Serum potassium and risk of death or kidney replacement therapy in older people with CKD stages 4-5: eight-year follow-up

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Serum Potassium and Risk of Death or Kidney Replacement Therapy in Older People With CKD Stages 4-5: Eight-Year Follow-up

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Rationale & Objective: Hypokalemia may accelerate kidney function decline. Both hypo- and hyperkalemia can cause sudden cardiac death. However, little is known about the relationship between serum potassium and death or the occurrence of kidney failure requiring replacement therapy (KRT). We investigated this relationship in older people with chronic kidney disease (CKD) stage 4-5.

Study Design: Prospective observational cohort study.

Setting & Participants: We followed 1,714 patients (≥65 years old) from the European Quality (EQUAL) study for 8 years from their first estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m^2 measurement.

Exposure: Serum potassium was measured every 3 to 6 months and categorized as ≤3.5, >3.5-≤4.0, >4.0-≤4.5, >4.5-≤5.0 (reference), >5.0-≤5.5, >5.5-≤6.0, and >6.0 mmol/L.

Outcome: The combined outcome death before KRT or start of KRT.

Analytical Approach: The association between categorical and continuous time-varying potassium and death or KRT start was examined using Cox proportional hazards and restricted cubic spline analyses, adjusted for age, sex, diabetes, cardiovascular disease, renin-angiotensin-aldosterone system (RAAS) inhibition, eGFR, and subjective global assessment (SGA).

Results: At baseline, 66% of participants were men, 42% had diabetes, 47% cardiovascular disease, and 54% used RAAS inhibitors. Their mean age was 76 ± 7 (SD) years, mean eGFR was 17 ± 5 (SD) mL/min/1.73 m^2, and mean SGA was 6.0 ± 1.0 (SD). Over 8 years, 414 (24%) died before starting KRT, and 595 (35%) started KRT. Adjusted hazard ratios for death or KRT according to the potassium categories were 1.6 (95% CI, 1.1-2.3), 1.4 (95% CI, 1.1-1.7), 1.1 (95% CI, 1.0-1.4), 1 (reference), 1.1 (95% CI, 0.9-1.4), 1.8 (95% CI, 1.4-2.3), and 2.2 (95% CI, 1.5-3.3). Hazard ratios were lowest at a potassium of about 4.9 mmol/L.

Limitations: Shorter intervals between potassium measurements would have allowed for more precise estimations.

Conclusions: We observed a U-shaped relationship between serum potassium and death or KRT start among patients with incident CKD 4-5, with a nadir risk at a potassium level of 4.9 mmol/L. These findings underscore the potential importance of preventing both high and low potassium in patients with CKD 4-5.

Visual Abstract online

Complete author and article information (including a list of the members of the EQUAL Study Investigators) provided before references.

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Patients with chronic kidney disease (CKD) stages 4-5, are prone to serum potassium disturbances. On the one hand, these patients can experience hyperkalemia due to impaired urinary potassium excretion and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors for cardiorenoprotection.[1] On the other hand, they may suffer from hypokalemia due to treatment with non-potassium-sparing diuretics or malnourishment.

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Both hypo- and hyperkalemia can cause muscle paralysis and potentially fatal cardiac arrhythmias.[2] Potassium is the principal ion involved in restoring the resting membrane potential across cell membranes, allowing for new action potentials to generate. Thereby, it facilitates neural and muscle function in the human body. In addition, hypokalemia is associated with a faster rate of kidney function decline in CKD patients most likely via chronic interstitial nephritis and fibrosis, known as hypokalemic nephropathy.[3-6]

Thus, serum potassium disturbances might be related to both progression to kidney failure for which kidney replacement therapy (KRT) is needed and mortality. It is important to know to which extent these modifiable risks exist among patients with CKD stages 4-5 and to establish whether there is an optimum serum potassium level. Knowledge of these potential effects would be especially relevant for older patients with CKD stages 4-5, who are at high risk of both kidney failure and mortality.[7,8] For example, in patients aged 65 to 74 years with an estimated glomerular filtration rate (eGFR) between 15 and 29 mL/min/1.73 m^2, the incidence rates of death and kidney failure were previously estimated at 11.7 (95% CI, 10.6-12.7) and 9.3 (95% CI, 8.4-10.2) per 100 person-years, respectively. Furthermore, older patients with CKD stages 4-5 are at a higher risk of comorbidities and subsequent

PLAIN-LANGUAGE SUMMARY

Abnormal potassium blood levels may increase the risk of death or kidney function decline, especially in older people with chronic kidney disease (CKD). We studied 1,714 patients aged ≥65 years with advanced CKD from the European Quality (EQUAL) study and followed them for 8 years. We found that both low and high levels of potassium were associated with an increased risk of death or start of kidney replacement therapy, with the lowest risk observed at a potassium level of 4.9 mmol/L. In patients with CKD, the focus is often on preventing high blood potassium. However, this relatively high optimum potassium level stresses the potential importance of also preventing low potassium levels in older patients with advanced CKD.

polypharmacy, both of which potentially affect serum potassium levels.

The interplay between serum potassium level and the combined outcome of death or KRT start may differ in older compared with younger individuals.[9-11] Considering the limitations to previous studies on this subject, we studied the association between serum potassium level and the combined outcome of death and KRT start in older patients with CKD stages 4-5.

Methods

Study Design and Population

The European Quality (EQUAL) study on treatment in advanced CKD is an ongoing prospective multicenter cohort study. The EQUAL study started in April 2012 in 6 European countries: Germany, Italy, Poland, Sweden, the Netherlands, and the United Kingdom, as described elsewhere in detail.[12] Briefly, patients aged ≥65 years with CKD stages 4-5 followed in a nephrology clinic were included when their eGFR dropped for the first time to or below 20 mL/min/1.73 m^2 in the last 6 months. Patients were excluded if they already had a history of KRT or when the eGFR drop was the result of an acute event. Identified patients who met the eligibility criteria were consecutively approached. After inclusion, they were evaluated every 3 to 6 months while receiving routine medical care as provided at their nephrology clinic until kidney transplantation, death, refusal for further participation, transfer to a nonparticipating center, loss to follow-up, or end of follow-up, whichever came first. End of follow-up for this study was at December 2021, when the data were extracted. All patients gave informed consent. The study was approved by all local medical ethics committees or corresponding institutional review boards.[12]

Data Collection

In the EQUAL study, data were routinely collected every 3 to 6 months and entered into a web-based clinical record form that was developed for this specific purpose. Additional follow-up visits were conducted after the first time the eGFR dropped below 10 mL/min/1.73 m^2 and/or at the start of dialysis. Demographics, ethnicity, primary kidney disease, comorbid conditions, physical examination, and laboratory data were collected. All laboratory investigations and physical examinations were performed through standard protocols and procedures according to routine care at the local participating centers.

To standardize these data, details on local laboratory methods, units of measurement, and normal ranges were captured using a questionnaire completed by all participating centers. Subsequently, all laboratory data were recalculated into one uniform unit of choice.[12] The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13] According to the codes of the European Renal Association, treating nephrologists classified the primary kidney disease of their patients.[14] For the present study we categorized patients into the following 4 causes of primary kidney disease: diabetes, hypertension, systemic or glomerular disease, and other or unknown kidney diseases. History of diabetes was defined based on diabetes mellitus registered as a comorbid condition or diabetic nephropathy as primary kidney disease. Current smoking was defined as current cigarette smoking including smoking in the past 3 months. Cardiovascular disease was defined as any history of a cerebral vascular accident, a myocardial infarction, or peripheral vascular disease. Nutritional status was measured by a 1-7 score on the SGA, with scores of 6-7 indicating normal nutritional status, scores of 4-5 indicating moderate protein-energy wasting (PEW), and scores of 1-3 indicating severe PEW.[15]

Outcome Definition

Our main outcome was the combined outcome death or KRT start. KRT was defined as kidney transplantation, hemodialysis, or peritoneal dialysis initiation. We also studied the following secondary outcomes separately: KRT start, death before KRT start, and cardiovascular death before KRT start. Cardiovascular death was defined as death due to cardiac arrest, myocardial infarction, heart failure, or cerebrovascular accident.

Statistical Analysis

Variables were described as mean ± standard deviation, median (interquartile range), or number (proportion) where appropriate. Potassium levels were analyzed continuously and according 7 predefined categories: ≤3.5, >3.5 to ≤4.0, >4.0 to ≤4.5, >4.5 to ≤5.0, >5.0 to ≤5.5, >5.5 to ≤6.0, and >6.0 mmol/L.

We assessed the relationship between serum potassium level and the primary combined outcome of death before KRT and KRT start during 8 years of follow-up using several methods.

For all following analyses, serum potassium was included as a time-dependent variable and updated at 3-6

monthly intervals unless the primary outcome was ascertained. First, we calculated combined death or KRT start rates within each serum potassium category. Second, we used a time-dependent Cox-proportional hazard model to calculate crude and multivariable adjusted hazard ratios (HRs) for the combined outcome of death or KRT start during 8 years of follow-up. Because normal serum potassium levels vary from 3.5 to 5.5 mmol/L and no optimum level has been definitively recommended within that range, the serum potassium category (>4.5 to ≤5.0 mmol/L) with the lowest combined death or KRT rate in our cubic spline analysis (see below) was taken as the reference category.[16] Analyses were adjusted for potential confounders measured at baseline: age, sex, current smoking, history of diabetes, history of cardiovascular disease, RAAS inhibitor use, kidney function, and SGA score (main model).

Third, we conducted time-dependent cause-specific hazards models to calculate cause-specific HRs for the secondary outcomes. In the cause-specific models, competing events (death or KRT start) were treated as censored observations.[17] Fourth, the continuous relationship between time-dependent serum potassium and death or KRT start was explored using a 4-knot restricted cubic spline for time-dependent serum potassium in the Cox model, adjusted for the previously mentioned confounders. The knots were chosen at the 5th, 35th, 65th, and 95th percentile of the serum potassium distribution.[18]

We assumed missing values to be missing at random. Missing data were handled using 2 different strategies. For missing serum potassium levels at baseline (n = 20, 1%) we carried the next observed serum potassium level backward, and for the missing values during 8-year follow-up (n = 530, 8%), we carried the last observed serum potassium level forward. For the missing baseline data of smoking (n = 357, 21%), history of diabetes (n = 40, 2%) or history of cardiovascular disease (n = 67, 4%), RAAS inhibitor use (n = 19, 1%), eGFR (n = 14, 1%), and SGA score (n = 201, 12%), we used multiple imputation to avoid bias and maintain power, using 10 imputations and including all relevant baseline variables and the outcome in the model.[19] In 1,126 participants (66%), complete data were available for the main model. No large differences were observed in baseline characteristics between the complete and incomplete cases (Table S1).

We performed 3 sensitivity analyses. First, we conducted a complete case analysis. Second, we repeated our main time-dependent Cox proportional hazards model with additional adjustment for baseline body mass index (BMI), serum phosphate, and serum albumin. This was done to assess the impact of these potential confounders related to nutritional status on the association between serum potassium level and the combined outcome of death or KRT start. Third, we repeated our Cox proportional hazards model using baseline serum potassium category as a fixed variable.

In the proportional hazards regression models, the proportionality assumption for each covariate was checked by adding a product term between that covariate and the logarithm of follow-up time. The proportionality assumptions were met in all models. All analyses were performed using R version 4.0.3 (R Core Team).

Results

Baseline Characteristics

Of all 1,736 EQUAL study participants, we included 1,714 patients (99%) for whom at least 1 serum potassium measurement was available. At baseline, the mean age was 76 ± 7 (SD) years, 66% of the participants were men, 42% had diabetes, 47% had cardiovascular disease, and 54% used RAAS inhibitors; the mean eGFR was 17 ± 5 (SD) mL/min/1.73 m^2, mean SGA was 6.0 ± 1.0 (SD), and mean serum potassium level was 4.6 ± 0.6 (SD) mmol/L. The prevalence of the 7 potassium categories was: 2%, 13%, 28%, 33%, 17%, 5%, and 2%, respectively, with a mean value of 3.3 ± 0.3 (SD) mmol/L in the lowest (≤3.5 mmol/L) and 6.3 ± 0.3 (SD) mmol/L in the highest (>6.0 mmol/L) category (Table 1). Compared with the reference (>4.5 to ≤5.0 mmol/L), the patients in the lowest potassium category had lower SGA scores, more often had diabetes, and less often had cardiovascular disease, whereas those in the highest serum potassium category were more often men, had a lower eGFR, and also less often had cardiovascular disease (Table 1).

Serum Potassium During Follow-up

In total 6,091 potassium measurements were performed during follow-up period, on average 3.6 measurements per participant. The distribution of serum potassium levels during follow-up was similar to that at baseline. Of all 1,714 participants, 126 participants (7%) experienced serum potassium ≤ 3.5 mmol/L, and 230 (13%) and 59 (3%) participants experienced serum potassium >5.5 to ≤6.0 mmol/L and >6.0 mmol/L during follow-up, respectively. Compared with normal serum potassium levels (>4.5 to ≤5.0 mmol/L), the low (≤3.5 mmol/L) or high (>6.0 mmol/L) serum potassium levels were less often persistent for 2 or more consecutive visits (Fig S1).

Combined Death and KRT Start Rates

The median time until death or KRT start was 2.6 (IQR, 2.5-2.8) years. In total, 414 (24%) died, 15 (1%) had a pre-emptive kidney transplantation, and 580 (34%) started dialysis during 3,851 person-years, resulting in an overall crude combined death or KRT start rate of 26.2 (95% CI, 24.6-27.8) per 100 patient-years. Start of KRT was more common than death before KRT among our older patients with an eGFR < 20 mL/min/1.73 m^2, which is in line with previous studies.[20,21] Of all 414 deaths before KRT initiation, 109 (26%) were due to cardiovascular disease. The absolute rates of combined death or KRT start were 40 (95% CI, 28-54) per 100 person-years in the lowest serum

Table 1. Baseline Characteristics of 1,714 Participants in the European Quality Study on Treatment of Older People With Advanced CKD According to 7 Serum Potassium Categories

		Serum Potassium Category, mmol/L						
	All Patients	≤3.5	>3.5 to ≤4.0	>4.0 to ≤4.5	>4.5 to ≤5.0	>5.0 to ≤5.5	>5.5 to ≤6.0	>6.0
Total	1,714	44 (2%)	228 (13%)	474 (28%)	559 (33%)	294 (17%)	84 (5%)	31 (2%)
Clinical Characteristics								
Age, y	76 ± 7	76 ± 6	77 ± 7	77 ± 7	76 ± 7	75 ± 7	76 ± 6	77 ± 7
Men	1,123 (66%)	29 (66%)	149 (65%)	285 (60%)	373 (67%)	204 (69%)	58 (69%)	25 (81%)
Systolic BP, mm Hg	143 ± 22	139 ± 23	142 ± 23	142 ± 23	144 ± 22	144 ± 22	144 ± 20	137 ± 17
Diastolic BP, mm Hg	74 ± 11	73 ± 12	74 ± 12	75 ± 12	74 ± 11	73 ± 10	74 ± 11	71 ± 9
BMI, kg/m^2	28 ± 5	30 ± 7	28 ± 5	28 ± 5	28 ± 5	29 ± 6	29 ± 5	27 ± 5
SGA								
1-3; severe PEW	33 (2%)	1 (3%)	3 (1%)	12 (3%)	12 (2%)	3 (1%)	1 (1%)	1 (4%)
4-5; moderate PEW	388 (26%)	16 (42%)	67 (33%)	100 (23%)	112 (23%)	72 (28%)	15 (21%)	6 (21%)
6-7; normal PEW	1,092 (72%)	21 (55%)	136 (66%)	314 (74%)	361 (74%)	185 (71%)	54 (77%)	21 (75%)
Current smoking	120 (9%)	3 (10%)	16 (8%)	30 (8%)	44 (10%)	21 (9%)	5 (9%)	1 (5%)
Primary kidney disease								
Diabetes	349 (21%)	9 (21%)	46 (20%)	87 (18%)	105 (19%)	67 (23%)	27 (32%)	8 (26%)
Hypertension	610 (36%)	12 (27%)	83 (36%)	193 (41%)	207 (37%)	76 (26%)	29 (34%)	10 (32%)
Systemic/glomerular disease	341 (20%)	12 (27%)	45 (20%)	81 (17%)	124 (22%)	64 (22%)	8 (10%)	7 (23%)
Other/unknown	414 (24%)	11 (25%)	54 (24%)	113 (24%)	123 (22%)	87 (29%)	20 (24%)	6 (19%)
Medical history								
Diabetes	708 (42%)	21 (49%)	82 (37%)	187 (40%)	229 (42%)	135 (47%)	42 (51%)	12 (40%)
Cardiovascular disease[a]	779 (47%)	14 (33%)	108 (49%)	223 (49%)	258 (48%)	121 (42%)	44 (55%)	11 (38%)
Chronic lung disease	263 (16%)	11 (26%)	42 (19%)	67 (15%)	76 (14%)	45 (15%)	18 (22%)	4 (13%)
Malignancy	349 (21%)	9 (21%)	55 (25%)	94 (21%)	123 (23%)	51 (18%)	10 (13%)	7 (23%)
RAAS inhibitor use	922 (54%)	21 (48%)	111 (49%)	237 (50%)	315 (56%)	173 (59%)	49 (59%)	16 (52%)
Blood chemistry								
Hemoglobin, g/dL[b]	11.6 ± 1.5	11.9 ± 1.6	11.7 ± 1.3	11.7 ± 1.5	11.6 ± 1.5	11.5 ± 1.5	11.3 ± 1.5	11.5 ± 1.7
Creatinine, mg/dL[c]	3.3 ± 1.1	3.4 ± 1.1	3.2 ± 1.0	3.3 ± 1.2	3.3 ± 1.1	3.4 ± 1.1	3.4 ± 1.2	3.9 ± 1.3
eGFR, mL/min/1.73 m^2[d]	17 ± 5	17 ± 6	18 ± 6	17 ± 6	17 ± 5	17 ± 5	17 ± 6	15 ± 4
Potassium, mmol/L	4.6 ± 0.6	3.3 ± 0.3	3.8 ± 0.1	4.3 ± 0.1	4.8 ± 0.1	5.3 ± 0.1	5.7 ± 0.1	6.3 ± 0.3
Bicarbonate, mmol/L	23 ± 4	27 ± 4	24 ± 4	24 ± 4	23 ± 4	22 ± 3	22 ± 4	21 ± 4
Cholesterol, mg/dL[e]	176 ± 50	184 ± 50	179 ± 55	177 ± 53	176 ± 46	172 ± 46	168 ± 46	161 ± 43
Phosphate, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3
Albumin, g/dL[f]	3.8 ± 0.6	3.5 ± 0.7	3.7 ± 0.5	3.8 ± 0.5	3.8 ± 0.6	3.8 ± 0.6	3.6 ± 0.9	3.7 ± 0.9

Values are given as mean ± SD for continuous variables and as number (percentage) for categorical variables. Abbreviations: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PEW, protein-energy wasting; RAAS, renin-angiotensin-aldosterone system; SGA, subjective global assessment.

[a]Cardiovascular disease was defined as any history of a cerebral vascular accident, a myocardial infarction, peripheral vascular disease, or heart failure.

[b]To convert the values for hemoglobin to millimoles per liter, multiply by 0.6206.

[c]To convert the values for creatinine to micromoles per liter, multiply by 88.42.

[d]Estimated GFR was estimated based on serum creatinine using the CKD-EPI formula.

[e]To convert the values for cholesterol to millimoles per liter, multiply by 0.0259.

[f]To convert the values for albumin to grams per liter, multiply by 10.

Table 2. Absolute Single and Combined Outcome Death or KRT Start Rates (95% CI) According to 7 Time-dependent Serum Potassium Categories During 8-Year Follow-up of 1,714 Incident Participants in the European Quality Study on Treatment of Older People With Advanced CKD

	Time-dependent Serum Potassium Category, mmol/L						
	≤3.5	>3.5 to ≤4.0	>4.0 to ≤4.5	>4.5 to ≤5.0	>5.0 to ≤5.5	>5.5 to ≤6.0	>6.0
Person-years	93	478	1,064	1,277	697	199	44
KRT start	18	82	146	176	110	49	14
Death before KRT start	19	66	111	106	70	30	12
Combined death or KRT start	37	148	257	282	180	79	26
Combined death or KRT start/100 person-years	40 (28-54)	31 (26-36)	24 (21-27)	22 (20-24)	26 (22-30)	40 (31-49)	59 (40-85)

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy.

potassium category of ≤3.5 mmol/L, 22 (95% CI, 20-24) per 100 person-years in the reference category of potassium >4.5 to ≤5.0 mmol/L, and 59 (95% CI, 40-85) per 100 person-years in the highest serum potassium category of >6.0 mmol/L (Table 2).

The multivariable adjusted HR of time-dependent serum potassium ≤ 3.5 mmol/L was 1.6 (95% CI, 1.1-2.3) compared with serum potassium > 4.5 and ≤ 5.0 mmol/L, whereas serum potassium above >6.0 mmol/L resulted in an adjusted HR of 2.2 (95% CI, 1.5-3.3) (Table 3). Similar associations were found when assessing KRT start, all-cause death, and cardiovascular death before KRT start as separate outcomes (Tables S2, S3, and S4).

U-shaped Relationship

Figure 1 shows the U-shaped relationship between time-dependent serum potassium and the combined outcome death or KRT start during 8-years of follow-up, expressed by the multivariable adjusted HR, with a nadir around 4.9 mmol/L. HRs for combined death or KRT increased substantially below a serum potassium level of ≤4.5 and above >5.4 mmol/L, with the effects of higher serum potassium levels being more pronounced. For example, patients with a serum potassium level of 6.5 mmol/L compared with the optimum level of 4.9 mmol/L had a 3-fold (95% CI, 2-fold to 3-fold) increased hazard of death or KRT start.

Sensitivity Analyses

We performed 3 sensitivity analyses. First, a complete case analysis based on 1,131 participants with complete data on confounding variables yielded similar results (Table S5). Second, additional adjustment for the nutritional markers BMI, serum phosphate, and serum albumin did not alter the results of our main analysis (Table S6). Third, taking serum potassium as a fixed category at baseline did attenuate the strength of the relationship between serum potassium category and 8-year all-cause death or KRT start as expected due to dilution of the effect of potassium over time (Table S7).

Discussion

In this large prospective European multicenter study among over 1,700 patients aged ≥65 years with CKD stages 4-5 and an incident eGFR < 20 mL/min/1.73 m^2, we found a U-shaped relationship between serum potassium and the combined outcome of death or KRT start. During 8 years of follow-up, the serum potassium level associated with the lowest hazard of death or KRT start was

Table 3. Combined Death or KRT Start According to 7 Time-dependent Serum Potassium Categories in 1,714 Participants in the European Quality Study on Treatment of Older People With Advanced CKD During 8 Years of Follow-up

Time-dependent Serum Potassium Category, mmol/L	Crude	Age and Sex Adjusted	Model 1	Model 2	Model 3	Model 4: Main Model
≤3.5	1.8 (1.3-2.5)	1.8 (1.3-2.6)	1.8 (1.3-2.6)	1.6 (1.2-2.3)	1.6 (1.2-2.3)	1.6 (1.1-2.3)
>3.5 to ≤4.0	1.4 (1.1-1.7)	1.4 (1.2-1.7)	1.4 (1.1-1.7)	1.4 (1.2-1.7)	1.4 (1.2-1.7)	1.4 (1.1-1.7)
>4.0 to ≤4.5	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.1 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (1.0-1.4)
>4.5 to ≤5.0	1	1	1	1	1	1
>5.0 to ≤5.5	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
>5.5 to ≤6.0	1.8 (1.4-2.3)	1.8 (1.4-2.3)	1.8 (1.4-2.4)	1.7 (1.4-2.2)	1.8 (1.4-2.3)	1.8 (1.4-2.3)
>6.0	2.7 (1.8-4.1)	2.7 (1.8-4.1)	2.8 (1.9-4.2)	2.3 (1.5-3.4)	2.2 (1.5-3.3)	2.2 (1.5-3.3)

All values are hazard ratios (95% CI).
Serum potassium level 4.5 to 5.0 mmol/L was taken as the reference category. CKD, chronic kidney disease, KRT, kidney replacement therapy. Model 1: Adjusted for age, sex, current smoking, history of diabetes mellitus and history of cardiovascular disease. Model 2: Additional adjustment for estimated glomerular filtration rate (eGFR). Model 3: Additional adjustment for subjective global assessment score. Model 4 (main model): Additional adjustment for renin-angiotensin-aldosterone system inhibitor (RAASi) use.

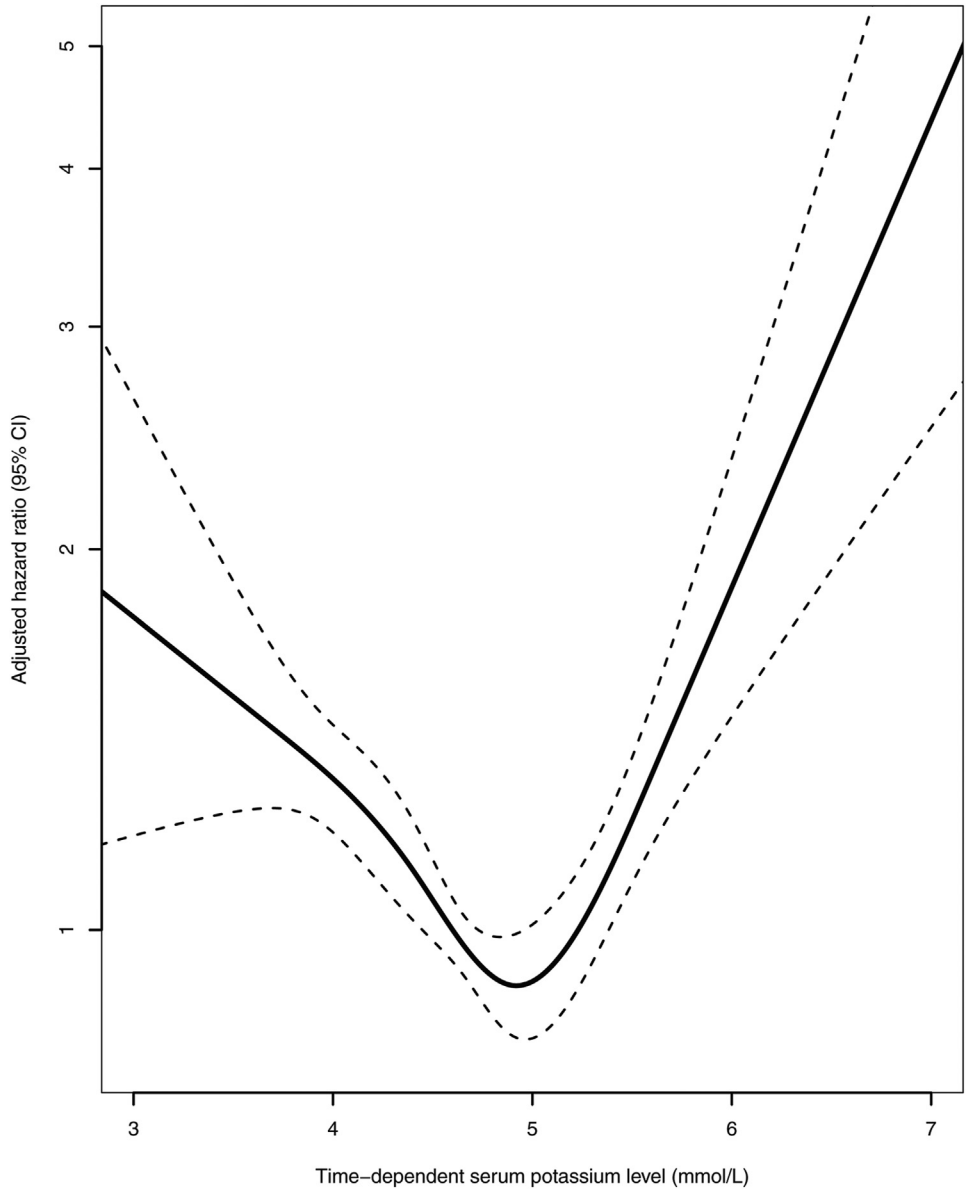

Figure 1. Hazard ratio for combined death or KRT start with 95% confidence intervals (dotted lines) related to time-dependent serum potassium in 1,714 incident participants in the European Quality study on treatment of older people with advanced CKD during 8 years of follow-up, calculated from our 4-knot restricted cubic spline and adjusted for age, sex, current smoking, history of diabetes mellitus, history of cardiovascular disease, estimated glomerular filtration rate, subjective global assessment score, and renin-angiotensin-aldosterone system inhibitor use. Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy.

about 4.9 mmol/L. Compared with this level, low (≤3.5 mmol/L) and high (>6.0 mmol/L) serum potassium concentrations were a 1.6- and 2.2-fold stronger hazard for death or KRT start after multivariable adjustment, respectively.

Although the relationship between serum potassium, CKD progression, and death has been studied before, there are several limitations to those previous studies that emphasize the relevance of our results. First, in the previous retrospective registry-based studies serum potassium was usually measured for a cause. For instance, potassium was measured in critically ill patients, which may have resulted in selection bias.[4,22-25] In contrast, in our prospective study, serum potassium data were routinely collected every 3-6 months.

Second, study populations of previous studies were often heterogenous, including prevalent patients from various CKD stages with an eGFR < 60 mL/min/1.73 m^2.[4,5,22-26] By contrast, we restricted our study population to incident CKD stages 4-5. Because the risk of dyskalemia, kidney failure, and mortality will differ among different stages of CKD, stage-specific effects might only be discovered in (subgroups of) cohorts restricted to specific stages of CKD.

Third, by including prevalent patients, these previous studies were susceptible to survivor bias.[4,5,22-25] Survivor bias is a form of selection bias that occurs when the risk for an outcome is estimated from data collected at a given time point among survivors rather than using data from incident cases.[27] As with other biases, an increased study size cannot compensate for survivor bias.[28]

Fourth, previous studies included participants who were often younger whereas we only included patients older than 65 years.[5,22,23,25] Because older patients are at higher risk of comorbidities and subsequent polypharmacy, both potentially affecting serum potassium levels, the interplay between serum potassium levels and the combined outcome of death or KRT start may differ in these patients.[9-11] A subanalysis of a meta-analysis including over 42,000 patients with CKD (mean age 70 years and eGFR of 42 mL/min/1.73 m^2) reported that serum potassium between 4.0 and 4.5 mmol/L was associated with the lowest risk of all-cause mortality and KRT start separately.[22] However, after restriction to baseline eGFR < 30 mL/min/1.73 m^2, the adjusted HRs for death were lowest between serum potassium 4.2 and 5.0 mmol/L, while adjusted HRs for KRT start increased gradually from serum potassium > 4.2 mmol/L.[22] The slightly higher optimum serum potassium level of about 4.9 mmol/L that we found may be explained by the fact that we included incident patients with more advanced CKD (mean eGFR 17 mL/min/1.73 m^2), adjusted for nutritional state and assessed death before KRT and KRT start as combined outcome.

Potassium homeostasis is mainly regulated by the kidneys, which are responsible for excreting 90% of the dietary potassium intake.[2] Hence, the risk of hyperkalemia increases with decreasing kidney function. We previously found a serum potassium level of approximately 5.1 mmol/L to be associated with the lowest mortality risk in hemodialysis patients.[29] This relatively high level may reflect that hemodialysis patients adapt to chronically increased potassium levels. Indeed, chronic potassium > 5.0 to ≤ 5.5 mmol/L has been shown not to be associated with death in CKD stages 4-5 patients, and hyperkalemia is better tolerated in CKD stages 4-5 compared with stage 3.[24,25]

Furthermore, the presence of severe hyperkalemia in a patient with kidney failure may in itself be a reason to initiate dialysis if other serum potassium lowering therapies fail. Apart from decreasing kidney potassium excretion, hyperkalemia may also occur as a side effect of medication among patients with CKD stages 4-5. Although their blood pressure–lowering and renoprotective effects may be substantial, treatment with RAAS inhibitors or steroidal mineralocorticoid receptor antagonists (MRAs)—such as spironolactone and eplerenone—increases the risk of hyperkalemia.[30] However, RAAS inhibitor discontinuation among CKD patients with hyperkalemia is related to a higher risk of mortality and cardiovascular events, suggesting that the beneficial effects of RAAS inhibitors may outweigh the risks associated with hyperkalemia.[31] Nonsteroidal MRAs are a new class of drugs developed to address the medical need for more effective treatments to protect the kidney and the heart in patients with CKD, with a safer profile and lower risk of hyperkalemia. The tissue distribution of nonsteroidal MRAs is balanced between the kidney and the heart, whereas steroidal MRAs more prominently accumulate in the kidney.[32]

Hypokalemia is also associated with a faster rate of kidney function decline in CKD patients.[3-6] Several possible explanations for the relationship between hypokalemia and CKD progression have been proposed. First, hypokalemia could contribute to interstitial renal scarring and eventually lead to renal fibrosis via inflammation and local activation of the RAAS. Second, higher oral potassium intake lowers the risk of hypertension and cardiovascular outcomes, most likely by increasing natriuresis and thereby reducing the unfavorable effects of sodium.[26,33,34] Finally, increased urinary potassium excretion, which can be considered as a proxy for higher potassium intake, has also been found to slow down progression of CKD.[35]

Following these results, currently a randomized clinical trial (ClinicalTrials.gov identifier NCT03253172) investigating the potential benefit of potassium supplementation in CKD stages 3b and 4 patients is being conducted in the Netherlands.[36,37] If potassium supplementation is found to be renoprotective, this trial also aims to distinguish whether this beneficial effect can be acquired solely by potassium chloride supplementation or whether it more likely depends on the broader advantages of dietary potassium sources such as fruits and vegetables. Dietary potassium sources do not contain potassium chloride but are rich in potassium citrate. Furthermore, potassium citrate may also correct CKD-related chronic metabolic acidosis and thus slow CKD progression.[38] In our study, adjustment for SGA score, albumin, and phosphate as measures of nutritional status only slightly attenuated the increased risk of low serum potassium (≤3.5 and >3.5 to ≤4.0 mmol/L) on death or KRT start. This may be explained by the fact that serum potassium does not necessarily reflect total body potassium; 24-hour urinary potassium excretion or food diaries, for example, may be better measures of potassium intake.[39,40]

There are several strengths to our study. First, this study comprised a large cohort of patients with incident CKD stages 4-5 from 6 European countries, increasing the generalizability of our results. Second, we only included older patients with CKD stages 4-5, which is relevant because the CKD population ages; compared with younger patients, older patients are at higher risk of comorbidities and polypharmacy, both potentially affecting serum potassium levels.[9-11] Therefore, knowledge about optimal potassium management is important in older CKD 4-5 patients.

Third, all laboratory measurements were performed according to study protocol and therefore information bias is unlikely. This contrasts with previous registry-based studies in which all data were collected from clinical records, potentially resulting in information bias as data

were collected for a clinical reason. Fourth, we adjusted for cigarette smoking, an important confounder that was unavailable in most previous studies. Because smoking is associated with both hypokalemia and increased risk of death, inadequate control for smoking can distort the true relationship between potassium and death, so-called reverse causation.[41] Finally, we used restricted cubic spline analysis to freely model serum potassium on a continuous scale and more precisely assess its effect on the risk of death or KRT start.

Nevertheless, our study has some limitations. First, as with most studies, we encountered missing data. However, by using multiple imputation to account for missing data, we maintained power and minimized bias. Second, we did not adjust for time-dependent confounding because we only had limited follow-up data on confounders that most likely change over time. Relevant information on medication that may have been started or stopped during follow-up, such as potassium binders or RAAS inhibitors, was also not sufficiently available. SGLT2 inhibitors and nonsteroidal MRAs are not yet approved by the European Medicines Agency (EMA) for patients with an eGFR < 20 mL/min/1.73 m^2 and will therefore not have affected our results.[42,43]

Third, even though we updated serum potassium as a time-dependent variable, we could only do so for every 3 to 6 months. However, as serum potassium fluctuates, misclassification may have diluted the effects that we found. Shorter intervals between measurements would have allowed for more precise estimations of the combined death or KRT risk. Fourth, we used all-cause mortality as part of the primary outcome, whereas sudden cardiac death may have been more relevant when assessing the dyskalemia-associated death risk. Sudden cardiac death can, however, be nondifferentially misclassified, whereas is all-cause death unequivocal. In general, nondifferential misclassification results in underestimation of the effect.[28]

In conclusion, we found a U-shaped relationship between serum potassium and the combined outcome of death or KRT start in patients aged ≥65 years with an incident eGFR < 20 mL/min/1.73 m^2 during 8 years of follow-up. Our results indicate a serum potassium level of approximately 4.9 mmol/L to be associated with the lowest hazard of death or KRT start. Compared with this optimum level, low (≤3.5 mmol/L) and high (>6.0 mmol/L) serum potassium concentrations were a 1.6- and 2.2-fold stronger hazard for death or KRT start after multivariable adjustment, respectively. This relatively high level may stress the importance of preventing both high and low serum potassium in older patients with CKD stages 4-5.

Supplementary Material

Supplementary File 1 (PDF)

Figure S1: Histogram showing the distribution of all serum potassium values at baseline and during follow-up separately.

Table S1: Baseline characteristics of 1,126 complete cases compared with 588 incomplete cases and the number of missing data among the incomplete cases in the EQUAL study on treatment of older people with advanced CKD.

Table S2: HRs with 95% CIs of KRT start according to 7 time-dependent serum potassium categories in 1,714 participants in the EQUAL study on treatment of older people with advanced CKD during 8 years of follow-up.

Table S3: HRs with 95% CIs of death before KRT start according to 7 time-dependent serum potassium categories in 1,714 participants in the EQUAL study on treatment of older people with advanced CKD during 8 years of follow-up.

Table S4: HRs with 95% CIs of cardiovascular death before KRT start according to 7 time-dependent serum potassium categories in 1,714 participants in the EQUAL study on treatment of older people with advanced CKD during 8 years of follow-up.

Table S5: HRs with 95% CIs of combined death or KRT start according to 7 time-dependent serum potassium categories in 1,714 participants in the EQUAL study on treatment of older people with advanced CKD during 8 years of follow-up, based on our complete case analysis.

Table S6: HRs with 95% CIs of combined death or KRT start according to 7 time-dependent serum potassium categories in 1,714 participants in the EQUAL study on treatment of older people with advanced CKD during 8 years of follow-up, with additional adjustment for albumin, BMI, and serum phosphate.

Table S7: HRs with 95% CIs of combined death or KRT start according to 7 baseline serum potassium categories in 1,714 participants in the EQUAL study on treatment of older people with advanced CKD during 8 years of follow-up.

Table S8: List of the EQUAL Study Investigators.

Article Information

EQUAL Study Investigators: In addition to authors Hoorn, Jager, Chesnaye, Evans, Caskey, Torino, Szymczak, Wanner, Dekker, and Hoogeveen, a full list of the EQUAL Study Investigators is provided in Table S8.

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Serum Potassium and Risk of Death or Kidney Replacement Therapy in Older People With CKD Stages 4-5

Study Design

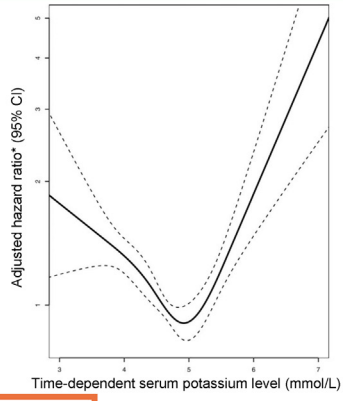
European Quality (EQUAL) Study

- **Prospective observational cohort study**
- **N = 1,714 patients aged ≥65 years with CKD (followed from first eGFR <20 mL/min/1.73m^2 measurement)**
- **Serum potassium measured every 3-6 months for 8 years until death or start of kidney replacement therapy (KRT)**
- **Time-dependent Cox model**

Results

Serum Potassium (mmol/L)	Death or KRT Hazard Ratio* (95% CI)
≤ 3.5	1.6 (1.1-2.3)
> 3.5 to ≤ 4.0	1.4 (1.1-1.7)
> 4.0 to ≤ 4.5	1.1 (1.0-1.4)
> 4.5 to ≤ 5.0	1
> 5.0 to ≤ 5.5	1.1 (0.9-1.4)
> 5.5 to ≤ 6.0	1.8 (1.4-2.3)
> 6.0	2.2 (1.5-3.3)

*Adjusted for age, sex, smoking, diabetes, CVD, RAAS inhibition, eGFR, and subjective global assessment



CONCLUSION: U-shaped relationship between serum potassium and death or KRT start among patients with incident CKD 4-5, with a nadir risk at a potassium level of 4.9 mmol/L.

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