1442 (15.3%)	2492 (13.7%)	972 (12.5%)	303 (11.0%)	111 (10.8%)	6068 (13.5%)
BB + thiazides + potassium supplement	162 (9.5%)	397 (9.9%)	854 (9.1%)	1315 (7.2%)	430 (5.5%)	135 (4.9%)	38 (3.7%)	3331 (7.4%)
Other combinations	1102 (64.9%)	2247 (56.3%)	4662 (49.5%)	8373 (46.1%)	3532 (45.5%)	1323 (48.1%)	567 (55.3%)	21 806 (48.7%)
Atrial fibrillation	189 (11.1%)	525 (13.1%)	1193 (12.7%)	2505 (13.8%)	1187 (15.3%)	465 (16.9%)	183 (17.9%)	6247 (13.9%)
Acute myocardial infarction	103 (6.1%)	300 (7.5%)	838 (8.9%)	2165 (11.9%)	1089 (14.0%)	443 (16.1%)	133 (13.0%)	5071 (11.3%)
Heart failure	148 (8.7%)	350 (8.8%)	876 (9.3%)	1943 (10.7%)	1115 (14.4%)	464 (16.9%)	207 (20.2%)	5103 (11.4%)
Stroke	247 (14.5%)	515 (12.9%)	1130 (12.0%)	2124 (11.7%)	920 (11.8%)	363 (13.2%)	143 (14.0%)	5442 (12.1%)
Chronic obstructive pulmonary disease	181 (10.7%)	381 (9.5%)	788 (8.4%)	1492 (8.2%)	707 (9.1%)	316 (11.5%)	146 (14.2%)	4011 (9.0%)

Continued

Table 1 *Continued*

	K: 2.9–3.4 mmol/L	K: 3.5–3.7 mmol/L	K: 3.8–4.0 mmol/L	K: 4.1–4.4 mmol/L	K: 4.5–4.7 mmol/L	K: 4.8–5.0 mmol/L	K: 5.1–5.8 mmol/L	Total
Antidiabetic drugs	121 (7.1%)	330 (8.3%)	941 (10.0%)	2158 (11.9%)	1213 (15.6%)	509 (18.5%)	214 (20.9%)	5486 (12.2%)
Insulin	20 (1.2%)	35 (0.9%)	112 (1.2%)	208 (1.1%)	126 (1.6%)	65 (2.4%)	27 (2.6%)	593 (1.3%)
Serum natrium, mean/SD	138.8 (±5.2)	139.5 (±4.2)	139.8 (±3.8)	139.9 (±3.6)	139.6 (±3.9)	139.2 (±4.3)	138.2 (±4.9)	139.7 (±3.9)
Missing	47	142	412	759	318	109	29	1816
Serum creatinine, mean/SD	77 (±16)	79.1 (±15.8)	80.1 (±15.8)	82.2 (±15.6)	83.9 (±15.8)	85.8 (±16.2)	87.5 (±16.8)	81.9 (±15.9)
Day at potassium measurement, mean/SD	34.8 (±25.7)	36.2 (±25.8)	36.9 (±25.7)	37.1 (±25.6)	36.4 (±25.4)	33.7 (±24.5)	33.7 (±24.5)	36.6 (±25.6)
Status: 90 days								
Alive	1622 (95.5%)	3886 (97.3%)	9244 (98.2%)	17 881 (98.5%)	7635 (98.3%)	2677 (97.3%)	988 (96.4%)	43 933 (98.1%)
Deceased	77 (4.5%)	108 (2.7%)	168 (1.8%)	269 (1.5%)	133 (1.7%)	74 (2.7%)	37 (3.6%)	866 (1.9%)

Data are presented as mean ± SD (age) or number of patients and percentage (all others).
ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
$n = 44\,799$.

years. The characteristics of the population, reported according to the seven potassium levels, are presented in *Table 1*. No significant difference in gender distribution was observed within the total population. Women were overall more susceptible to hypokalaemia, whereas men more often had hyperkalaemia. The overall potassium distribution was mean 4.20 mmol/L and median 4.2 mmol/L. The 25th and 75th percentiles for potassium were 3.92 and 4.5 mmol/L, respectively. Mean serum sodium was 139.7 (± 3.9). Of the patients, 5486 were prescribed antidiabetic drugs and ~1% were treated with insulin. The other co-morbid conditions such as atrial fibrillation, heart failure, and acute myocardial infarction were present in a rate of ~10% each.

The major antihypertensive drug combinations were ACEIs/ARBs combined with thiazides and potassium supplement 13.5%; ACEIs/ARBs with β-blockers 12%; ACEIs/ARBs with thiazide diuretics 11.4%; β-blockers combined with thiazides and potassium supplement 7.4%; and ACEIs/ARBs with calcium channel blockers 7%. In total, 21 494 patients were prescribed potassium supplements. Serum potassium level was measured 36.6 (± 25.6) days, on average, after administration of minimum two concomitant antihypertensive drugs. Supplementary material online, *S1* illustrates that in the first 45 days from dual antihypertensive therapy initiation, most potassium measurements are effectuated (65.1%) and most events (death) registered (72.9%). As there can be seen in Supplementary material online, *S2*, 74.8% of the total population was administered diuretics and 70% ACEIs/ARBs. There can also be observed that the administration of diuretics in the low normal potassium level was slightly higher than the administration of ACEIs/ARBs. Likewise, ACEIs/ARBs prescription was marginally higher than diuretic prescription in the upper potassium interval.

Survival analysis

Survival curves are illustrated in *Figure 1*. Of the patients, 866 (1.9%) died during the 90-day follow-up. Mortality in the seven strata was low: 4.5, 2.7, 1.8, 1.5, 1.7, 2.7, and 3.6%, respectively. The highest 90-day mortality rates were observed in 2005 and 2010 with 80 and 83 observations, respectively. Univariate HRs of each potassium level are shown in *Figure 2*. The lowest mortality risk was observed in the interval of 4.1–4.4 mmol/L, while hypo- and hyperkalaemia were associated with increased mortality. Risk of all-cause mortality was also increased in potassium intervals: 3.5–3.7 and 4.8–5.0 mmol/L. Likewise, we observed a trend towards excess mortality in the intervals of 3.8–4.0 and 4.5–4.7 mmol/L.

The results of the multivariable analysis with potassium 4.1–4.4 mmol/L as reference are shown in *Figure 3*. After adjusting the model for age, sex, biologically relevant co-morbidities, and concomitant medication, the mortality remained significantly increased for all potassium ranges outside the interval of 3.8–4.7 mmol/L.

Being a female or over the age of 70 years were overall associated with increased mortality. Patients with co-morbid conditions such as chronic obstructive pulmonary disease, atrial fibrillation, heart failure, and stroke also had an increased risk of death. Considering the different antihypertensive drug combinations, we observed a trend that ACEIs/ARBs in combination with thiazide diuretics were a safe treatment (HR: 0.65, 95% CI: 0.42–1.01, $P = 0.05$). However, the combination of β-blockers with thiazide diuretics and potassium supplements was associated with an increased

mortality risk (HR: 1.46, 95% CI: 1.03–2.08, $P = 0.03$). Moreover, other single-pill antihypertensive drug combinations than the top five included in the adjusted model were significantly associated with increased risk of death, with HR 1.85.

The U-shaped restricted cubic splines curve shown in *Figure 4* indicated that the lower and the higher the serum potassium level, the greater the mortality risk. Additionally, the splines curve indicated differences in risk within the normal potassium ranges, where potassium interval of 4.1–4.4 mmol/L was associated with the lowest risk of death.

Other analyses

Three additional sensitivity analyses were applied to verify the initial findings. The results of these analyses are illustrated in *Table 2*. First, we selected our hypertensive population based on ICD codes from the National Patient Registry, and we included in the analysis the patients who received minimum two concomitant antihypertensive drugs in the interval of 90 days before the diagnosis or 30 days after the diagnosis. Potassium interval of 3.8–4.0 mmol/L was no longer significantly associated with increased risk, although with a clear tendency towards our initial findings (HR: 1.14, 95% CI: 0.98–1.32, $P = 0.10$).

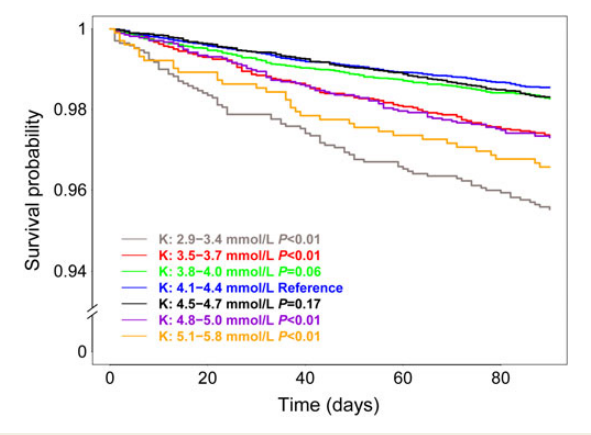

Figure 1 Kaplan–Meier analysis of the survival probability among the different potassium intervals. $n = 44\,799$.

Second, we excluded patients who were administered loop diuretics according to the Prescription Registry as loop diuretics could indicate heart failure. This analysis also showed that potassium level of 3.8–4.0 mmol/L was not significantly associated with the increased risk of death, although evidently with the same overall trends as in our initial findings (HR: 1.24, 95% CI: 0.94–1.64, $P = 0.12$).

Third, we excluded patients who, prior hypertension date, were diagnosed with myocardial infarction or heart failure as both could be treated with medication used for hypertension. This analysis showed that potassium levels outside the interval of 4.1–4.7 mmol/L were associated with increased mortality risk.

Discussion

This study analysed the short-time mortality risk in relation to different potassium intervals in hypertensive patients administered various classes of blood-pressure-lowering drugs. The major finding was that even mild deviations within the normal potassium range (3.5–5.0 mmol/L) were associated with increased mortality. Although it was expected that hypo- and hyperkalaemia would be associated with increased risk of death, it was unexpected that three normal potassium levels (K: 3.5–3.7, 3.8–4.0, and 4.8–5.0 mmol/L) were also associated with a significantly increased mortality in hypertensive patients.

We considered the time frame of potassium measurement within 90 days from start of antihypertensive treatment optimal for analysing the acute mortality risk in patients with hypertension for two reasons. First, Mcdowell and Ferner[19] showed in a review about monitoring of hypertensive patients for adverse drugs reactions that the peak follow-up time of potassium and creatinine was 3 months and 1 year after treatment initiation, respectively. Second, Podrid[7] illustrated in a review that potassium concentrations were directly related to the dosage of the administered diuretic. Low potassium can be observed from 4 to 40 weeks after treatment with diuretics in patients with hypertension. Moreover, Supplementary material online, *S1* reveal that the majority of the population had a potassium measurement in the first 45 days (65.1%) and that most of the patients deceased (72.9%) in the same timeframe. However, methodologically, it would not have been appropriate to reduce the follow-up time as a considerable number of patients did not have their potassium measured and we would have missed

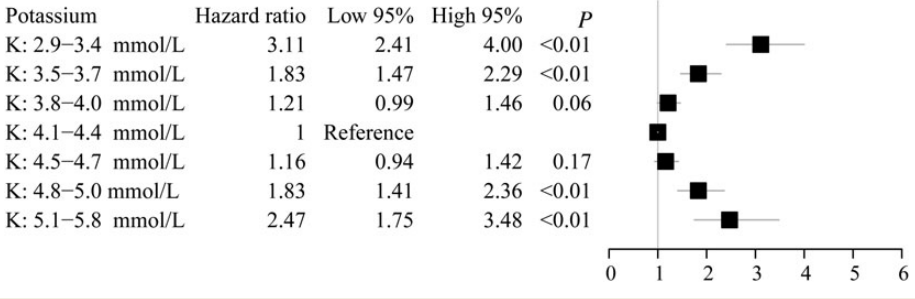

Figure 2 All-cause mortality in hypertensive patients stratified by potassium intervals (90-day follow-up). $n = 44\,799$. Reference interval represented by the interval K: 4.1–4.4 mmol/L.

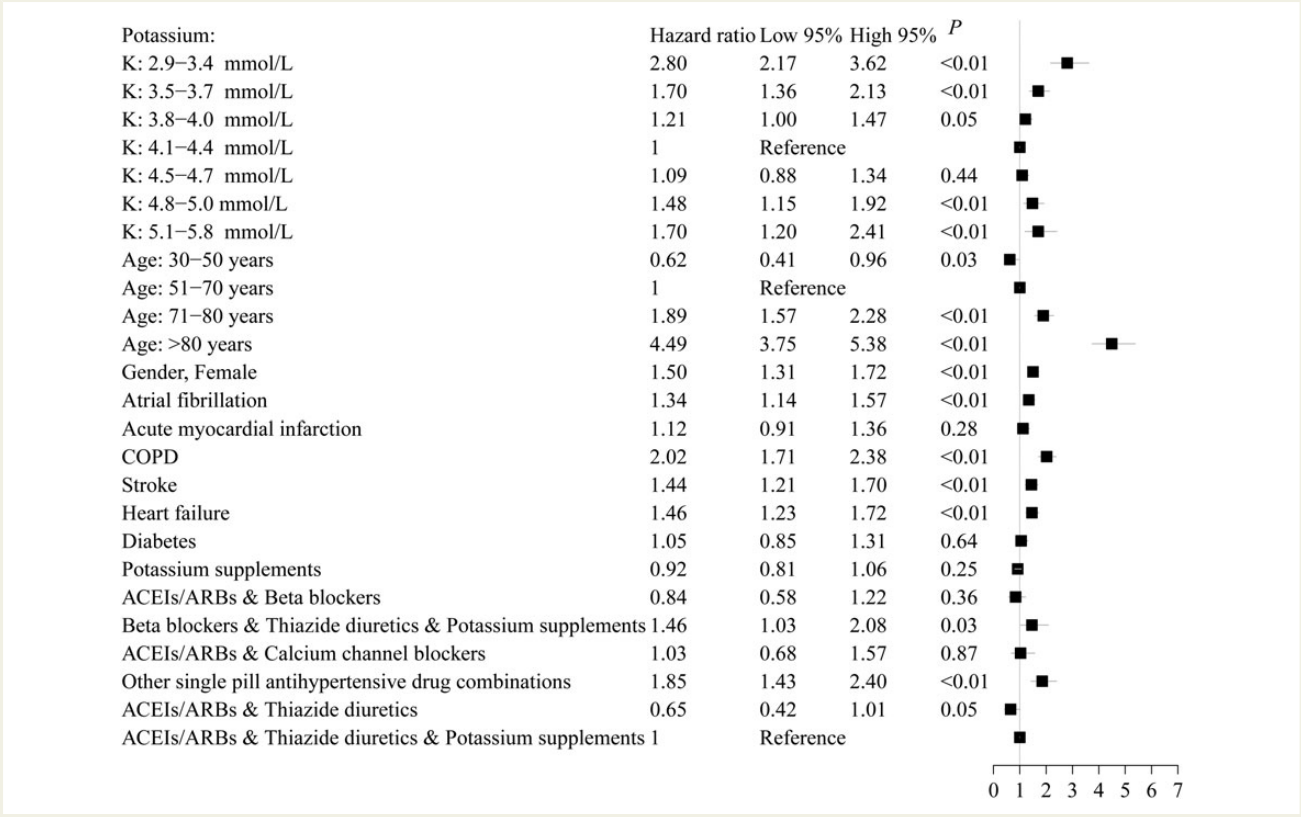

Figure 3 All-cause mortality in hypertensive patients stratified by potassium intervals (90-day follow-up). $n = 44\,799$. Model adjusted for covariates. Reference interval represented by the interval K: 4.1–4.4 mmol/L; and single-pill combination of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, thiazide diuretics, and potassium supplements. ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

27.1% of the events. Furthermore, a longer follow-up time would have been a great bias, as data showed a trend in less potassium measurement and less events over time. In as such, within a window period of 90 days from hypertension treatment, we intended to register both the immediate and the slow onset potassium disarrays. It is important to acknowledge that all patients have been treated with two antihypertensive drugs for two concomitant quarters (180 days) before the first potassium measurement.

As for the definition of hypertension, Olesen *et al.*[11] have validated the model of identifying hypertensive patients according to blood-pressure-lowering drug prescriptions. Nevertheless, we performed a sensitivity analysis where we attempted to identify major difference in identification of hypertensive population based on ICD codes vs. pharmacological treatment. We did not observe any major difference in the association of the defined potassium intervals and mortality risk. Moreover, the combination of ACEIs/ARBs with loop diuretics can indicate heart failure and not hypertension.[1] For this reason, we completed a second sensitivity analysis where patients with loop diuretic prescription were excluded. This analysis did not show any considerable difference in results when compared with the initial analysis. Additionally, we performed a third analysis where patients with history of myocardial infarction and heart failure were excluded. This was because combination of ACEIs with β-blockers could indicate one of the above mentioned conditions and not hypertension.[20,21] This analysis did not show major difference when compared with the other two sensitivity analysis, or main analysis. Overall, these analyses showed almost identical results to our primary analysis, with small variations in statistical significance probably related to fewer individuals in each potassium interval group. All these analyses indicated that serum potassium >4.0 and <4.7 mmol/L is optimal in hypertensive patients.

To our knowledge, few, if any, studies[3,9] have investigated which potassium interval is the safest in hypertensive patients; most studies have analysed the effect of different classes of antihypertensive drugs on potassium homeostasis, mortality, and cardiovascular and non-cardiovascular events. Alderman *et al.* demonstrated that patients are more prone to hypokalaemia if treated with chlorthalidone compared with amlodipine or lisinopril, and that hypokalaemic patients have a higher mortality risk than do those with normokalaemia.[12] Moreover, Ikram mentioned in his article 'a crossover study design in hypertensive patients with coronary disease' that mild degrees of hypokalaemia induced by thiazide diuretics increased the tendency to arrhythmia when compared with normokalaemia on a potassium-sparing diuretic.[22–24] These findings are in agreement with our study. We observed increased all-cause mortality in hypokalaemic patients, and that thiazides in combination with ACEIs/ARBs seemed to be particularly safe for hypertensive patients when compared with the reference (ACEIs/ARBs combined with

thiazide diuretics and potassium supplements). Alderman *et al.* also demonstrated that ACEIs increase the risk of elevated potassium and that this patient group had 'a significantly increased risk of combined cardiovascular disease compared with normokalaemics'. Similarly, our study demonstrated that hyperkalaemic patients are associated with increased mortality risk compared with normokalaemic patients, and that patients in this group are characterized by a higher administration rate of ACEIs/ARBs than are hypokalaemic and normokalaemic patients. Nevertheless, several studies and guidelines recommend dual therapy of ACEIs/ARBs with calcium channel blockers, diuretics, or β-blockers.[1,25,26] This statement is strongly supported by our study that showed that single-pill combination of ACEIs/ARBs with β-blockers and thiazide diuretics was associated with decreased mortality risk, in spite of insignificant *P*-values.

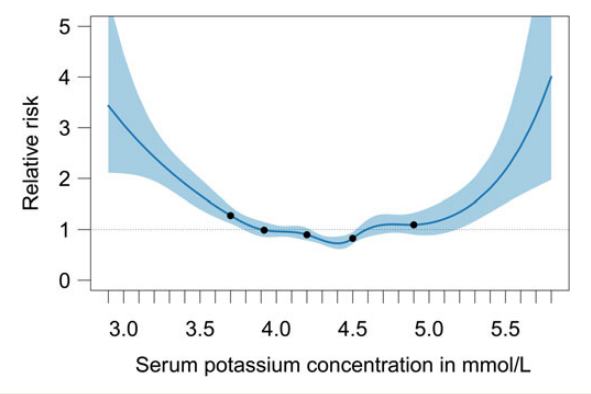

Figure 4 Restricted cubic splines showing the adjusted hazard ratios for all-cause mortality as a function of potassium concentration. Knots at the 10th, 25th, 50th, 75th, and 90th percentiles of potassium. Model adjusted for age, sex, chronic obstructive pulmonary disease, stroke, acute myocardial infarction, atrial fibrillation, heart failure, diabetes mellitus, potassium supplement, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in combination with thiazides, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in combination with calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in combination with β-blockers, β-blockers in combination with thiazides and potassium supplements, and other single-pill antihypertensive drug combinations. $n = 44\,799$. This figure shows an approximation of the function relating serum potassium to the hazard rate of death, and should not be interpreted with respect to some reference.

The study by Macdonald and Struthers was the only study/review we identified that contained exact recommendations for a potassium interval in patients with hypertension.[9] The authors indicated that it is favourable for hypertensive patients to maintain potassium between 3.5 and 5.0 mmol/L. This was based on studies that evaluate the link between hypokalaemia and development of ventricular arrhythmias and sudden cardiac death. However, most of the cited studies did not directly examine the relationship between serum potassium and mortality in hypertensive patients.

Overall, we were unable to identify any studies that provide direct evidence to select optimum levels of serum potassium in disease or health. Here, we demonstrate a significantly increased risk of death among hypertensive patients with serum potassium <4.1 or >4.7 mmol/L.

Study limitations

The limitations largely relate to the observational nature of the study. However, the Danish National Health registries contain uniquely detailed information, and we were able to extract reliable data on co-morbid illnesses and concomitant medication, as well as potassium measurements and date of death, overall strengthening the reliability of our findings. All factors that were considered possible confounders were included in the Cox multivariable analysis.

Limitations of this study are represented by the lack of information regarding the cause of death. In certain circumstances, it might

Table 2 Sensitivity analysis 1 (hypertensive patients found according to International Classification of Disease codes) and sensitivity analysis 2 (patients with loop diuretic prescription excluded from main analysis) and sensitivity analysis 3 (Patients with acute myocardial infarction or heart failure diagnosis before hypertension diagnosis were excluded from the main analysis)

Potassium (mmol/L)	Hypertension definition based on ICD codes (n = 26 126)				Patients with loop diuretic prescription were excluded (n = 35 393)				Patients with an acute myocardial infarction or heart failure diagnosis before hypertension were excluded (n = 35 827)			
	HR	Low 95%	High 95%	*P*	HR	Low 95%	High 95%	*P*	HR	Low 95%	High 95%	*P*
2.9–3.4	1.91	1.63	2.24	<0.01	3.49	2.43	5.00	<0.01	2.99	2.21	4.06	<0.01
3.5–3.7	1.49	1.28	1.74	<0.01	2.03	1.48	2.79	<0.01	1.89	1.44	2.48	<0.01
3.8–4.0	1.14	0.98	1.32	0.10	1.24	0.94	1.64	0.12	1.31	1.04	1.66	0.02
4.1–4.4	1		Reference		1		Reference		1		Reference	
4.5–4.7	1.18	0.98	1.43	0.07	0.95	0.69	1.30	0.74	1.18	0.91	1.53	0.22
4.8–5.0	1.38	1.07	1.78	0.01	1.50	1.01	2.22	0.04	1.85	1.34	2.55	<0.01
5.1–5.8	2.20	1.66	2.91	<0.01	1.89	1.11	3.24	0.02	2.13	1.37	3.29	<0.01

Model adjusted for covariates. Reference interval represented by the interval K: 4.1–4.4 mmol/L.
All-cause mortality in hypertensive patients stratified by potassium intervals (90-day follow-up).
ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

be difficult to determine the primary cause of death when a patient can be attributed one or more codes in situations where autopsy is missing.

As the Danish National Health registries do not contain reliable diagnostic codes for differentiating whether hypertension was diagnosed in hospital vs. general practitioner, we used an alternative modality based on a validated algorithm for identifying patients with hypertension. Despite the high predictive value and specificity of this method, misclassification of some patients as hypertensive could occur. With regard to the definition of diabetes, we could encounter similar problems as with hypertension. Patients with diabetes who were treated by their general practitioner and never hospitalized do not have diabetes diagnostic codes available. Therefore, we considered that more than two prescriptions of glucose-lowering drugs may increase the predictive value in our cohort. However, misclassification cannot be excluded.

Furthermore, our population may not extend to other populations, which can lead to difficulty in reproducing these results worldwide. Despite the fact that we performed three sensitivity analyses to adjust for major confounders, we cannot exclude a possible effect of unmeasured confounders. Additionally, the characteristics of the patients with hypertension, who had a serum potassium measurement within 90 days from dual single-pill therapy, may be different from the hypertensive patients who did not have a potassium measurement in this time interval. Moreover, it is discussable whether the use of the first serum potassium measurement within the 90 days of antihypertensive treatment was optimal for the analysis of 90-day mortality. However, we observed decrease in both potassium measurements and death rate in time. Last but not least, we cannot affirm whether mortality is increased due to the influence of potassium influence on myocardial membrane potential or it is a marker of other processes.

Conclusion

In conclusion, our results strongly indicate that serum potassium levels <4.1 or >4.7 mmol/L are associated with a significantly increased mortality in hypertensive individuals.

Clinical implications

This study indicates that low- and high-normal potassium levels may be associated with increased risk of death, which suggests that a narrower normal interval might improve outcome in patients with hypertension. Most drugs against hypertension influence in some way potassium homeostasis. Therefore, monitoring soon after the onset of medication would probably be relevant to achieve stable potassium levels and improve survival. Future studies that focus on frequency of potassium measurement, potassium fluctuations over time, and effect of potassium regulation on mortality can surely complement this study's findings.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

R.N.M., K.A., and M.L.K. performed statistical analysis. P.S. and C.T.-P. handled funding and supervision. C.T.-P., K.A., M.L.K., and R.N.M. acquired the data. C.T.-P., K.A., P.S., M.L.K., L.K., and G.G. conceived and designed the research. M.L.K., K.A., and P.S. drafted the manuscript. C.T.-P., P.S., L.K., G.G., K.A., and R.N.M. made critical revision of the manuscript for key intellectual content.

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