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Serum potassium, end stage renal disease and mortality in chronic kidney disease

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Abstract

Background/Aims—Hypokalemia and hyperkalemia are often noted in chronic kidney disease (CKD) patients but their impact on mortality and end stage renal disease (ESRD) is less well understood. We aimed to study the associations between potassium disorders, and mortality and progression to ESRD in a CKD population.

Methods—Using our Electronic Health Record-based CKD registry, 36,359 patients with eGFR < 60 ml/min/1.73m² and potassium levels measured from January 1, 2005 to September 15, 2009 were identified. We examined factors associated with hypokalemia (<3.5 mmol/l) and hyperkalemia (>5.0 mmol/l) using logistic regression models and associations between serum potassium levels (both as continuous and categorical variables) and all-cause mortality or ESRD using Cox-proportional hazards models.

Results—Serum potassium <3.5 mmol/l was noted among 3% and >5.0 mmol/l among 11% of the study population. In the multivariable logistic regression analysis, lower eGFR, diabetes and use of ACE inhibitors or Angiotensin-Receptor Blockers were associated with higher odds of having hyperkalemia. Heart failure and African American race were associated with higher odds of hypokalemia. After adjustment for covariates including kidney function, serum potassium <4.0 mmol/l and >5.0 mmol/l were significantly associated with increased mortality risk but there was no increased risk for progression to ESRD. Time-dependent repeated measures analysis confirmed these findings. When potassium was examined as a continuous variable, there was a U-shaped association between serum potassium levels and mortality.

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Disclosures

The authors have no relevant financial interest in the study.

Conclusion—In patients with stage 3–4 CKD, serum potassium level <4.0 mmol/l and >5.0 mmol/l are associated with higher mortality but not with ESRD.

Keywords

Potassium; mortality; ESRD; chronic kidney disease

Background

The kidneys play a crucial role in potassium homeostasis and the importance of their contribution in the maintenance of potassium balance is reflected by the high rates of potassium disorders in patients with decreased kidney function (1, 2). Indeed, individuals with chronic kidney disease (CKD) and those with end-stage renal disease (ESRD) can experience both hyperkalemia and hypokalemia; the former typically occurs by virtue of their low kidney function or as a consequence of drugs such as Angiotensin Converting Enzyme inhibitors (ACEIs) or Angiotensin-Receptor Blockers (ARBs) while the latter is typically a consequence diuretic administration (3).

Among dialysis patients, hyperkalemia has been associated with higher mortality due to its arrhythmogenic effects (4, 5). Hypokalemia has also been linked to higher mortality in dialysis patients, not only because of the electrophysiological effects of potassium, but also because hypokalemia often reflects a poor underlying nutritional status (6). In CKD patients not on dialysis, however, the impact of potassium disorders on outcomes is unclear. Recent evidence suggests that the relationship between serum potassium and mortality follows a U-shaped curve, wherein both low and high serum potassium are associated with an increase in mortality (7, 8). However, the data is heterogeneous with a variable follow-up ranging from 1 day to 4 years and variable number of potassium values per patient (9). In addition, low serum potassium has been postulated to be a risk factor for the progression of CKD, as it had been shown to induce kidney damage via modulation of renal inflammation and impaired angiogenesis (10–12). To our knowledge, the association between serum potassium and ESRD has not been studied in detail. Therefore, we examined the associations between serum potassium and all-cause mortality and ESRD in a cohort of stage 3 and stage 4 CKD patients following in our health care system.

Methods

We conducted an analysis using our preexisting Electronic Health Record (EHR)-based CKD registry. The development and validation of our EHR-based CKD registry at Cleveland Clinic have been described in detail elsewhere (13).

Study Population

Patients who met the following criteria from January 1, 2005 to September 15, 2009, were included in the study population: (1) had at least one face-to-face outpatient encounter with a Cleveland Clinic health care provider, (2) had two or more estimated GFR (eGFR) values <60 ml/min per 1.73 m² more than 90 days apart, and (3) had a potassium measured on the date of the second eGFR <60 ml/min per 1.73 m². Patients aged <18 years old, who entered

the registry after 9/15/2009 and those who were diagnosed with ESRD needing dialysis or renal transplant before the date of second eGFR <60 ml/min/1.73 m² were excluded.

Definitions and Outcome Measures

Renal Function—We applied the CKD-EPI equation to patients in our health system who had two outpatient serum creatinine levels between January 1, 2005, and September 15, 2009, to calculate eGFR (14). All creatinine measurements were performed by the modified kinetic Jaffe reaction, using a Hitachi D 2400 Modular Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) in our laboratory. CKD was defined according to current guidelines as follows: stage 3 CKD (eGFR 30–59 ml/min per 1.73 m²) and stage 4 CKD (eGFR 15–29 ml/min per 1.73 m²). We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min per 1.73 m²) and stage 3b (eGFR 30–44 ml/min per 1.73 m²).

Serum Potassium—Only outpatient serum potassium laboratory measures obtained with a same reference range were included in this analysis. Serum potassium levels measured on the day of CKD confirmation (second eGFR <60 ml/min per 1.73 m² at least 90 days after the first eGFR), as described, were used for the analysis in which single potassium measured was considered. For our time-dependent repeated measures analysis, we included the baseline potassium as well as the first potassium with appropriate reference range measured each month during the study follow-up. We used carry-forward values to fill in data for months with no potassium measurement.

Comorbid Conditions and Laboratory Parameters—Demographic details were extracted from the EHR. Diabetes mellitus, hypertension, coronary artery disease, and other comorbid conditions were defined using pre-specified criteria and validated (13). Serum potassium levels and other relevant outpatient laboratory details were obtained from our electronic laboratory records.

Outcomes—The primary outcomes of interest, all-cause mortality and ESRD were ascertained from our EHR and linkage of our CKD registry with the Social Security Death Index and United States Renal Data Services (USRDS). Patients were followed from their date of inclusion in the registry (date of second qualifying eGFR) until September 15, 2009.

Statistical Analyses

CKD patients with measured outpatient serum potassium values at the time of second eGFR <60 ml/min per 1.73 m² were further classified into three groups: <3.5 mmol/l, 3.5–3.9 mmol/l, 4.0–4.9 mmol/l, 5.0–5.5 mmol/l and >5.5 mmol/l based on clinical relevance and previous reports. Associations of the baseline characteristics for these groups were assessed using Chi-square and ANOVA tests for categorical and continuous variables respectively.

Two separate logistic regression analyses were conducted to examine the association of low (<3.5 mmol/l) or high (>5.0 mmol/l) serum potassium levels with potential covariates. For each of these models, the reference group was all patients with normal serum potassium levels based on our laboratory reference values (3.5–5 mmol/l). Covariates were based on information known prior to second eGFR <60 and chosen *a priori* based on factors

previously shown or thought to be related to both serum potassium, ESRD and mortality. These include age, gender, race, body mass index (BMI), eGFR, diabetes, hypertension, malignancy, coronary artery disease, heart failure, chronic obstructive pulmonary disease (COPD) and/or asthma, use of ACE/ARB, and use of Beta Blockers.

To evaluate whether survival and ESRD among persons with CKD was associated with serum potassium levels, we used Kaplan-Meier plots and log-rank tests with date of second eGFR <60 ml/min/1.73 m² as the time of origin. Progression to ESRD and pre-ESRD death are competing events; therefore we fitted cumulative incidence functions that adjust for competing risks and compared these results to the traditional cause specific analysis. In addition, a separate analysis that included all deaths (both before and after ESRD) was also conducted. We used Cox proportional hazards models to assess the association between serum potassium and mortality and ESRD while adjusting for other covariates mentioned above, as well as cerebrovascular disease, peripheral vascular disease, potassium sparing diuretics, non-potassium sparing diuretics, potassium supplementation, serum bicarbonate, log glucose and albumin. To incorporate serum potassium results obtained after inception we fitted a Cox proportional hazards model with time-dependent repeated measures of potassium while adjusting for all variables mentioned before. We used splines to relax linearity assumptions for continuous variables included in the models. We also examined the relationship between continuous baseline serum potassium and each outcome using restricted cubic splines.

We tested 2-way interactions between baseline serum potassium and the following covariates: age, gender, race, diabetes and eGFR in the adjusted Cox proportional hazards model. 0.3% of patients had missing serum glucose and/or bicarbonate data and 13% of patients had missing albumin. We used mean value imputation to include all patients in the cox model. To evaluate the effect of the imputation we also fit a model with time-dependent serum potassium with complete case data. We did not adjust for proteinuria in our main models because we only had data in 49% of the sample. However, we performed a sensitivity analysis fitting cox models with time-dependent serum potassium as described above and adjusting for proteinuria in a sensitivity analysis.

All data analyses were conducted using Unix SAS version 9.2 (SAS Institute, Cary, NC) and R 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria). The *cmprsk* package was used for competing risk analysis. The CKD registry and this study were approved by the Cleveland Clinic Institutional Review Board.

Results

Patient characteristics

There were 42,912 patients with stage 3 and 4 CKD from our CKD registry, and of those, 36,359 (85%) had serum potassium levels measured on the date of second eGFR <60 ml/min per 1.73 m² with reference ranges 3.5–5 mmol/l and constituted the study population (Supplemental Figure 1). Patients who had had measurements with different assays (n=4,725, 11%) were excluded. Mean age of the study population was 72 ± 11.9 years with 55% being females and 13% African Americans. Demographic variables and comorbid

conditions were significantly different among patients with various ranges of serum potassium levels (Table 1). Serum potassium <3.5mmol/l was noted among 3% and >5.0 mmol/l was observed among 11% of the study population.

Factors associated with low and high serum potassium levels

Low serum potassium levels (<3.5 mmol/l)—In the multivariable analysis, the following variables were associated with higher odds of having low potassium levels compared to normal: African American race, lower eGFR, malignancy, and heart failure (Table 2). Conversely, the following variables were associated with having lower odds of having low serum potassium levels: older age, male gender, being overweight, diabetes, hypertension and use of ACE/ARB (Table 2).

High serum potassium levels (>5.0 mmol/l)—In the multivariable analysis, the following variables were associated with higher odds of having high potassium levels compared to normal: male gender, lower eGFR, BMI <18.5 kg/m², diabetes, malignancy, and use of ACE/ARB (Table 2). The following variables were associated with having lower odds of having high serum potassium levels: higher age and higher BMI (Table 2).

Serum potassium levels, ESRD and all-cause mortality

Among our study population, 6,114 of them died before reaching ESRD and 772 reached ESRD during an average follow-up of 2.3 years. A total of 6,379 patients died overall. Both the Kaplan-Meier and competing risk analyses showed a significant difference in overall mortality and ESRD among those with different potassium levels ($p<0.001$, Figure 1) and the results were similar in both analytical approaches. In the multivariate model (time-dependent repeated measures analysis) adjusting for demographics, comorbid conditions, medications use, lower levels of serum potassium (<3.5 and 3.5–3.9 mmol/l) were associated with higher risk for mortality. Similar higher risk for mortality was noted for those with higher levels of serum potassium (5.0–5.4 and >5.5 mmol/l) (Table 3). No such associations between potassium levels and ESRD were noted (Table 3). In a model in which only baseline serum potassium was considered as the explanatory variable, serum potassium levels >5.5 mmol/l was associated with higher risk for death (Supplemental table 1). There was a U-shaped association between serum potassium levels and mortality when serum potassium was examined as a continuous variable (Figure 2).

Effect modification by age and CKD stage

We found significant 2-way interactions between serum potassium and age and eGFR on mortality, which indicated that the increased mortality hazard associated with abnormal levels of serum potassium was different at different ages ($p=0.04$) and eGFR stages ($p<0.001$). Age appears to modify the association with younger patients showing stronger association and seems to either attenuate or lose of statistical significance in elderly population (Supplemental table 2). The interaction with CKD stage suggested that serum potassium is associated with increased mortality among patients with stage 3a but not in other stages of CKD (data not shown).

Sensitivity analyses

In a sensitivity analysis in which we included patients who had proteinuria data (n=17,790), similar results were noted (data not shown). Results from the model including only patients with complete data (complete case analyses) were qualitatively similar to those in the model using mean value imputation and a class level for missing BMI groups.

Discussion

In this large cohort of patients with stage 3 and 4 CKD, the prevalence of hypokalemia (K <3.5 mmol/L) and hyperkalemia (K >5.0 mmol/L) were 3% and 11% respectively. Hyperkalemia was more frequently observed in patients with lower eGFR, treated with ACEI/ARB and those with conditions known to cause cellular shifts such as diabetes. On the other hand, hypokalemia was more often seen in African Americans and in patients taking diuretics. We observed a U-shaped association between serum potassium and death with both lower and higher levels of potassium being associated with increased risk of death. However, neither low nor high serum potassium levels were associated with progression to ESRD.

Hypokalemia and hyperkalemia are frequently observed in patients with CKD. As the eGFR falls, the renal excretion of potassium is reduced, and the prevalence of hyperkalemia increases from 2% in patients with eGFR > 60 ml/min/1.73m² to 42% in patients with eGFR <20 ml/min/1.73 m²(15, 16). Other factors that have been linked to hyperkalemia include cellular shifts from underlying acidosis or diabetes and treatment with RAAS blockers such as ACEI or ARB (17–20). Hypokalemia on the other hand, is often seen in the setting of diuretic use and has been proposed as a marker of poor nutritional status (21). Our findings were concordant with the previous studies: hyperkalemia was more frequently observed in patients with lower GFR, treated with ACEI/ARB and those with diabetes. These same factors were associated with lesser risk for hypokalemia. On the other hand, diuretics were associated with higher odds of hypokalemia and lower odds of hyperkalemia. Black race was also associated with higher odds of hypokalemia. Previous reports have shown that African Americans have lower mean serum potassium concentration than whites in non-CKD population and the risk for unprovoked hypokalemia was five times that of Whites (22–25). Our findings extend this to African Americans with CKD and suggest the need to monitor them closely for development of hypokalemia.

Hypokalemia has been previously linked to increased mortality in patients with heart failure and acute myocardial infarction (26, 27). In a propensity-matched analysis, Bowling et al., reported an association between low serum potassium (defined as <4 mmol/l) and mortality in those with CHF and CKD (28). In a CKD population with mean eGFR of 25.4 ml/min/1.73 m², an association between low serum potassium and mortality was reported. Our findings extend these observations to those without heart failure and to those with stage 3 CKD. Low serum potassium levels affect the myocardial resting membrane potential which can lead to ventricular arrhythmias and sudden cardiac death (29). Low potassium levels can also be a reflection of a poor nutritional status, which in turn portends poor prognosis (30) but in the repeated measures analysis, the association between hypokalemia (both in the 3.5–3.9 mmol/l and <3.5 mmol/l) and mortality remains despite adjusting for serum albumin.

In our study population, serum potassium >5.0 mmol/l is also associated with increased mortality in non-dialysis-dependent CKD patients, a finding that is typically attributed to the arrhythmogenic effects of potassium. In a secondary analysis of the Renal Research Institute (RRI) study CKD cohort, an increased risk of the composite of death or cardiovascular events requiring hospitalization was observed but did not show an increase in overall mortality (8). The differences between our study and the RRI study could be attributed to the reference ranges used (4–5.5 mmol/l in RRI vs. 4.0–4.9 mmol/l in our study). However, another study included hospitalized CKD patients and demonstrated higher risk for death within 1 day among those with hyperkalemia (31). Our study shows a clear association between serum potassium and mortality with hypokalemia <4.0 mmol/L and hyperkalemia >5.0 mmol/L (Table 3).

However, when looking at the interaction between age groups and potassium, we found a statistically significant association between serum potassium of 3.5–3.9 mmol/L and mortality for patients aged <80 years old but not in those aged >80 (Supplemental Table 2). A potential explanation could relate to the high morbidity load of patients aged above 80 that would put them at risk of death regardless of their serum potassium. Baseline kidney function seem to modify the associations between serum potassium and outcomes as patients with hypo/hyperkalemia and stage 3a CKD (eGFR 45–59 ml/min/1.73m²) were more likely to die than those with stage 3b and stage 4 CKD (eGFR <45 ml/min/1.73m²). Such findings could be attributed to the fact that higher occurrence of chronic hyperkalemia in CKD patients might be better tolerated than acute hyperkalemia. This in turn might lead to a reduced sensitivity to cardiac complications (32). Whether such phenomenon exists for hypokalemia warrants further studies.

It has been suggested that potassium disorders could lead to progression of renal disease. Hypokalemia in particular could contribute to interstitial renal scarring and experimental studies suggest that chronic hypokalemia can lead to renal fibrosis via modulation of renal inflammation and local activation of the RAAS (11, 33, 34). Current clinical evidence provide conflicting findings as some studies suggest that hypokalemia was associated with progression to ESRD, while others did not observe such association after adjustment for nutritional indices (serum albumin) (8, 35). Hayes et al noted that hypokalemia was associated with renal progression but the association with hard renal outcome, such as reaching ESRD was unclear (36). Table 3 shows that there could be a higher risk for ESRD in those with serum potassium 3.5–3.9 mmol/l but the overall p-value for the model wasn't significant suggesting that no associations exist between hypokalemia and ESRD. Despite the large sample size and inclusion of relevant confounders, we didn't observe an association between hypokalemia and kidney disease progression.

Strengths of this analysis include a large diverse patient population with stage 3 and 4 CKD, availability of several confounding variables and the use of time-dependent repeated measures analyses. However, retrospective analyses are prone to residual confounding. While we included several variables that could affect serum potassium levels and are related to mortality (diabetes, serum bicarbonate, medications etc.), we lacked details about nutritional data. Further, our patients have been followed in a health care system and hence these data might not be applicable to the community-dwelling adults with CKD

In summary, hypokalemia and hyperkalemia are often noted in those with CKD. Several clinical and demographic factors are associated with potassium disorders. Both serum potassium levels <4.0 mmol/l and >5.0 mmol/l are associated with all-cause mortality but not with ESRD in those with stage 3 and stage 4 CKD. These associations are modified by the stage of kidney disease and age and further studies are needed to understand the potential mechanisms that explain these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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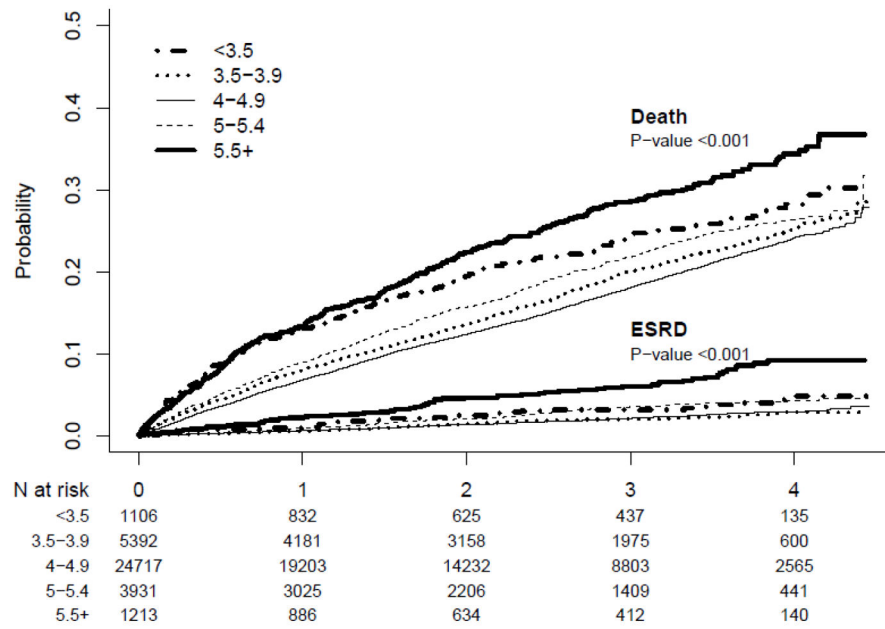


Figure 1. Cumulative incidence curve for death and ESRD for various categories of serum potassium (Graph shows that the unadjusted risk for mortality and ESRD differ among patients with different serum potassium levels)

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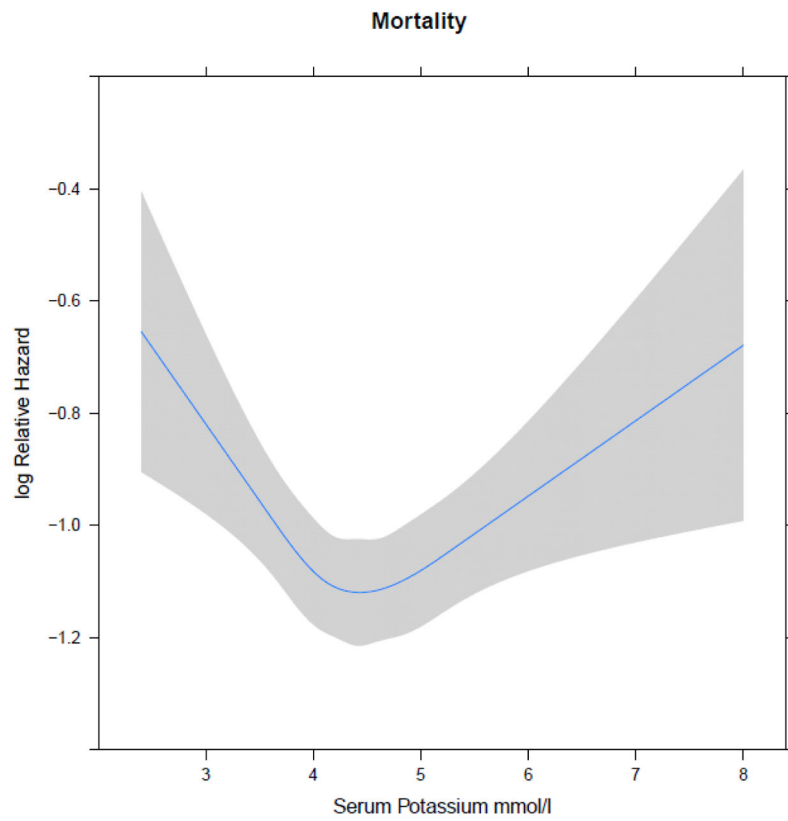


Figure 2. Relationship between serum potassium (as a continuous measure) and all-cause mortality (The graph shows a U-shaped relationship between continuous potassium and mortality. Splines were used to allow for non-linear relationship. Knots were placed at potassium values of 3.6, 4.1, 4.4, 4.7 and 5.3).

Table 1

Characteristics of study population based on serum potassium levels

Variable~	Total (N=36359)	<3.5 (N=1106)	3.5-3.9 (N=5392)	4-4.9 (N=24717)	5-5.4 (N=3931)	>5.5 (N=1213)
Age	72.3±11.9	68.7±13.4	72.0±11.9	72.7±11.7	71.9±12.1	70.4±12.9
Male gender	45.1	33.5	37.1	45.8	52.7	53.2
African American	13.2	26.3	18.1	11.6	11.2	19.3
eGFR	47.0±10.4	46.2±11.1	48.3±9.8	47.6±10.0	43.8±11.4	39.9±12.2
CKD stage						
Stage 3a (45-59)	64.6	63.3	69.6	66.8	52.0	38.8
Stage 3b (30-44)	26.9	26.4	24.4	25.9	33.6	36.8
Stage 4 (15-29)	8.5	10.3	6.0	7.3	14.4	24.4
BMI* kg/m ²	29.2±6.4	29.4±7.0	29.3±6.5	29.2±6.3	29.0±6.4	29.5±7.5
BMI group						
<18.5 kg/m ²	1.3	1.4	1.3	1.2	1.7	2.3
18.5-24.9 kg/m ²	23.4	26.6	23.4	23.1	23.9	25.0
25-29.9 kg/m ²	34.8	29.6	33.3	35.4	35.9	31.6
30+ kg/m ²	36.2	38.2	37.1	36.2	34.3	36.0
Missing	4.3	4.3	4.9	4.1	4.1	5.1
Smoking status						
No	76.2	68.1	73.7	77.2	76.4	73.0
Yes	6.7	8.1	6.9	6.4	7.3	8.6
Missing	17.1	23.8	19.3	16.4	16.3	18.5
COPD	38.6	9.3	9.1	8.4	8.5	8.7
Diabetes	21.9	16.3	15.9	21.7	29.5	34.2
Hypertension	84.3	76.9	81.9	84.8	86.9	83.8
Coronary artery disease	21.5	14.1	16.9	21.8	27.3	24.1
Congestive heart failure	8.2	9.6	7.3	7.9	9.6	11.2
Cerebrovascular disease	9.0	6.1	7.6	9.2	10.3	10.6
Peripheral vascular disease	2.7	2.1	1.9	2.7	3.6	4.1
Malignancy	24.4	24.7	24.2	24.4	24.2	24.8
Use of ACEI/ARBs	62.1	50.6	55.1	62.2	71.2	73.0

Variable [~]	Total (N=36359)	<3.5 (N=1106)	3.5-3.9 (N=5392)	4-4.9 (N=24717)	5-5.4 (N=3931)	>5.5 (N=1213)
Use of Beta Blockers	54.7	49.6	50.8	54.5	61.0	59.9
Use of Statins	55.6	47.0	49.5	56.6	60.4	56.8
Diuretic use	65.9	75.9	75.1	63.8	63.1	67.4
K supplement	13.3	30.8	19.5	11.9	10.1	10.2
Serum Sodium mmol/l [*]	139.4±3.2	138.9±4.2	139.6±3.2	139.5±3.0	139.0±3.5	137.9±4.4
Serum bicarbonate mmol/l [*]	26.0±3.3	27.5±4.2	26.8±3.3	26.1±3.1	25.0±3.4	23.6±4.1
Serum albumin g/dl [*]	4.1±0.46	3.9±0.61	4.0±0.50	4.1±0.44	4.1±0.47	4.0±0.54
Serum glucose mg/dl [*]	100.0[89.0,120.0]	106.0[91.0,129.0]	101.0[89.0,120.0]	99.0[88.0,117.0]	101.0[89.0,126.0]	103.0[88.0,137.0]

[~] All variables presented as % unless otherwise specified.

^{*} Data not available for all subjects.

Missing values: BMI = 1562, Serum Sodium mmol/l = 106, Serum CO₂ mmol/l = 110, Glucose mg/dl = 105, albumin 4,751. Values presented as Mean ± SD, Median [P25, P75], or N (column %). All variables statistically significant across groups except continuous BMI, COPD/asthma, and malignancy

Table 2

Associations of low (K <3.5 mmol/l) and high serum potassium levels (K >5 mmol/l) in non-dialysis dependent CKD

Effect	Hypokalemia OR (95% CI)*	Hyperkalemia (OR (95% CI)*
Age (per 10 years incremental increase)	0.80 (0.76, 0.84)	0.90 (0.87, 0.92)
Male sex	0.65 (0.57, 0.74)	1.37 (1.28, 1.47)
African American race	2.34 (2.03, 2.69)	0.92 (0.83, 1.02)
eGFR (per 5 ml/min decrease)	1.06 (1.03, 1.09)	1.25 (1.23, 1.27)
BMI group (Ref: 18.5–24.9 kg/m ²)		
<18.5 kg/m ²	0.74 (0.43, 1.25)	1.60 (1.23, 2.08)
18.5–24.9 kg/m ²	Ref	Ref
25–29.9 kg/m ²	0.80 (0.68, 0.94)	0.87 (0.80, 0.96)
30 kg/m ²	0.87 (0.74, 1.02)	0.77 (0.70, 0.85)
Missing	0.86 (0.63, 1.18)	0.97 (0.81, 1.16)
Diabetes	0.77 (0.65, 0.92)	1.53 (1.41, 1.66)
Hypertension	0.75 (0.64, 0.88)	1.03 (0.93, 1.15)
Malignancy	1.17 (1.01, 1.35)	1.12 (1.03, 1.21)
Coronary artery disease	0.84 (0.70, 1.02)	1.09 (1.00, 1.19)
Congestive heart failure	1.50 (1.20, 1.87)	0.95 (0.84, 1.07)
COPD	1.13 (0.91, 1.39)	1.02 (0.90, 1.16)
Use of ACEI/ARBs	0.71 (0.62, 0.82)	1.40 (1.29, 1.52)
Use of Beta Blockers	1.04 (0.91, 1.19)	1.06 (0.98, 1.14)

Table 3

Associations between serum potassium levels and outcomes (ESRD and death) in non-dialysis dependent CKD

	Overall Mortality HR (95%CI)	ESRD HR (95%CI)
<3.5 mmol/l	1.95 (1.74, 2.18)	0.97 (0.67, 1.40)
3.5–3.9 mmol/l	1.16 (1.09, 1.25)	1.39 (1.13, 1.70)
4–4.9 mmol/l	Reference	Reference
5–5.4 mmol/l	1.12 (1.03, 1.21)	1.17 (0.96, 1.42)
5.5 mmol/l	1.65 (1.48, 1.84)	1.20 (0.91, 1.58)

* Models adjusted for age, gender, race, diabetes, hypertension, malignancy, Congestive heart failure, coronary artery disease, COPD/asthma, BMI group, history of ACE/ARB, potassium sparing diuretics, not potassium sparing diuretics, beta blockers, eGFR, potassium supplementation, cerebrovascular disease, peripheral vascular disease, serum bicarbonate, log glucose and albumin. Mean value imputation was used for serum bicarbonate, glucose and albumin

** First potassium per patient per month was used in the analysis. Missing data is filled as follows: potassium value is carried forward until a new potassium value is observed. All subjects and all follow up are included regardless of the amount of time elapsed since last potassium measurement. Median time from last potassium measured to death/censor is 5.4 months.