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Potassium trajectories prior to dialysis and mortality following dialysis initiation in patients with advanced chronic kidney disease

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Abstract

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Author Contributions:

Research idea: CPK, AAD; study design: AAD, KS, PKP, SK, YO, FT, MZM, ES, KK-Z, CPK; data acquisition: AAD, PKP, ES, MZM, KK-Z, CPK; data analysis/interpretation: AAD, KS, PKP, FT, CPK; statistical analysis: AAD, KS, FT, CPK; supervision or mentorship: CPK. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the authors own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Funders of this study had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Statement of Ethics:

The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

Conflict of Interest:

CPK received honoraria from Amgen, Astra Zeneca, Bayer, Cara Therapeutics, Reata, Takeda and Tricida. KK-Z has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, ASN (American Society of Nephrology), Astra-Zeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, IFKF (International Federation of Kidney Foundations), ISH (International Society of Hemodialysis), International Society of Renal Nutrition & Metabolism (ISRNM), JSDT (Japanese Society of Dialysis Therapy), Hospira, Kabi, Keryx, Kissei, Novartis, OPKO, NIH (National Institutes of Health), NKF (National Kidney Foundations), Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, VA (Veterans' Affairs), Vifor, UpToDate, ZS-Pharma. The remaining authors declare that they have no relevant financial interests.

Introduction: Patients with advanced non-dialysis dependent chronic kidney disease (NDD-CKD) have a reduced ability for maintaining plasma potassium (K) in normal range. Deviation from normal plasma K ranges is associated with increased mortality, however the average trajectory of plasma K over time in patients with advanced NDD-CKD and the outcomes associated with plasma K trajectory are unknown.

Methods: We identified 34,167 US veterans with advanced NDD-CKD transitioning to dialysis between 10/2007–03/2015 with at least 1 K measurement each year over a 3-year period prior to dialysis transition (3-year prelude). The K trajectory defined as the change in K (slope) per year over the entire 3-year prelude was estimated using linear mixed effects models. The association between unadjusted (crude) K slope (categorized as stable [−0.09 to 0.09 mEq/L/year], decreasing [≤ −0.10 mEq/L/year], and increasing [≥ 0.10 mEq/L/year]) and time to all-cause and cardiovascular mortality during the 6 months following dialysis initiation was assessed using multivariable-adjusted survival models.

Results: The crude and multivariable-adjusted K slopes (mean, 95% CI) over the 3-year prelude were 0.008 [0.0059, 0.0110] and −0.15 mEq/L/year [−0.19, −0.11], respectively. Decreasing K slope was associated with higher multivariable-adjusted risk of all-cause mortality (adjusted hazard ratio [95% CI] vs stable K slope: 1.08 [1.00–1.17]). No association was observed between K slope and cardiovascular mortality.

Discussion/Conclusion: The average intraindividual plasma K trajectory is remarkably stable in patients with advanced NDD-CKD. A decreasing K slope is associated with higher all-cause mortality risk.

Keywords

potassium; chronic kidney disease; mortality; dialysis; slope

Introduction

The kidneys play an important role in potassium (K) homeostasis, hence dyskalemias (hypo-/hyperkalemia) are more common in patients with chronic kidney (CKD), especially amongst those with advanced CKD and comorbid diabetes, congestive heart failure (CHF), and hypertension [1, 2]. Dyskalemias are established risk factors for cardiovascular events (e.g. arrhythmias, sudden cardiac death) and mortality in the general population [3, 4] as well as those with CKD, CHF, and diabetes [5–9]. Additionally, patients with advanced non-dialysis dependent CKD (NDD-CKD) may be chronic users of medications impacting K homeostasis, such as renin-angiotensin-aldosterone system inhibitors (RAASi) and diuretics to manage highly prevalent comorbid conditions like hypertension and cardiovascular diseases (CVD) [10, 11].

The frequency of dyskalemias, and especially hyperkalemia, increases in patients with advanced NDD-CKD [10, 12, 13]. Due to reduced kidney function, the response to a hyperkalemic challenge is progressively diminished with advanced NDD-CKD [14], which is characterized by more severe hyperkalemia in response to K challenge [15]. Adaptive mechanisms such as increased renal excretion per nephron and increased supplementary gastrointestinal excretion help maintain normal plasma K levels in patients with NDD-CKD

[1], but it is unclear if the overall mean plasma K concentration over time (i.e. the trajectory of plasma K over time) is gradually rising in patients with progressive NDD-CKD as a result of the progressive loss of kidney function or other concomitant physiologic, pathophysiologic or pharmacologic factors. Patients with NDD-CKD transitioning to dialysis present a uniquely fragile population with a high comorbidity burden and high mortality rates within the first few months following transition to dialysis [16]. Due to their advanced CKD, patients transitioning to dialysis are most susceptible to hyperkalemia in the period preceding the initiation of renal replacement therapy. While the frequency and severity of episodes of hyperkalemia is known to increase in the later stages of NDD-CKD, the nature of average K trajectory and its association with clinical outcomes is unknown.

The aim of this study was to assess the trajectory of plasma K in patients with advanced NDD-CKD prior to dialysis initiation and its association with mortality after dialysis initiation. We hypothesized that due to the progressive decline in kidney function, plasma K will tend to increase as patients progressing towards dialysis, and that an increase in plasma K over time is independently associated with higher post-dialysis mortality.

Materials and Methods

Study population

We analyzed data from the Transition of Care in Chronic Kidney Disease (TC-CKD) cohort, a nationally representative historical cohort of US veterans with incident end stage renal disease (ESRD) transitioning to dialysis from October 1, 2007 (first dialysis transition date) through March 31, 2015 (last dialysis transition) [17, 18]. The United States Renal Data System (USRDS) was used to identify a total of 102,477 United States (US) veterans as a source population, with a median (interquartile range [25th-75th percentile]) of 6.2 (2.8–9.3) years and 1.6 (0.6–2.3) years of data availability prior to and following dialysis initiation, respectively. Initially, 60,128 US veterans with non-missing plasma K measurements prior to dialysis initiation were identified. Further, the study sample was refined to those with K measured at least once each year in a 3-year period prior to dialysis initiation (prelude), yielding a study sample of 34,167 patients (shown in online supplementary Fig. 1).

K slope

Our main exposure variable was the K trajectory (slope) over the entire 3-year prelude period. To assess if slope becomes progressively steeper as patients approach the need for renal replacement therapy, we also calculated slopes separately for each 1-year period (cross-sections) over the 3-year prelude period. K slope was assessed using linear mixed effects models with random intercepts and slopes; we examined both unadjusted (crude) slopes, and also adjusted slopes to examine the effect of fixed (time-independent) characteristics (age, sex, race, and comorbidities (diabetes, congestive heart failure [CHF], peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, paraplegia/hemiplegia, anemia, atrial fibrillation, hypertension, ischemic heart disease, liver diseases, and cancer)) and time-varying characteristics (medications including RAASi, Na-polystyrene sulphonate [SPS], loop diuretics, K sparing diuretics, beta blockers,

calcineurin inhibitors, azole antifungals, insulin, oral hypoglycemics, calcium channel blockers and digoxin, and estimated glomerular filtration rate (eGFR)) on K trajectories.

Outcomes

The main outcomes of interest were time to all-cause and cardiovascular mortality following dialysis initiation. Information on all-cause mortality data, censoring events, and associated dates were obtained from VA and USRDS data sources. Cardiovascular mortality data was obtained from USRDS. We limited the follow-up period for mortality assessment to 6 months following dialysis initiation, due to the short-term nature of complications following K disturbances [19, 20] which makes an association with long-term mortality physiologically less plausible.

Covariates/Confounders

The USRDS Patient and Medical Evidence file was used to source data on patient baseline demographic characteristics and type of vascular access at dialysis initiation. Smoking and marital status was extracted from VA records [21, 22]. Comorbidities at the time of dialysis initiation were identified using the *International Classification of Disease, Ninth Revision, Clinical Modification* diagnostic and procedure codes and Current Procedural Terminology codes from the VA Inpatient and Outpatient Medical SAS, and the VA/Centers for Medicare and Medicaid Services (CMS) databases. The Charlson Comorbidity Index score was calculated using the Deyo modification for administrative datasets after excluding kidney disease [23]. Medication prescribed were collected from both the VA pharmacy dispensation records and CMS Medicare Part D. For the slope analysis, we modelled medication data as a time-varying characteristic throughout the 3-year prelude period, due to the acute impact of certain medications on plasma K levels. However, for the mortality analysis where medication use was treated as a confounder, patients with at least one prescription over the 3-year prelude period were recorded as being treated with the medication. The VA research database served as a source for extracting laboratory data as previously described [24, 25]. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration approach [26]. For the slope analysis, eGFR was treated as a time-varying characteristic throughout the 3-year prelude period, to model the impact of single eGFR levels on individual K values. Whereas, for the mortality analysis, a 3-year prelude averaged outpatient eGFR was used, as in this analysis it served as a confounder in the association between the overall K slope and mortality.

Statistical analysis

Baseline patient characteristics were presented as counts (percentages) for categorical variables and mean (SD) for continuous normally distributed variables or median (25–75th percentile) for continuous skewed variables. The K slope was estimated in incrementally adjusted mixed effects models to assess the effects of the selected fixed (time-independent) and time-varying characteristics. Random effects on intercept and slope allowed for variability between patients that were not captured by the fixed effects. An unstructured covariance matrix was used for the mixed effects model. Mixed effects model assumption of linearity, homoscedasticity, and normality of residuals were visually inspected by plotting residuals vs time (independent variable), fitted K values vs residuals, and QQ-plot and

histogram, respectively, and no violations were observed. The models were conducted as 1) Model 1: unadjusted; 2) Model 2: accounted for effects of time-independent age, sex, and race; 3) Model 3: accounted for effects of time-independent age, sex, race, comorbidities; 4) Model 4: accounted for effects of time-independent age, sex, race, and comorbidities and time-varying medications; 5) Model 5: accounted for effects of time-independent age, sex, race, and comorbidities and time-varying medications and eGFR. Additionally, K slopes were cross-sectionally assessed in each 1-year period i.e. 1 year prior, 1 to 2 years prior, and 2 to 3 years prior to dialysis initiation, over the 3-year prelude period. The K slope was estimated over each 1-year period and the effect of the selected fixed effects and time-varying effects on K slope was assessed using incremental models as described above for the overall 3-year prelude period. The reported K slopes represent a population-level slope and are the average of predicted (intraindividual) K slopes for each patient. The association between intra-individual crude K slope and all-cause and cardiovascular mortality was assessed using Cox proportional hazard models and Fine and Grey competing risk regression by treating all other causes of death as competing risks, respectively. The proportional hazard assumption for the survival models was tested by visual inspection of the log (-log [survival rate]) against the log (survival time) plot and showed no violations. The crude K slope was divided into three categories as “stable” (−0.09 to 0.09 mEq/L/year); “decreasing” (≤ −0.10 mEq/L/year); and “increasing” (≥ 0.10 mEq/L/year). The stable category was used as a reference in the survival models. Follow-up in the survival models started at dialysis initiation (which also represented the end of the slope assessment period) and patients were censored at either death, loss to follow-up, transplantation date, end of follow-up (6 months following dialysis initiation) or date of administrative censoring (September 1, 2015 and July 30, 2015 for all-cause and cardiovascular mortality, respectively), whichever occurred first. Models were incrementally adjusted for the following confounders based on theoretical considerations: model 1 unadjusted; model 2 adjusted for model 1 plus age, sex, race, marital status, and smoking status; model 3 adjusted for model 2 plus comorbidities, Charlson comorbidity Index, cumulative length of hospitalizations, and body mass index (BMI) averaged over 3-year prelude period, and vascular access type; model 4 adjusted for model 3 plus medications (RAASi, SPS, loop diuretics, potassium sparing diuretics, digoxin, beta blockers, calcium channel blockers, insulin, oral hypoglycemics, calcineurin inhibitors, trimethoprim, and azole antifungals) and; model 5 adjusted for model 4 plus average eGFR and number of potassium measurements over the 3-year prelude period, and last K value preceding dialysis initiation. Restricted cubic spline models with 2 degrees of freedom were used to investigate nonlinearity in the association between K slope as a continuous variable and mortality.

The multivariable-adjusted association of crude K slope categories with mortality was assessed across subgroups of age, race, prevalent diabetes and CHF, use of SPS and RAASi, eGFR, and number of K measurements. Potential interactions between K slope categories and selected subgroups were tested by including interactions terms. Missingness was low (race [<0.01%], marital status [0.05%], smoking status [0.07%], eGFR [0.5%], BMI [0.9%], vascular access type [8.6%]) and hence missing values were not imputed. Of the 34,167 patients in our study, complete data was available for 30,703 (89.9%) for the main

multivariable-adjusted survival model (model 5); thus, all survival models (model 1–5) were conducted using these 30,703 patients.

A two-sided p-value of <0.05 was used as a threshold of statistical significance for all statistical analyses. All analyses were conducted in SAS Enterprise guide v7.1 (SAS Institute; Cary, NC) and STATA/MP Version 15 (STATA Corporation, College Station, TX). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical centers, with exemption from informed consent.

Results

Baseline characteristics

The mean (SD) age of the sample was 67.0 (10.8) years; 98% were males; 29% were African Americans; 99% had hypertension; 78% were diabetic; and 64% had CHF. The mean (SD) eGFR over the 3-year prelude was 27 (16) ml/min/1.73m^2. Patients had a median number (25^{th}-75^{th} percentile) of K measurements of 19 (8, 35), with a mean (SD) K of 4.47 (0.42) mEq/L over the 3-year prelude period. Baseline characteristics are presented in Table 1. Hyperkalemia events were observed in 68% (K >5.0 mEq/L), 41% (K >5.5 mEq/L), and 18% (K >6.0 mEq/L) of the patients (shown in Table 1).

K slope prior to dialysis initiation

In the crude 3-year model a negligible increasing K slope was observed as patients progressed towards dialysis (K slope [95% CI]: 0.008 mEq/L/year [0.0059, 0.011]; Model 1, Fig. 1; Supplementary Table 1). The K slope increase remained negligible after multivariable adjustment for demographics (model 2), comorbidities (model 3), and medications (model 4), and only after adjustment for eGFR (model 5), a reversal in the directionality of K slope was observed (adjusted K slope [95% CI]: −0.15 mEq/L/year [−0.19, −0.11]; shown in Model 5, Fig. 1; online supplementary Table 1). When assessed in each 1-year period over the 3-year prelude period, a significantly decreasing K slope was observed after multivariable adjustments in the last year preceding dialysis initiation (K slope [95% CI]: −0.21 mEq/L/year [−0.35, −0.07]; shown in online Model 5, supplementary Table 2C).

K slope prior to dialysis initiation and all-cause mortality

There were a total of 5,362 (15.7%) all-cause deaths during the 6-month period following dialysis initiation (crude mortality rate 345.9 per 1,000 patient-years; 95% CI, 336.6–355.4). Fig. 2 shows the multivariable-adjusted hazard ratios (HRs) of all-cause mortality associated with each crude K slope category. In the multivariable-adjusted model (Model 5), a decreasing K slope was associated with 8% higher risk of all-cause mortality, whereas increasing K slope was not associated with all-cause mortality (adjusted HRs [95% CI] for decreasing and increasing K slope [vs. stable slope], 1.08 [1.00–1.17] and 1.00 [0.93–1.08], respectively, as shown in model 5, Fig. 2; Supplementary Table 3).

In subgroup analyses, a similar pattern of association was observed between the K slope categories and all-cause mortality across the majority of the subgroups (as shown in online supplementary Fig. 2A). Statistically significant interaction was observed for race, with

significantly greater contributions to mortality for African Americans with decreasing slope. When assessed as a continuous variable, crude K slope had no association and a U-shaped association with all-cause mortality in unadjusted (model 1) and multivariable-adjusted (model 5) spline models, respectively (as shown in Fig. 3A and 3B).

K slope prior to dialysis initiation and cardiovascular mortality

A total of 1,915 (5.6%) cardiovascular deaths were observed during the 6-month follow up period following dialysis initiation (crude mortality rate 124.6 per 1,000 patient-years; 95% CI, 119.1–130.4). Fig. 4 shows the multivariable-adjusted subhazard ratios (SHRs) of cardiovascular mortality associated with each crude K slope category. In the multivariable-adjusted model (Model 5), neither increasing nor decreasing K slope were associated with significantly increased hazards of cardiovascular death (adjusted SHRs [95% CI] for decreasing and increasing K slope [vs. stable slope], 1.06 [0.98–1.15] and 1.02 [0.95–1.10], respectively, as shown in model 5, Fig. 4; Supplementary Table 4).

In subgroup analyses, similar patterns of association were observed between K slope categories and cardiovascular mortality in the majority of the subgroups. Statistically significant interactions were observed for CHF with significantly lower contributions to cardiovascular mortality for those without CHF and with increasing slope (as shown in Supplementary Fig. 2 B). K slope had no association and a linear-appearing association with cardiovascular mortality in unadjusted (model 1) and multivariable-adjusted (model 5) spline models, respectively (as shown in Fig. 5A and 5B).

Discussion/Conclusion

In this nationally representative cohort of US veterans with advanced NDD-CKD who transitioned to dialysis, we observed a stable K trajectory as patients progressed towards dialysis initiation. The crude K slope remained flat in spite of the significant decreases in eGFR seen in patients progressing towards initiation of renal replacement therapy. Once adjusting for potential characteristics that impact plasma potassium concentration (such as medications and eGFR levels), the adjusted K slope displayed a decrease over time, with the steepest decline observed in the last year preceding dialysis initiation. We also observed that K slope had a U-shaped association with all-cause mortality during the 6 months following dialysis initiation, with an increased risk of mortality associated especially with a declining slope (8% increase risk of all-cause mortality). Though, the hazard ratio associated with a declining K slope might not be large, it suggests that a declining K slope might be informative for physicians to assess future risk of mortality. On the other hand, K slope did not show a significant relationship with cardiovascular mortality during the 6 months following dialysis initiation.

The homeostatic potential of the kidneys in advanced CKD is severely diminished. As the kidneys progressively fail, K homeostasis is maintained by increased K excretion per reduced nephron and supplemented by gastrointestinal excretion [1]. Patients with advanced CKD have higher prevalence of comorbid chronic conditions such as hypertension and CVD, for which the recommended therapies (e.g. RAASi, diuretics and others) can have a substantial impact on plasma K concentration [27–29]. In addition to these, several other

factors impact plasma K in patients with advancing CKD, including various comorbidities (such as diabetes mellitus or CHF) and dietary K intake [1, 30]. In spite of the multiple complex changes occurring in patients with advanced NDD-CKD with failing kidneys, in our study we found remarkably stable K slopes as patients progressed to dialysis, even while the incidence of transient hyperkalemic events was extremely high (with almost 70% of patients experiencing at least one episode of mild hyperkalemia). This can be potentially explained by the interplay between kidney function, corrective pharmacotherapy, and K intake, where the mechanisms exerted by each on K levels counteract each other over a longer period, thus keeping the overall plasma K levels almost stable in the body. The decreasing slope detected after adjustment for measured confounders suggests the potential presence of unmeasured confounder(s) that could lower plasma K in patients as they progress towards ESRD. One such potential factor is decreased dietary intake of K. The development and worsening of protein-energy wasting is a known complication of patients with advancing CKD [31], which could explain a decrease in K intake over time. Concomitantly, there may also be therapeutically imposed dietary restrictions with a similar effect. Similar to the crude K slope over the 3-year period, the crude K slope in each 1-year period over the 3-year period remained flat, likely due to the counteracting interplay of kidney function, corrective pharmacotherapy, and K intake as described above. After accounting for the measured confounders, the steepest decline in K slope was observed in the last 1-year preceding dialysis as compared to other 1-year periods farther away from dialysis initiation i.e. 1 to 2 years prior and 2 to 3 years prior dialysis initiation. As discussed above, this might likely be due to unmeasured confounding such as restricted dietary K intake due to severely reduced kidney function[32] and effects of protein-energy wasting, vs. intentional dietary K restriction. The K slope in the last 1-year prior to dialysis might be the most relevant indicator of pathophysiological changes during this critical period and eventual post-dialysis outcomes.

Dyskalemias are known to be associated with increased risk of mortality in patients with CKD [5, 8, 13, 20, 33]. In our study, we observed an increased risk of all-cause mortality associated with a declining slope, independent of underlying plasma K concentration. The potential mechanisms underlying this observation are unclear. A declining slope may predispose to a higher risk of hypokalemia, which can lead to adverse events like arrhythmias, stroke, heart attack, and hypertension [29, 33–35] especially when exposed to rapidly decreasing plasma K concentrations during hemodialysis therapy [36]. However, we observed no association between K slope and cardiovascular mortality, questioning the causal relevance of declining slopes to future mortality events. Another potential explanation for the observed association is that a declining K slope may be a marker of progressively deteriorating nutritional status, which is a potent risk factor for poor outcomes in patients with NDD-CKD and ESRD [31, 37].

The assessment of K slope in advanced CKD patients transitioning to dialysis and the association with post-dialysis mortality has practical implications. Our results show that K slope remains stable in advanced CKD. This indicates that in advanced CKD stages, though patients are prone to frequent dyskalemia (especially hyperkalemia, but also hypokalemia), various pathophysiological and/or therapeutic processes tend to keep the K slope steadily flat. The hierarchical multivariable adjustment of the K slopes allows us to speculate about

the mechanisms that are responsible for the observed slopes. The finding that adjustment for longitudinal eGFR resulted in a negative K slope suggests that the stability of K over time may not have been simply a result of the measured therapeutic interventions (e.g. K lowering medications), but could have also been affected by unmeasured factors such as a decrease in K intake over time. The latter could occur as a result of intentional dietary K restriction and/or as a consequence of uremia-associated decrease in appetite. Current expert opinions [27, 32, 38, 39] recommend dietary K restriction in advanced CKD due to higher risk of acute hyperkalemia. However, evidence suggesting a robust relationship between dietary K intake and plasma K concentration is weak and needs to be further explored [32, 40]. Notwithstanding the potential that lower K intake could contribute to the maintenance of stable K levels over time in patients with progressive loss of kidney function, the extent to which dietary interventions are a necessary intervention in the broader CKD population remains unclear. Such interventions could be helpful to preserve K homeostasis, but in some cases they could also result in transient hypokalemic events and in a declining K trajectory. The association of hypokalemia with poorer outcomes has been described repeatedly in previous studies [5, 8, 10, 12, 33], and our findings now suggest that a declining K trajectory also has a robust association with mortality following dialysis initiation. Our results suggest that avoiding a declining K trajectory in patients with advanced CKD may be beneficial, but the effect of dietary and other manipulations of K homeostasis and K trajectory on clinical outcomes will need to be examined in prospective clinical trials, which would directly inform clinical practice. Another potential practical implication of our findings concerning the higher mortality associated with declining K slopes, is the incorporation of K slopes in models predicting future mortality outcomes, adding to the predictive ability of established abnormalities of K homeostasis.

To our knowledge, this is the first study that assessed the K slope and associated outcomes in a large cohort of advanced NDD-CKD patients. However, our study results need to be interpreted in light of several limitations. First, we used observational data, hence, we cannot infer causality but only associations. Second, the cohort consisted of predominantly male US veterans (98%), and thus the results may not be generalizable to women or broader general population. Third, we used pre-dialysis assessment of K slope in a cohort of incident dialysis patients, and thus survivorship bias prevents us to extending any of our conclusions to patients with advanced CKD who did not reach ESRD. Finally, due to the nature of the study, we cannot eliminate the possibility of unmeasured confounders such as a lack of data about dietary K intake and other nutritional markers.

In conclusion, in patients with advanced NDD-CKD transitioning to dialysis the average intra-individual plasma K trajectory is remarkably stable, in spite of frequent occurrences of transient hyperkalemic episodes. A declining plasma K slope is associated with increased risk of all-cause mortality, suggesting that K slope may serve as a prognostic marker for future clinical events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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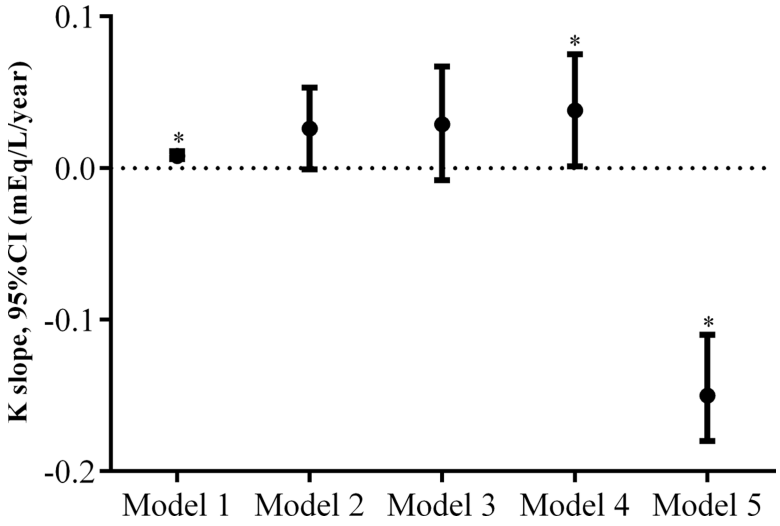


Fig 1.

Potassium slope over 3-year prelude period prior to dialysis initiation.

Data are presented as mean (95% CI) unless otherwise stated.

Models are as follows: model 1: unadjusted; model 2: model 1 plus age, sex, race; model 3: model 2 plus comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, lung disease, peptic ulcer disease, paraplegia/hemiplegia, anemia, atrial fibrillation, hypertension, ischemic heart disease, diabetes, liver disease, malignancies); model 4: model 3 plus time-varying medications (RAASi, SPS, loop diuretics, potassium sparing diuretics, beta blockers, calcineurin inhibitors, azole antifungals, insulin, oral hypoglycemics, calcium channel blockers, and digoxin); model 5: model 4 plus time-varying eGFR.

* $p < 0.05$

CI: confidence interval; eGFR: estimated glomerular filtration rate; K: potassium; RAASi: renal-angiotensin-aldosterone system inhibitors; SPS: Na-polystyrene sulphonate

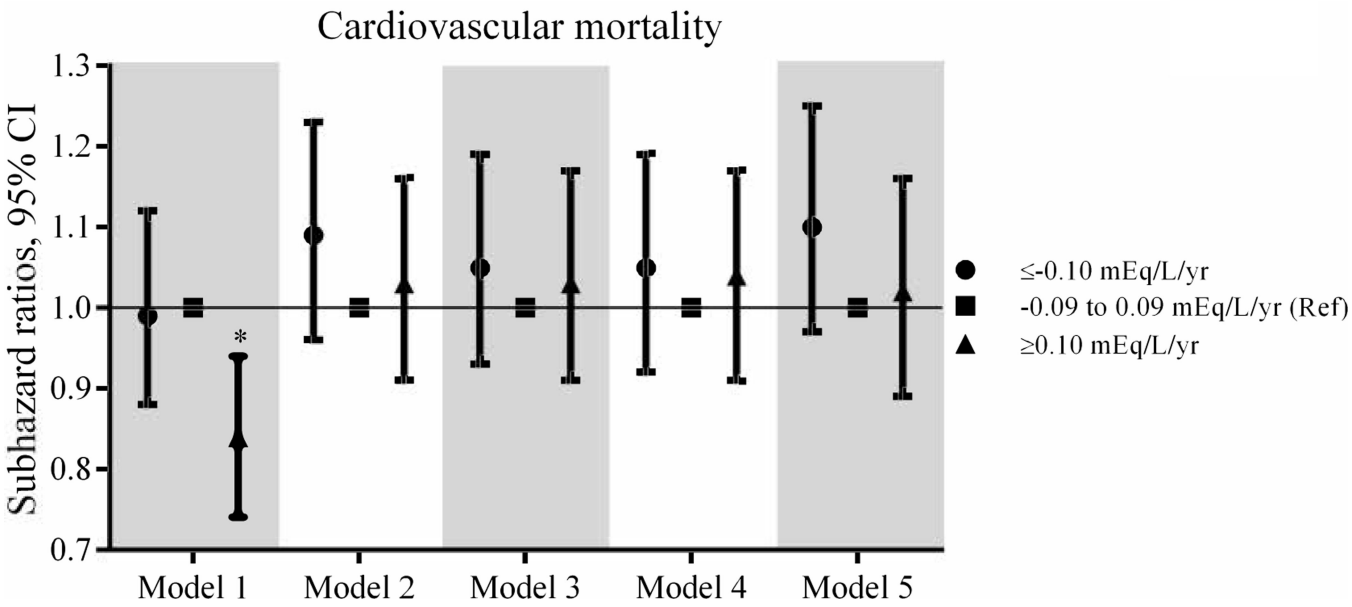
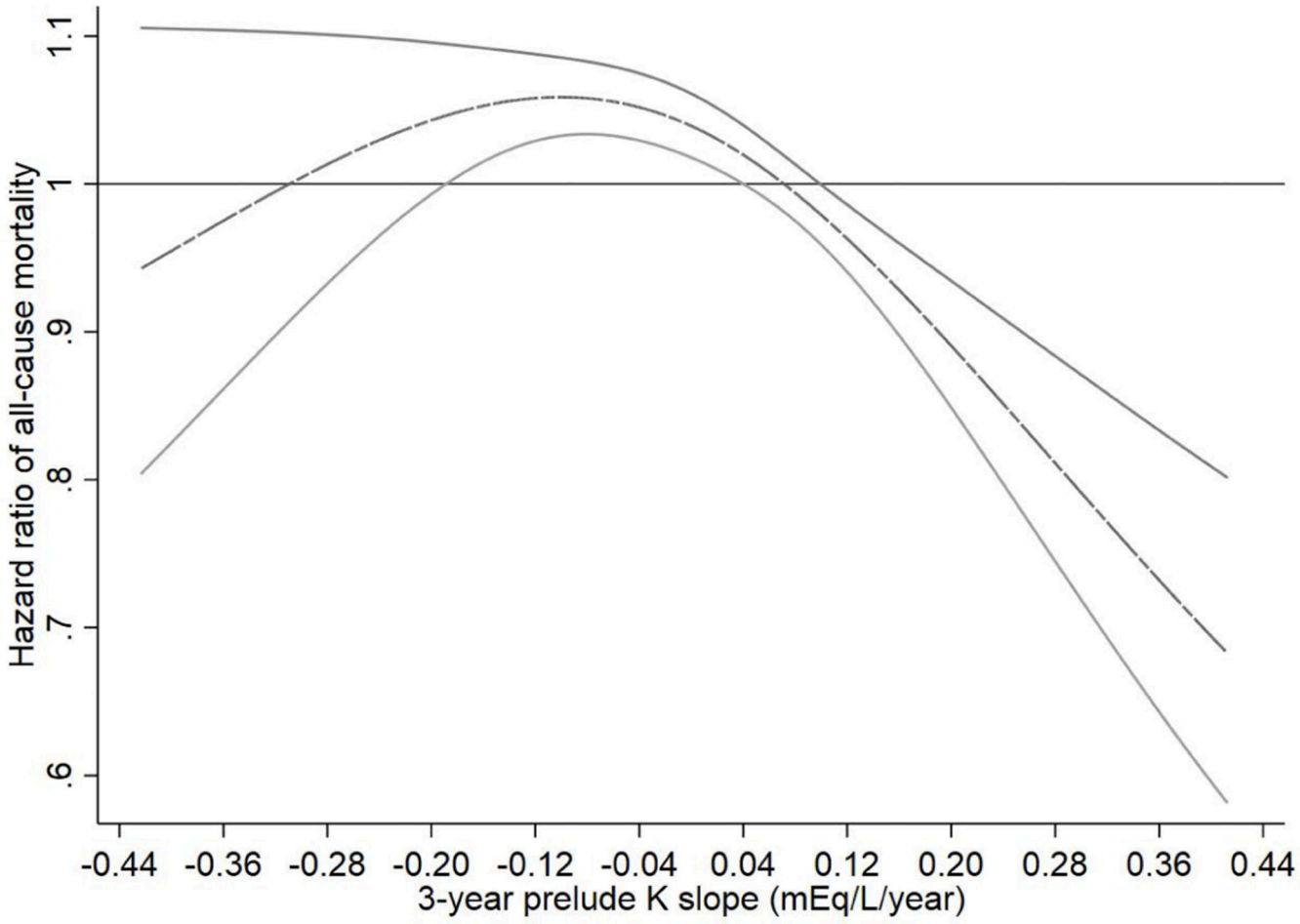


Fig 2.

Association of crude potassium slope categories with all-cause mortality during 6 months following dialysis initiation.

Models are as follows: model 1: unadjusted; model 2: adjusted for variables in model 1 plus demographics (age, sex, race, marital status, smoking status); model 3: adjusted for variables in model 2 plus comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, lung disease, peptic ulcer disease, paraplegia/hemiplegia, anemia, atrial fibrillation, hypertension, ischemic heart disease, diabetes, liver disease, malignancies), Charlson comorbidity index, cumulative length of hospitalizations and BMI over the 3-year prelude period, and vascular access type; model 4: adjusted for variables in model 3 plus medications (RAASi, SPS, loop diuretics, potassium sparing diuretics, digoxin, beta blockers, calcium channel blockers, insulin, oral hypoglycemics, calcineurin inhibitors, trimethoprim, azole antifungals); model 5: adjusted for variables in model 4 plus average eGFR and number of K measurements over the 3-year period, and last K value prior to dialysis initiation.

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; K: potassium; RAASi: renal-angiotensin-aldosterone system inhibitors; SPS: Na-polystyrene sulphonate



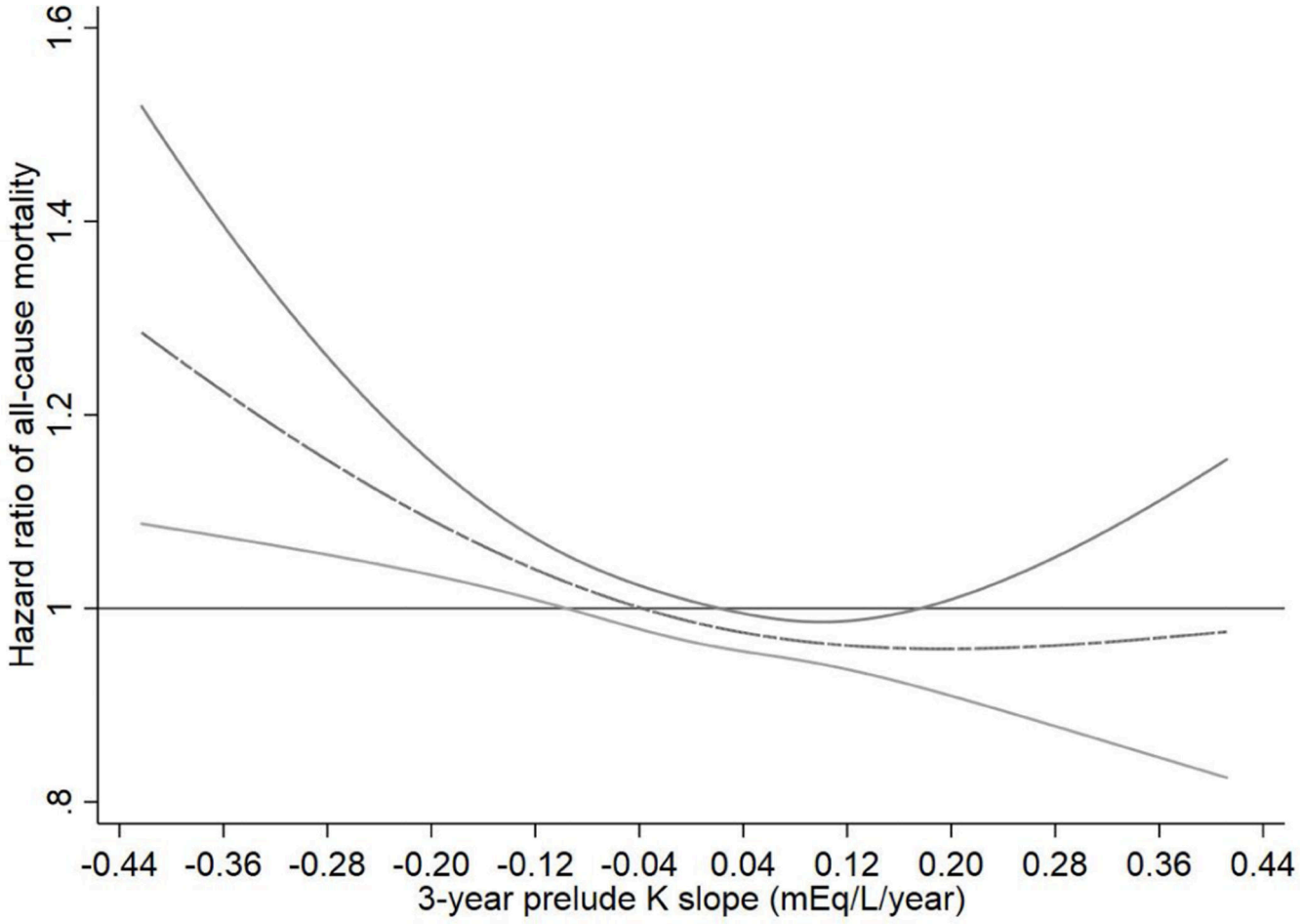


Fig 3.

Association of crude potassium slope over 3-year prelude with all-cause mortality during 6 months following dialysis initiation in (A) unadjusted and (B) multivariable-adjusted models.

Dashed and solid lines represent hazard ratio and 95% confidence interval, respectively.

The x-axis shows potassium slope levels, trimmed at 0.5% and 99.5%.

Panel A is unadjusted association between crude K slope and all-cause mortality

Panel B is multivariable-adjusted association between crude K slope and all-cause mortality

Multivariable models adjusted for age, sex, race, marital status, smoking status, comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, lung disease, peptic ulcer disease, paraplegia/hemiplegia, anemia, atrial fibrillation, hypertension, ischemic heart disease, diabetes, liver disease, malignancies), Charlson comorbidity index, cumulative length of hospitalization and BMI over the 3-year prelude period, vascular access type, medications (RAASi, SPS, loop diuretics, potassium sparing diuretics, digoxin, beta blockers, calcium channel blockers, insulin, oral hypoglycemics, calcineurin inhibitors, trimethoprim, azole antifungals), average eGFR and number of K measurements over the 3-year period, and last K value prior to dialysis initiation.

BMI: body mass index; eGFR: estimated glomerular filtration rate; K: potassium; RAASi: renal-angiotensin-aldosterone system inhibitors; SPS: Na-polystyrene sulphonate

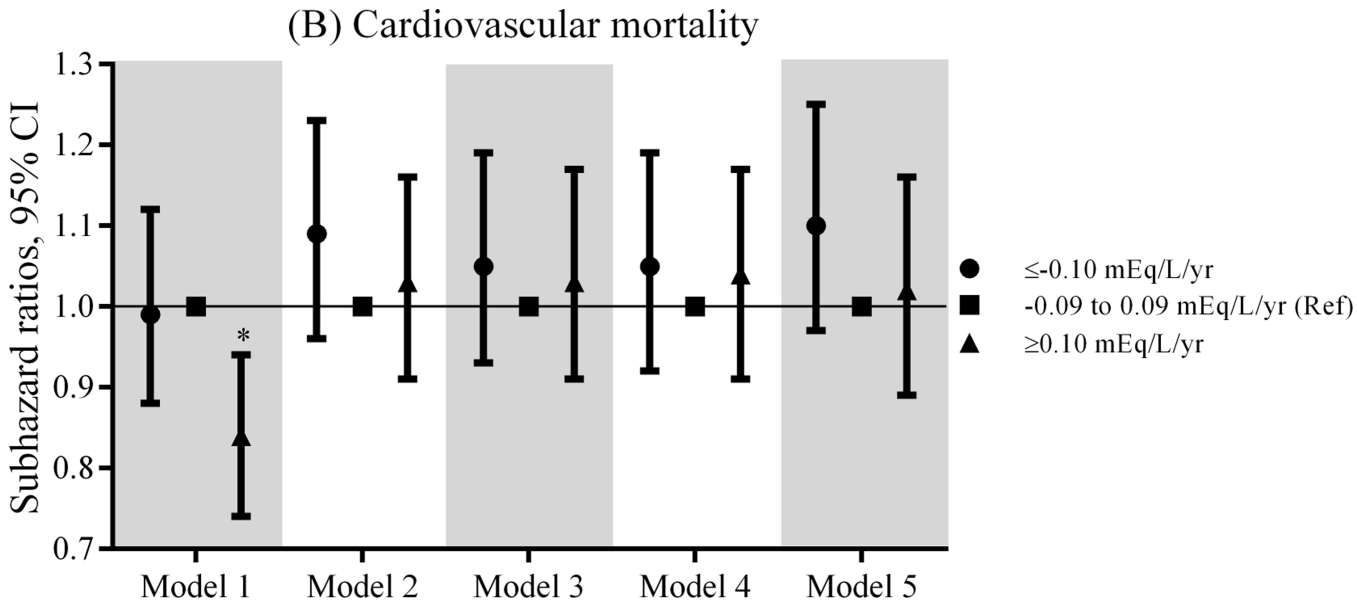
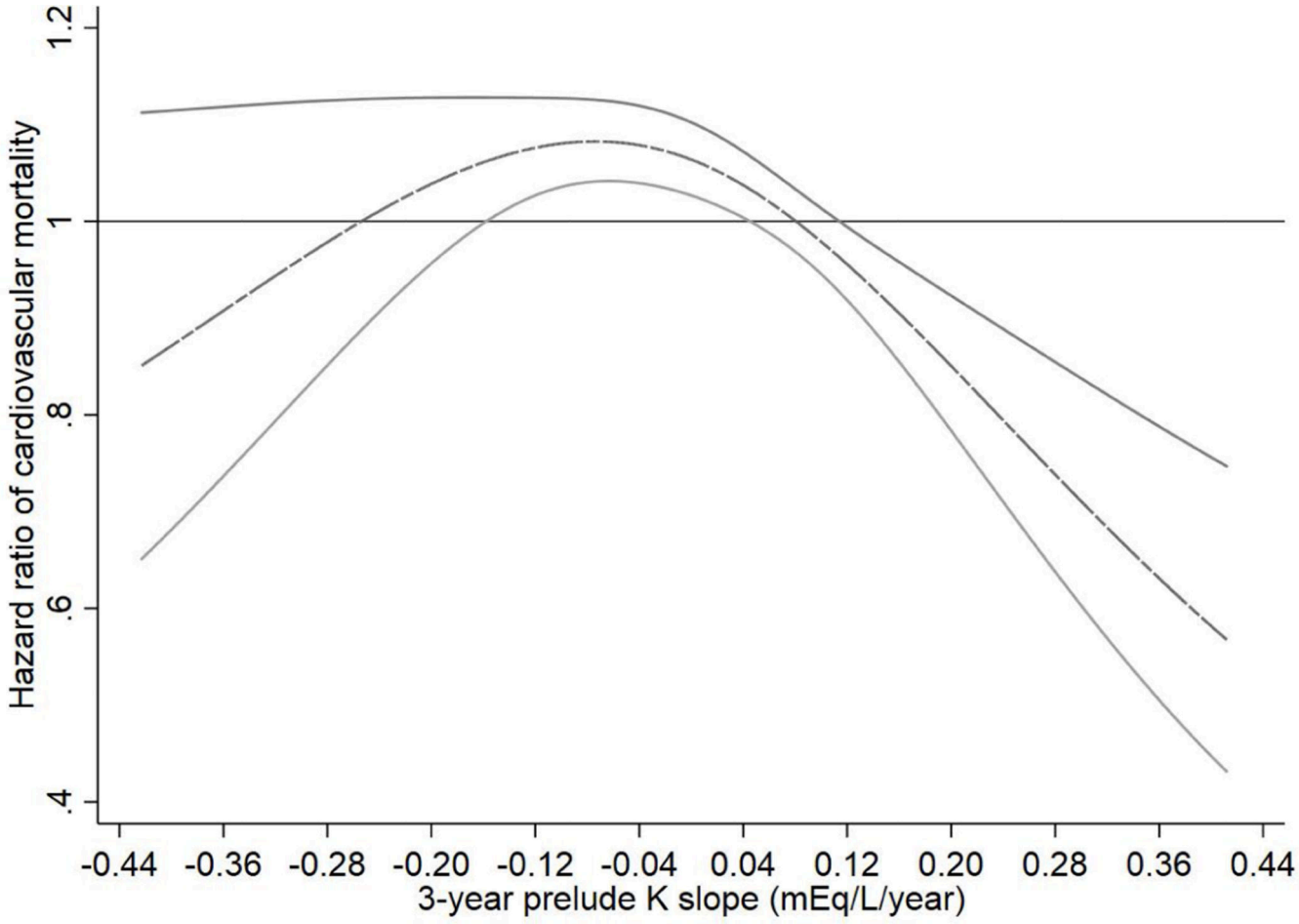


Fig 4.

Association of crude potassium slope categories with cardiovascular mortality during 6 months following dialysis initiation.

Models are as follows: model 1: unadjusted; model 2: adjusted for variables in model 1 plus demographics (age, sex, race, marital status, smoking status); model 3: adjusted for variables in model 2 plus comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, lung disease, peptic ulcer disease, paraplegia/hemiplegia, anemia, atrial fibrillation, hypertension, ischemic heart disease, diabetes, liver disease, malignancies), Charlson comorbidity index, cumulative length of hospitalizations and BMI over the 3-year prelude period, and vascular access type; model 4: adjusted for variables in model 3 plus medications (RAASi, SPS, loop diuretics, potassium sparing diuretics, digoxin, beta blockers, calcium channel blockers, insulin, oral hypoglycemics, calcineurin inhibitors, trimethoprim, azole antifungals); model 5: adjusted for variables in model 4 plus average eGFR and number of K measurements over the 3-year period, and last K value prior to dialysis initiation.

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; K: potassium; RAASi: renal-angiotensin-aldosterone system inhibitors; SPS: Na-polystyrene sulphonate



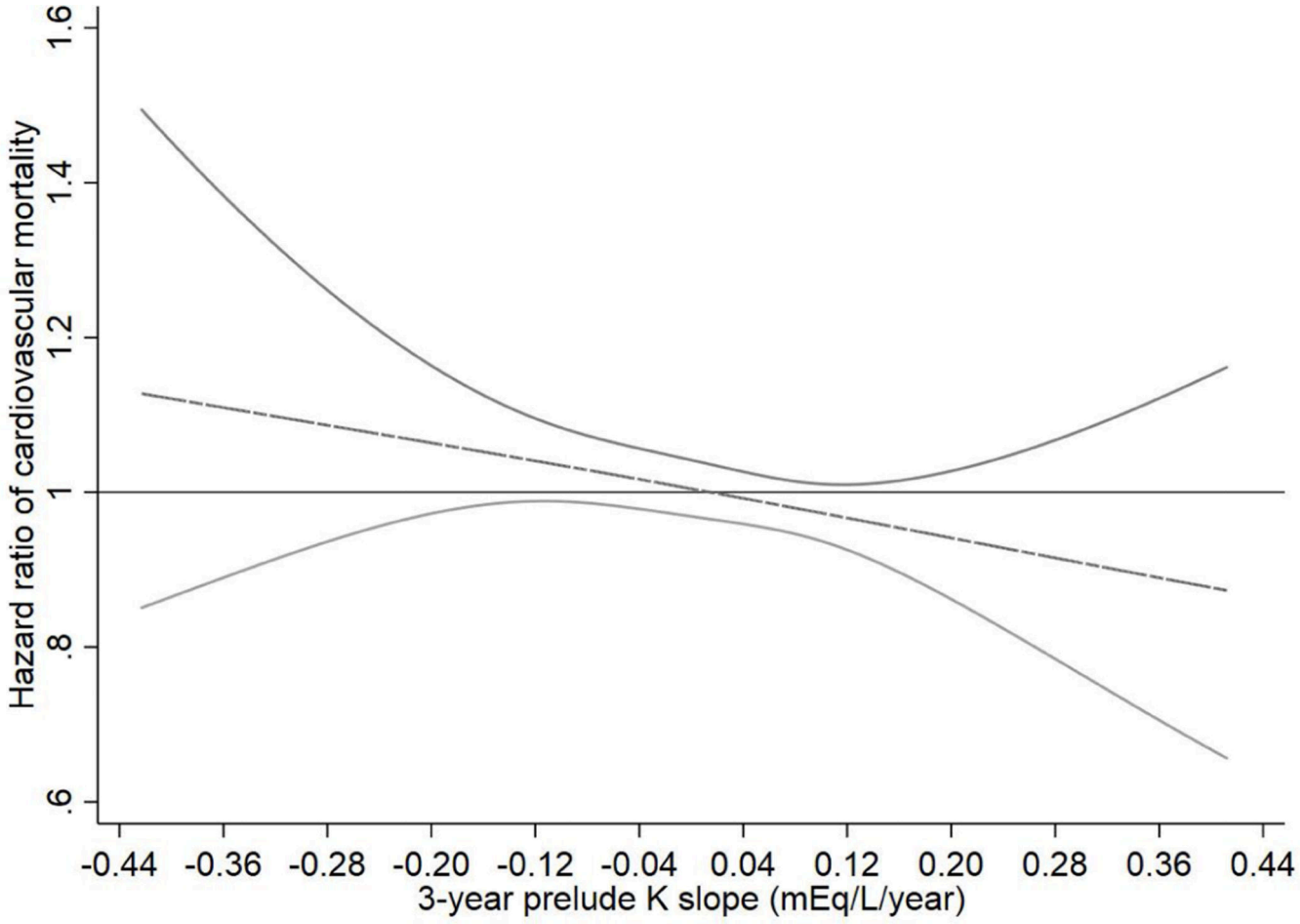


Fig 5.

Association of crude potassium slope over 3-year prelude with cardiovascular mortality during 6 months following dialysis initiation in (A) unadjusted and (B) multivariable-adjusted models.

Dashed and solid lines represent hazard ratio and 95% confidence interval, respectively.

The x-axis shows potassium slope levels, trimmed at 0.5% and 99.5%.

Panel A is unadjusted association between crude K slope and cardiovascular mortality

Panel B is multivariable-adjusted association between crude K slope and cardiovascular mortality

Multivariable models adjusted for age, sex, race, marital status, smoking status, comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, lung disease, peptic ulcer disease, paraplegia/hemiplegia, anemia, atrial fibrillation, hypertension, ischemic heart disease, diabetes, liver disease, malignancies), Charlson comorbidity index, cumulative length of hospitalization and BMI over the 3-year prelude period, vascular access type, medications (RAASi, SPS, loop diuretics, potassium sparing diuretics, digoxin, beta blockers, calcium channel blockers, insulin, oral hypoglycemics, calcineurin inhibitors, trimethoprim, azole antifungals), average eGFR and number of K measurements over the 3-year period, and last K value prior to dialysis initiation.

BMI: body mass index; eGFR: estimated glomerular filtration rate; K: potassium; RAASi: renal-angiotensin-aldosterone system inhibitors; SPS: Na-polystyrene sulphonate

Table 1.

Patient baseline characteristics over the 3-year prelude period.

Characteristic	All (n=34,167)
Age (years)	67 (10.8)
Sex (male)	33,495 (98)
Race	
White	23,309 (68.2)
Black	9,885 (28.9)
Other	971 (2.8)
Marital status (married)	18,846 (55.1)
Smoking Status	
Current	12,247 (35.8)
Past	11,351 (33.2)
Never	10,544 (30.8)
Comorbidities	
Congestive heart failure	21,722 (63.6)
Diabetes mellitus	26,488 (77.5)
Peripheral vascular disease	18,099 (52.9)
Cerebrovascular disease	15,011 (43.9)
Lung disease	19,135 (56)
Peptic ulcer disease	3,702 (10.8)
Hypertension	33,848 (99.1)
Ischemic heart disease	22,790 (66.7)
Malignancies	10,651 (31.2)
Liver disease	6,736 (19.7)
Paraplegia/Hemiplegia	1,981 (5.8)
Anemia	28,743 (84.1)
Atrial fibrillation	8,318 (24.3)
Charlson comorbidity index	5 (3, 7)
Cumulative length of hospitalizations (days)	9 (1, 24)
Body mass index (kg/m^2)	29.6 (6.2)
Vascular access type	
Arteriovenous fistula	6,949 (20.3)
Arteriovenous graft	805 (2.4)
Catheter	23,313 (68.2)
Other	165 (0.5)
Missing	2935 (8.6)
Medications	
RAASi	26,898 (78.7)
SPS	9,003 (26.3)
Loop diuretics	27,320 (79.9)
Potassium sparing diuretics	5,620 (16.4)

Characteristic	All (n=34,167)
NSAID	249 (0.7)
Digoxin	2,447 (7.2)
Beta Blockers	28,321 (82.9)
Calcium channel blockers	27,020 (79.1)
Insulin	18,220 (53.3)
Oral hypoglycemics	13,224 (38.7)
Mannitol	160 (0.5)
Suxamethonium	30 (0.1)
Calcineurin inhibitors	694 (2.0)
Trimethoprim	1,859 (5.4)
Pentamidine	19 (0.1)
Penicillin G	87 (0.2)
Azole antifungals	8,113 (23.7)
Laboratory parameters[a]	
K (mEq/L)	4.47 (0.42)
Last K value[b] (mEq/L)	4.49 (0.66)
eGFR (mL/min/1.73m^2)	27 (16)
Number of K measurements	19 (8, 35)
At least 1 dyskalemia event	
K < 3.5 mEq/L	10,472 (30.7)
K > 5.0 mEq/L	23,320 (68.3)
K > 5.5 mEq/L	14,038 (41.1)
K > 6.0 mEq/L	6,081 (17.8)
Percentage dyskalemia events[d]	
K < 3.5 mEq/L	6.1%
K > 5.0 mEq/L	16.9%
K > 5.5 mEq/L	5.2%
K > 6.0 mEq/L	1.3%
Distribution of dyskalemia events[d]	
K < 3.5 mEq/L	0 (0–1)
K > 5.0 mEq/L	2 (0–6)
K > 5.5 mEq/L	0 (0–2)
K > 6.0 mEq/L	0 (0–0)

Data presented as n (%), mean (SD), or median (25^{th}–75^{th} percentile), unless noted otherwise

[a] mean (SD) over 3-year prelude period, unless noted otherwise

[b] potassium value closest to dialysis

[d] denominator n= 948,604 i.e. total number of plasma potassium measures for all patients over the 3-year prelude period.

eGFR: estimated glomerular filtration rate; K: plasma potassium; NSAID: nonsteroidal anti-inflammatory drugs; RAASi: renin-angiotensin-aldosterone system inhibitors; SD: standard deviation; SPS: Na-polystyrene sulphonate