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Laxative Use and Risk of Dyskalemia in Patients with Advanced CKD Transitioning to Dialysis

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ABSTRACT

Background Patients with advanced CKD experience increased intestinal potassium excretion. This compensatory mechanism may be enhanced by laxative use; however, little is known about the association of laxative use with risk of dyskalemia in advanced CKD.

Methods Our study population encompassed 36,116 United States veterans transitioning to ESKD from 2007 to 2015 with greater than or equal to one plasma potassium measurement during the last 1-year period before ESKD transition. Using generalized estimating equations with adjustment for potential confounders, we examined the association of time-varying laxative use with risk of dyskalemia (*i.e.*, hypokalemia [potassium <3.5 mEq/L] or hyperkalemia [>5.5 mEq/L]) versus normokalemia (3.5–5.5 mEq/L) over the 1-year pre-ESKD period. To avoid potential overestimation of dyskalemia risk, potassium measurements within 7 days following a dyskalemia event were disregarded in the analyses.

Results Over the last 1-year pre-ESKD period, there were 319,219 repeated potassium measurements in the cohort. Of these, 12,787 (4.0%) represented hypokalemia, and 15,842 (5.0%) represented hyperkalemia; the time-averaged potassium measurement was 4.5 mEq/L. After multivariable adjustment, time-varying laxative use (compared with nonuse) was significantly associated with lower risk of hyperkalemia (adjusted odds ratio [aOR], 0.79; 95% confidence interval [95% CI], 0.76 to 0.84) but was not associated with risk of hypokalemia (aOR, 1.01; 95% CI, 0.95 to 1.07). The results were robust to several sensitivity analyses.

Conclusions Laxative use was independently associated with lower risk of hyperkalemia during the last 1-year pre-ESKD period. Our findings support a putative role of constipation in potassium disarrays and also support (with a careful consideration for the risk-benefit profiles) the therapeutic potential of laxatives in hyperkalemia management in advanced CKD.

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Potassium is the most abundant cation in the human body, with approximately 2% being located in extracellular fluid and 98% being in the intracellular compartment, and it plays a crucial role in cell membrane electrophysiology.[1,2] The normal potassium homeostasis is maintained primarily by the kidneys, and hence, patients with CKD, particularly those with its advanced stages, are at a greater risk of developing dyskalemias (*i.e.*, hypo- and hyperkalemia, especially the latter) and potentially life-threatening complications, such as cardiac arrhythmias.[2]

Under physiologic circumstances, dietary potassium is absorbed mostly in the small intestine, and whereas approximately 90% of potassium is excreted by the kidneys, the remaining 10% is accounted for by intestinal excretion *via* the large conductance calcium-activated potassium channel

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subunit-α1 (also known as BK channel) expressed on the apical surface of colonic epithelial cells.[3] When the kidney function declines and the dietary potassium load cannot be fully excreted by the kidneys, the gut increases its potassium excretion primarily by enhancing potassium secretion through an increase of the BK channel expression, rather than by reducing dietary potassium absorption, and thereby becomes especially important for maintaining potassium homeostasis.[4,5] In patients with ESKD receiving hemodialysis treatment, for example, a series of potassium balance studies have demonstrated that potassium excretion in stool was three times higher than in healthy controls, reaching approximately 80% of dietary potassium (up to 3000 mg/d) for some patients on hemodialysis.[6] It is, therefore, conceivable that slow intestinal transit time and impaction of feces can enhance intestinal potassium absorption, leading to hyperkalemia, whereas conditions with faster intestinal transit time induced sometimes by laxatives can reduce potassium absorption, leading to hypokalemia. These conditions are particularly relevant for patients with advanced CKD, who often experience problems with constipation (due in part to low-fiber diet to avoid hyperkalemia), which is usually severe and requires treatment with pharmacologic agents.[7–9]

Despite the clinical relevance and the plausible link between laxative use and potassium disturbances among patients with advanced stages of CKD, to the best of our knowledge no previous studies have investigated the association of laxative use with the risk of hypo- or hyperkalemia in these patients. In this study, we hypothesized that laxative use will be independently associated with higher risk of hypokalemia and lower risk of hyperkalemia in patients with advanced CKD. To test this hypothesis, we examined the association of laxative use with the risk of dyskalemia during the last 1 year before transition to ESKD using a clinically relevant, large, nationally representative cohort of United States veterans with advanced nondialysis-dependent CKD (NDD-CKD) transitioning to dialysis.

Significance Statement

Intestinal potassium excretion is increased in patients with advanced CKD. It is possible that this compensatory mechanism is enhanced by laxative use, but little is known about the association of laxative use with risk of dyskalemias in advanced CKD. In a cohort of 36,116 United States military veterans who transitioned to ESKD, the authors found that time-varying laxative use was significantly associated with lower risk of hyperkalemia (potassium >5.5 mEq/L) but was not associated with risk of hypokalemia (potassium <3.5 mEq/L) during the last year prior to ESKD. These findings suggest a putative role of constipation in potassium disarrays and also support (with a careful consideration for risks and benefits) the therapeutic potential of laxatives for hyperkalemia management in advanced CKD.

METHODS

Study Population

We used longitudinal data from the United States Renal Data System (USRDS) Transition of Care in Chronic Kidney Disease (TC-CKD) study, a nationally representative, retrospective cohort study of United States veterans transitioning to ESKD.[10–13] In this study, 102,477 United States veterans who transitioned to ESKD from October 1, 2007 to March 31, 2015 (the maximum time window of ESKD transition available in the TC-CKD) were identified from USRDS as a source population. Among these, 60,128 patients with at least one plasma potassium (K^+) measurement recorded at any Veterans Affairs (VA) facility prior to dialysis initiation were identified. After excluding patients without any K^+ measurements during the last 1-year pre-ESKD period (*i.e.*, evaluation period; n=14,409), those who did not have any medication dispensation information during the same 1-year evaluation period (n=1077), and those with missing covariates including time-varying eGFR corresponding to repeated K^+ measurements (n=8526), 36,116 patients were included in the final analytical cohort (Supplemental Figure 1). Among patients with any laboratory data during the last 1-year pre-ESKD period, 95.4% had at least one K^+ measurement.

Exposure Variable

The primary exposure of interest was laxative use during the last 1-year pre-ESKD period. Given the time-varying nature of laxative use (due in part to symptom improvement and/or adverse events, such as diarrhea) and its potential short-term influence on K^+ levels, laxative use was treated as a time-varying exposure in this study. Time-varying laxative use was defined on the basis of the laxative exposure status at the time of each K^+ measurement during the last 1-year pre-ESKD period by taking into account the days' supply of each dispensed laxative (*i.e.*, whether the day of K^+ measurement was covered by any dispensed laxative). Laxative agents were ascertained according to dispensation information for the following six types of laxatives: stool softeners, hyperosmotics, stimulants, bulk formers, chloride channel activator, and lubricants (Supplemental Table 1).

Covariates

Patient demographic characteristics, including age, sex, and self-identified race, were ascertained from the following three national databases: USRDS, VA, and Centers for Medicare and Medicaid Services (CMS). Data on marital and smoking status were obtained from VA records only.[14–16] Preexisting comorbidities were identified from the VA Inpatient and Outpatient Medical SAS Datasets using the International Classification of Disease, Ninth Revision, Clinical Modification diagnostic and procedure codes and Current Procedural Terminology codes, as well as from VA/CMS data.[17] The Charlson Comorbidity Index score was calculated using the Deyo modification for administrative datasets, without including kidney disease.[18] Cardiovascular disease was defined as the presence of

diagnostic codes for coronary artery disease, angina, myocardial infarction, or cerebrovascular disease.[19] Bowel disorders were defined as the presence of diagnostic codes for inflammatory bowel disease, irritable bowel syndrome, or diarrhea.[20] Dispensed medications were ascertained in both inpatient and outpatient settings sourced from CMS Medicare Part D and VA pharmacy dispensation records,[21] and select medications were treated as time-varying covariates similar to the use of laxatives (as detailed above). For baseline description, patients with at least one dispensation over the 1-year pre-ESKD evaluation period were recorded as treated with the medication. Data on body mass index and laboratory tests (*i.e.*, K^+ and eGFR) were obtained from VA research databases as previously described,[22–24] and their time-averaged values (defined as the average of each covariate during the 1-year pre-ESKD period) were used only to characterize patients. Time-varying eGFR was defined using eGFR values on the same day as K^+ measurements and used for the analyses. The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation using serum creatinine and demographic data.[25] In-hospital AKI was defined as an absolute increase in serum creatinine of ≥0.3 mg/dl within 48 hours or a ≥50% increase in serum creatinine from its baseline relative to each hospitalization event.[26] All patients in the final analytical dataset (n=36,116) had complete covariate data.

Outcome Assessment

The primary outcome of interest was risk of dyskalemia, assessed at each time point of repeated K^+ measurements with variable intervals of time during the last 1-year pre-ESKD period. On the basis of *a priori* information and clinical and biologic relevance of dyskalemia events that can recur in the same patient with advanced CKD,[27] dyskalemia was defined as K^+ levels of either <3.5 mEq/L (hypokalemia) or >5.5 mEq/L (hyperkalemia; versus 3.5–5.5 mEq/L [normokalemia]) and treated as a repeated, time-varying multinomial outcome (*i.e.*, hypokalemia, normokalemia [reference], and hyperkalemia). Because multiple sequential abnormal K^+ values in a short period of time can belong to the same dyskalemia event, which may lead to overestimation of dyskalemia risk associated with laxative use, we disregarded K^+ measurements within 7 days following a dyskalemia event in the analyses.

Statistical Analyses

Baseline patient characteristics were summarized for the entire analytical population (n=36,116) and by laxative use status, and they are presented as number (percentages) for categorical variables and mean (SD) for continuous variables with a normal distribution or median (interquartile interval [IQI]) for those with a skewed distribution. Differences between groups were assessed using independent samples t tests or Mann–Whitney U tests and chi-squared tests for continuous and categorical variables, respectively, as appropriate. The distributions of the number of K^+ measurements and the time interval between each K^+ measurement and dialysis initiation were visually depicted using a histogram. Because our primary interest was to examine the association between time-varying laxative use and short-term risk of dyskalemia assessed at each time point of repeated K^+ measurements with variable intervals of time during the last 1-year pre-ESKD period, we used multivariable-adjusted generalized estimating equation models with an independent working correlation structure, accounting for various potential confounders. Models were incrementally adjusted for the following fixed and time-varying characteristics on the basis of theoretical considerations and their availability in this study. Model 1 was unadjusted. Model 2 was adjusted for age, sex, race, and marital status. Model 3 additionally accounted for smoking status; body mass index averaged over the 1-year pre-ESKD period; comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders, and constipation); Charlson Comorbidity Index; and cumulative length of hospital stay, in-hospital AKI, number of medical visits, and number of K^+ measurements during the 1-year pre-ESKD period. Model 4 additionally included time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium-sparing diuretics, calcium channel blockers, β-blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and β2-agonists), and model 5 further accounted for time-varying eGFR.

We performed several sensitivity analyses to evaluate the robustness of our main findings. In order to enrich our sample, we included patients with missing covariates (n=8526) and repeated our main analysis after imputing missing data (n=44,642 after including those with missingness). Missing baseline covariates were imputed using multiple imputation, whereas missing time-varying eGFR values corresponding to repeated K^+ measurements were imputed by estimating the eGFR values on the basis of intraindividual eGFR slopes calculated from linear mixed effects models using all available eGFR measured over the last 1-year pre-ESKD period. The association between time-varying laxative use and dyskalemia was also examined in a time-to-event model using a repeated events survival analysis (*i.e.*, Wei–Lin–Weissfeld marginal model).[28] We also examined the laxative-dyskalemia association on the basis of data at the first K^+ measurement during the last 1-year pre-ESKD period using multivariable-adjusted logistic regression models. To examine the association of laxative use with dyskalemia across a wider range of K^+ levels, the main analysis was repeated using more granular K^+ categories (*i.e.*, <3.5, 3.5 to <4.0, 4.0 to <4.5, 4.5 to <5.0 [reference], 5.0 to <5.5, 5.5 to <6.0, and ≥6.0 mEq/L). The main analysis was also repeated in subgroups of patients categorized by age, race, diabetes mellitus, congestive heart failure, renin-angiotensin system inhibitor use, sodium polystyrene sulfonate use, time-averaged eGFR, and number of K^+ measurements during the 1-year pre-ESKD period. Potential interactions

were formally tested by including interaction terms. Additionally, to assess the association of laxative use with dyskalemia across different types of laxatives, we identified three major types of laxatives (*i.e.*, stool softeners, hyperosmotics, and stimulants, irrespective of concomitant use of other laxatives), and the association between time-varying use of laxative of interest and dyskalemia was examined in the main multivariable-adjusted generalized estimating equation models.

A two-sided *P* value of 0.05 was used as a threshold of statistical significance for all analyses. All analyses were conducted in SAS Enterprise guide v7.1 (SAS Institute; Cary, NC). The study was approved by the institutional review boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

RESULTS

Patient Characteristics

Baseline patient characteristics in the entire analytical cohort and those in patients categorized by laxative use status are summarized in Table 1. Overall, the mean (SD) age was 69.7 (11.1) years; 97.9% of patients were men, 28.5% were Black, and 75.2% were diabetic. Over the last 1-year pre-ESKD period, the median (IQI) eGFR was 16.0 (11.8–23.9) ml/min per 1.73 m^2; and the mean (SD) time-averaged K^+ was 4.5 (0.5) mEq/L, with a median (IQI) of five (2–12) K^+ measurements per patient (Supplemental Figure 2). The median (IQI) time interval between each K^+ measurement and dialysis initiation was 127 (41–238) days (Supplemental Figure 3). Laxatives were dispensed for 40.5% of patients, whereas 22.5% had a diagnosis of constipation. Compared with patients without laxative use, those with laxative use were younger, more likely to be Black, less likely to be married, and more likely to use all medications examined except trimethoprim. They also had longer cumulative hospital stay, higher numbers of medical visits and K^+ measurements, and greater prevalence of in-hospital AKI during the last 1-year pre-ESKD period (Table 1).

Laxative Use and Dyskalemia

Over the last 1-year pre-ESKD period, there were a total of 319,219 repeated K^+ measurements in the cohort, of which 12,787 (4.0%) were <3.5 mEq/L (*i.e.*, hypokalemia) and 15,842 (5.0%) were >5.5 mEq/L (*i.e.*, hyperkalemia). Figure 1 and Supplemental Table 2 show the association of time-varying laxative use with dyskalemia during the last 1-year pre-ESKD period. In the crude model (*i.e.*, model 1), the use (versus nonuse) of laxatives was not associated with risk of hypokalemia (odds ratio [OR], 0.99; 95% confidence interval [95% CI], 0.95 to 1.06) but was associated with lower risk of hyperkalemia (OR, 0.68; 95% CI, 0.65 to 0.72). After adjustment for potential confounders, the association with lower risk of hyperkalemia was somewhat attenuated but remained statistically significant, whereas no significant association was observed for the risk of hypokalemia (adjusted ORs of hypo- and hyperkalemia, 1.01; 95% CI, 0.95 to 1.07 and 0.79; 95% CI, 0.76 to 0.84, respectively, in model 5) (Figure 1, Supplemental Table 2). Results were largely similar even after accounting for missing data, using a repeated events survival analysis, and using a logistic regression analysis on the basis of data at the first K^+ measurement during the last 1-year pre-ESKD period (Supplemental Tables 3–5). When we repeated our main analysis using more granular K^+ categories, the $K^+<3.5$-mEq/L (versus 4.5- to <5.0-mEq/L) category showed no statistical significance (adjusted OR, 1.04; 95% CI, 0.97 to 1.10), but there was a graded association between time-varying laxative use and risk of hyperkalemia (adjusted ORs of K^+ 5.5 to <6.0 and ≥ 6.0 mEq/L [versus 4.5 to <5.0 mEq/L], 0.81; 95% CI, 0.76 to 0.85 and 0.79; 95% CI, 0.73 to 0.86, respectively) (Supplemental Table 6).

In subgroup analyses, the trend of association between time-varying laxative use and risk of dyskalemia was qualitatively similar across subgroups, with a few notable exceptions (Figure 2). The risk of hypokalemia was marginally higher among patients ≥ 65 years (adjusted OR, 1.08; 95% CI, 1.00 to 1.16), whereas a marginally lower risk of hypokalemia was observed in those <65 years (adjusted OR, 0.90; 95% CI, 0.83 to 0.99) with a statistically significant interaction. In addition, the association between laxative use and risk of hyperkalemia was significantly modified by the number of K^+ measurements, with a significant contribution of laxative use to the lower hyperkalemia risk only among patients with five or more K^+ measurements (Figure 2). When the association of time-varying laxative use with risk of dyskalemia was assessed separately for three different types of laxatives (*i.e.*, stool softeners, hyperosmotics, and stimulants), the association was similar irrespective of the type of laxative (Figure 3).

DISCUSSION

In this large national cohort of United States veterans transitioning to dialysis, we examined the association of time-varying laxative use with risk of dyskalemia during the last 1-year pre-ESKD period, and we found that laxative use was not associated with risk of hypokalemia ($K^+<3.5$ mEq/L) but was significantly associated with 21% lower risk of hyperkalemia ($K^+>5.5$ mEq/L), after adjusting for potential confounders. Findings were generally consistent in selected subgroups and robust to sensitivity analyses accounting for missing data and applying different analytical procedures, including time-to-event and logistic regression models.

With the advent of new potassium-binding agents (*e.g.*, patiromer and zirconium cyclosilicate) along with accumulating evidence on the relationship between potassium disorders and adverse cardiovascular and kidney outcomes,[2,29] increasing efforts have been made to align practical approaches to the diagnosis and management of dyskalemia in patients with CKD.[27] In the recent Kidney Disease Improving Global Outcomes executive conclusions about potassium homeostasis

Table 1. Baseline patient characteristics overall and stratified by laxative use status

Characteristics	Total, *n*=36,116	Laxative Use, *n*=14,639	Nonuse of Laxatives, *n*=21,477	*P* Value
Age, mean (SD), yr	69.7 (11.1)	67.6 (10.5)	71.0 (11.4)	<0.001
Men, *n* (%)	35,388 (97.9)	14,262 (97.4)	21,126 (98.4)	<0.001
Race, *n* (%)				<0.001
White	24,715 (68.4)	8938 (61.1)	15,777 (73.5)	
Black	10,292 (28.5)	5221 (35.7)	5071 (23.6)	
Others	1109 (3.1)	480 (3.3)	629 (2.9)	
Married, *n* (%)	20,002 (55.4)	7083 (48.4)	12,919 (60.2)	<0.001
Smoking status, *n* (%)				<0.001
Current	12,919 (35.8)	5749 (39.3)	7170 (33.4)	
Past	12,175 (33.7)	4576 (31.3)	7599 (35.4)	
Never	11,022 (30.5)	4314 (29.5)	6708 (31.2)	
Body mass index,[a] mean (SD), kg/m^2	29.2 (6.3)	29.5 (6.6)	28.9 (6.1)	<0.001
Comorbidities, *n* (%)				
Diabetes mellitus	27,154 (75.2)	11,290 (77.1)	15,864 (73.9)	<0.001
Congestive heart failure	22,576 (62.5)	9236 (63.1)	13,340 (62.1)	0.06
Cardiovascular disease	27,127 (75.1)	11,016 (75.3)	16,111 (75.0)	0.61
Cerebrovascular disease	15,531 (43.0)	5982 (40.9)	9549 (44.5)	<0.001
Peripheral vascular disease	18,485 (51.2)	7256 (49.6)	11,229 (52.3)	<0.001
Chronic pulmonary disease	19,587 (54.2)	8053 (55.0)	11,534 (53.7)	0.01
Liver disease	7048 (19.5)	3101 (21.2)	3947 (18.4)	<0.001
Peptic ulcer disease	3867 (10.7)	1532 (10.5)	2335 (10.9)	0.22
Atrial fibrillation	8630 (23.9)	3168 (21.6)	5462 (25.4)	<0.001
Malignancies	11,034 (30.6)	4338 (29.6)	6696 (31.2)	0.002
Bowel disorders[b]	9128 (25.3)	3688 (25.2)	5440 (25.3)	0.77
Constipation	8122 (22.5)	4320 (29.5)	3802 (17.7)	<0.001
Charlson Comorbidity Index, median (IQI)	5 (3–7)	5 (3–7)	5 (3–7)	<0.001
Cumulative length of hospitalization, median (IQI), d	3 (0–13)	6 (0–19)	1 (0–9)	<0.001
No. of medical visits	23 (12, 38)	33 (21, 49)	18 (9, 30)	<0.001
Medications, *n* (%)				
RASi	19,839 (54.9)	8748 (59.8)	11,091 (51.6)	<0.001
Sodium polystyrene sulfonate	6347 (17.6)	3794 (25.9)	2553 (11.9)	<0.001
Loop diuretics	25,939 (71.8)	12,120 (82.8)	13,819 (64.3)	<0.001
Thiazide diuretics	9438 (26.1)	4770 (32.6)	4668 (21.7)	<0.001
Potassium-sparing diuretics	3553 (9.8)	1878 (12.8)	1675 (7.8)	<0.001
Calcium channel blockers	24,856 (68.8)	11,040 (75.4)	13,816 (64.3)	<0.001
β-blockers	27,074 (74.9)	12,188 (83.3)	14,886 (69.3)	<0.001
Phosphate binders	11,739 (32.5)	6630 (45.3)	5109 (23.8)	<0.001
Digoxin	1796 (4.9)	772 (5.3)	1024 (4.8)	0.03
Insulin	16,738 (46.4)	8232 (56.2)	8506 (39.6)	<0.001
Oral hypoglycemics	8797 (24.4)	3666 (25.0)	5131 (23.9)	0.01
Calcineurin inhibitors	560 (1.6)	273 (1.9)	287 (1.3)	<0.001
Trimethoprim	915 (2.5)	391 (2.7)	524 (2.4)	0.17
Azole antifungals	4365 (12.1)	2648 (18.1)	1717 (7.9)	<0.001
Opioid analgesics	16,856 (46.7)	9506 (64.9)	7350 (34.2)	<0.001
β2-agonists	9882 (27.4)	5441 (37.2)	4441 (20.7)	<0.001
eGFR,[a] median (IQI), ml/min per 1.73 m^2	16.0 (11.8–23.9)	15.6 (11.7–22.3)	16.3 (11.9–25.2)	<0.001
K^+,[a] mean (SD), mEq/L	4.5 (0.5)	4.4 (0.5)	4.5 (0.5)	<0.001
No. of K^+ measurements,[a] median (IQI)	5 (2–12)	11 (5–19)	3 (1–7)	<0.001
In-hospital AKI, *n* (%)	11,309 (31.3)	7557 (51.6)	3752 (17.5)	<0.001

Baseline was defined on the basis of the last 1-year pre-ESKD period. RASi, renin-angiotensin system inhibitor.
[a]Values are time averaged over the 1-year pre-ESKD period.
[b]Bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea.

and management of dyskalemia in kidney diseases,[27] a number of strategic approaches have been suggested for the management of chronic hyperkalemia in CKD. Among these, "gastrointestinal potassium wasting" was proposed as a potential management option for hyperkalemia in CKD.[27] Notwithstanding the putative role of the gastrointestinal tract in potassium wasting among patients with CKD, previous studies have primarily reported its adverse consequences on

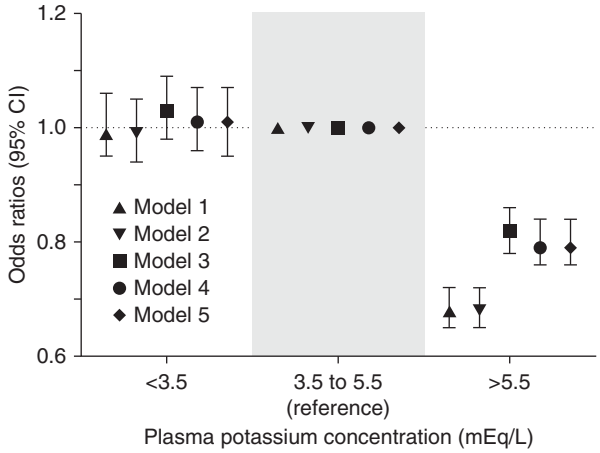

Figure 1. Adjusted ORs and 95% CIs of dyskalemia associated with time-varying laxative use (versus non use of laxatives) during the last 1-year pre-ESKD period (n=36,116). Time-varying laxative use was significantly associated with lower risk of hyperkalemia but was not associated with risk of hypokalemia. Model 1 is unadjusted. Model 2 is adjusted for age, sex, race, and marital status. Model 3 is adjusted for the variables in model 2 plus smoking status; body mass index averaged over the 1-year pre-ESKD period; comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders [bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea], and constipation); Charlson Comorbidity Index; and cumulative length of hospital stay, in-hospital AKI, number of medical visits, and number of K^+ measurements during the 1-year pre-ESKD period. Model 4 is adjusted for the variables in model 3 plus time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium-sparing diuretics, calcium channel blockers, β-blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and β2-agonists), and model 5 is adjusted for the variables in model 4 plus time-varying eGFR.

potassium balance, with a particular focus on profound hypokalemia associated with a massive gastrointestinal loss of potassium (*e.g.*, hypokalemic nephropathy due to laxative abuse),[30–32] and there is currently scant evidence showing the clinical utility of "gastrointestinal potassium wasting" as a therapeutic tool for hyperkalemia management in CKD. In one pre-/poststudy investigating the effect of laxatives on interdialytic K^+ concentration in 26 patients on hemodialysis, increasing the number of stools from one to two to four per day with laxatives significantly lowered interdialytic K^+ concentration (from mean 5.9±0.2 to 5.5±0.2 mmol/L) without inducing diarrhea or evidence of hypovolemia, suggesting the potential utility of laxatives as a management option for hyperkalemia in CKD.[5] However, this study was small in size and included only patients on hemodialysis; hence, the question remains whether the use of laxatives exerts a similar potassium-lowering effect in the NDD-CKD population and if so, what their risk-benefit balance is. In this study, we, therefore, used a sophisticated modeling technique in a large and unique cohort of patients with advanced NDD-CKD, and for the first time, we demonstrated the association of laxative use with lower risk of hyperkalemia, but not with risk of hypokalemia, during the 1-year period before transition to ESKD, supporting the potential clinical utility of laxatives for hyperkalemia management even in patients with NDD-CKD.

Of note, in the subgroup analysis, we observed significant interactions of laxative use with age and number of K^+ measurements, with its different contributions to the risk of dyskalemia. Specifically, in a subgroup of patients ≥65 years, the use of laxatives contributed to the higher risk of hypokalemia, whereas there was an opposite contribution of laxative use to the risk of hypokalemia in those <65 years, albeit with a borderline significance for both associations. Similarly, the contribution of laxative use to the lower risk of hyperkalemia was evident only among those with five or more (versus less than five) K^+ measurements. Although it is possible that these significant interactions were merely due to residual confounding or chance findings (*e.g.*, patients with lower [versus higher] numbers of K^+ measurements might have progressed more rapidly to ESKD before additional K^+ measurements) and hence, did not reflect any pathophysiologic interactions, the finding may suggest that older (versus younger) patients may be more prone to laxative-induced hypokalemia and may thus require more careful attention to their K^+ trajectories when treated with laxatives. Nevertheless, except for these subgroups, the consistent null association between laxative use and risk of hypokalemia is reassuring the theoretical concern about the perceived risk of laxative-induced hypokalemia. In addition, the robust association between laxative use and lower risk of hyperkalemia irrespective of the type of laxative underscores the importance of enhancing intestinal transit for potassium management in patients with advanced CKD. Albeit speculative, given that stool softeners act by enhancing interaction of water and lipids with stool and appear to have fewer adverse effects than hyperosmotics and stimulants,[33] stool softeners might be a preferable type of laxatives in terms of potassium balance in these patients. Meanwhile, considering the unique property of bisacodyl, a cAMP-mediated stimulant laxative that has been suggested to enhance fecal potassium secretion by stimulating cAMP-mediated upregulation of colonic BK channels and has indeed been shown to reduce intradialytic hyperkalemia in patients on hemodialysis,[5] bisacodyl might be a reasonable choice of laxative in terms of lowering elevated K^+ levels in advanced CKD. All of these findings may have clinical and research implications, paving the way for the development of a novel strategic approach using laxatives for the management of hyperkalemia in advanced CKD, which would be particularly relevant in the settings of limited availability of antihyperkalemic agents or in cases refractory to other antihyperkalemia therapies. Nevertheless, it may also be important to note that frequent laxative use can lead to undesirable consequences, including lower

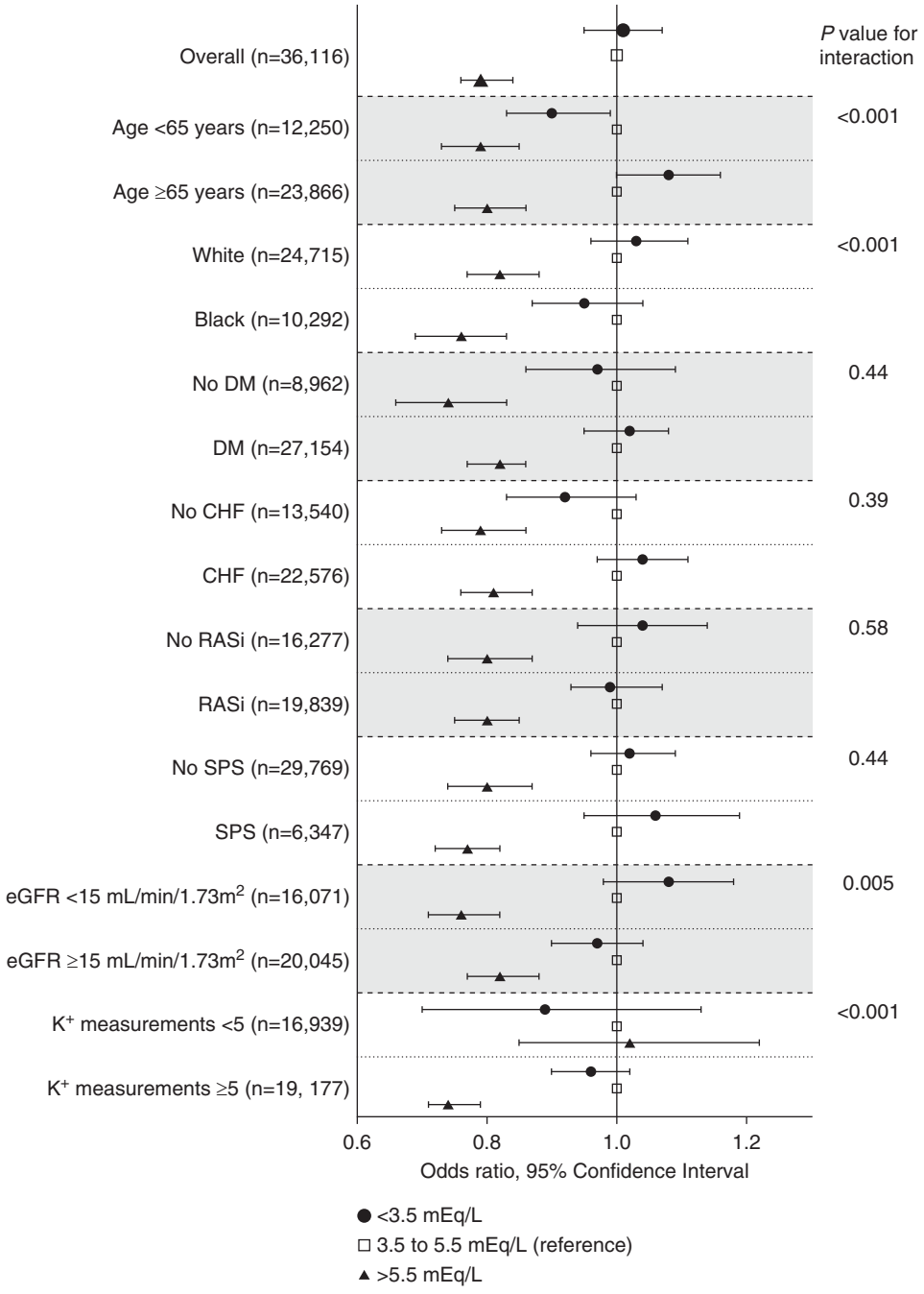

Figure 2. Adjusted ORs and 95% CIs of dyskalemia associated with time-varying laxative use (versus non use of laxatives) during the last 1-year pre-ESKD period in predefined subgroups. Time-varying laxative use was significantly associated with lower risk of hyperkalemia but was not associated with risk of hypokalemia in most subgroups. Data are adjusted for age; sex; race; marital status; smoking status; body mass index averaged over the 1-year pre-ESKD period; comorbidities (diabetes mellitus [DM], congestive heart failure [CHF], cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders [bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea], and constipation); Charlson Comorbidity Index; cumulative length of hospital stay, in-hospital AKI, number of medical visits, and number of K^+ measurements during the 1-year pre-ESKD period; time-varying medications (renin-angiotensin system inhibitor [RASi], sodium polystyrene sulfonate [SPS], loop diuretics, thiazide diuretics, potassium-sparing diuretics, calcium channel blockers, β-blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and β2-agonists); and time-varying eGFR.

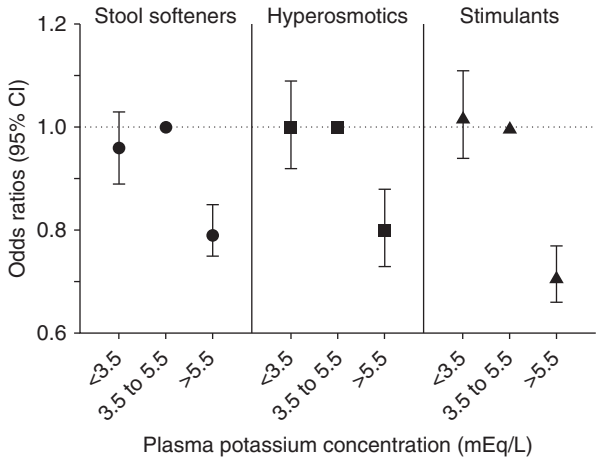

Figure 3. Adjusted ORs and 95% CIs of dyskalemia associated with time-varying laxative use (versus non use of laxatives) during the last 1-year pre-ESKD period by different laxative types. Time-varying laxative use was significantly associated with lower risk of hyperkalemia but was not associated with risk of hypokalemia irrespective of the type of laxative. Data are adjusted for age; sex; race; marital status; smoking status; body mass index averaged over the 1-year pre-ESKD period; comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders [bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea], and constipation); Charlson Comorbidity Index; cumulative length of hospital stay, in-hospital AKI, number of medical visits, and number of K^+ measurements during the 1-year pre-ESKD period; time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium-sparing diuretics, calcium channel blockers, β-blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and β2-agonists); and time-varying eGFR.

nutrient absorption.[34] The effect of active interventions with laxatives on total body potassium balance and their risk-benefit profiles in advanced CKD may deserve future investigations, including clinical trials.

Despite the advantages of this study, including its large sample size of patients with advanced CKD, our results must be interpreted in light of some limitations. Our patients were United States veterans who were mostly men (97.9%), and hence, the results may not apply to women or non–United States veterans. All patients in this cohort survived to the point of initiating dialysis, and thus, those who had died of hyperkalemia before reaching ESKD were not included in the cohort. However, given the low reported rate of dyskalemia-related deaths in patients with advanced NDD-CKD,[35] the effect of such potential selection bias on the number of excluded patients would be small. Furthermore, examination of patients who survived to the point of initiating dialysis allowed us to assess mechanistic associations between laxative use and dyskalemia over the 1-year period immediately preceding dialysis initiation without the potential bias introduced by censoring during this period. Information about laxatives prescribed by non-VA/CMS providers and/or obtained over the counter was not available; therefore, it is possible that patients using laxatives only from these non-VA/CMS sources were misclassified as nonuse of laxatives. Nevertheless, such misclassification would tend to bias the true effects toward the null, and our results still showed significant associations between laxative use and risk of dyskalemias. Because of the relatively low proportion of individual laxatives, the associations of specific laxatives with dyskalemia were not assessed. It may also be important to note that the use of laxatives did not necessarily reflect constipation status, especially given the lack of information about subjective symptoms of constipation and the fact that only a minority of patients with constipation seek medical care.[36] Lastly, as with all observational studies, we cannot infer any causal relationships and eliminate the possibility of unmeasured confounders (*e.g.*, dietary habits and potassium intake) that might have affected the association between laxative use and risk of dyskalemia.

In conclusions, in this large nationwide cohort of 36,116 patients who transitioned to dialysis, we found that time-varying laxative use was associated with lower risk of hyperkalemia during the last 1-year pre-ESKD period, independent of several potential confounders. Our findings suggest the putative role of constipation in potassium disarrays and with a careful consideration for the risk-benefit profiles, the therapeutic potential of laxatives or other stool-softening interventions for hyperkalemia management in advanced CKD.

DISCLOSURES

J.D. Gatwood reports ownership interest in Kali Care; research funding from AstraZeneca, GlaxoSmithKline, Kali Care, and Merck & Co.; honoraria from Hematology/Oncology Pharmacist Association; being a scientific advisor or member with Jazz Pharmaceuticals (spouse); and speakers bureau with Jazz Pharmaceuticals (spouse). K. Kalantar-Zadeh reports personal fees from Abbott, Abbvie, Alexion, Amgen, AstraZeneca, Aveo, and Chugai; other from DaVita; personal fees from Fresenius Medical Services, Genentech, Haymarket, Hospira, Kabi, Keryx, Navartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, UpToDate, Vifor, and ZS-Pharma; grants and personal fees from the National Institutes of Health; and personal fees from Amag Pharma, Baxter, Patient-Centered Outcomes Research Institute, and Dr. Schaer, outside the submitted work. C.P. Kovesdy received consultant fees from AstraZeneca, Bayer, Cara Therapeutics, Reata, Takeda, and Tricida; royalties from UpToDate; research funding from Akebia, Bayer, Gilead, and GSK; honoraria from Amgen, AstraZeneca, Bayer, Cara, Reata, Takeda, and Tricida; is an associate editor for *CJASN* and *Nephron*; and is an editorial board member for *American Journal of Kidney Disease*, *Nephrology Dialysis Transplantation*, *International Urology and Nephrology*, *Kidney Medicine*, and *Kidney International Reports*. M.Z. Molnar reports honoraria from Abbvie, CareDx, Merck Co., and Natera; being a scientific advisor or member as an editorial board member for *Clinical Kidney Journal*, *Frontiers in Medicine*, *International Urology and Nephrology*, *International Scholarly Research Notices Nephrology*, *Journal of Renal Nutrition*, *Renal Failure*, and *Transplant International*; and other interests/relationships *via* compensation from Baxter for presenting in their journal club. Y. Obi reports consultancy agreements with Obi Clinic; and being a scientific

advisor or member as an editorial board member of *Renal Replacement Therapy*. E. Streja reports research funding from AstraZeneca; honoraria from Edwards (one presentation on CMS data in September 2019); and being a scientific advisor or member with *Journal of Renal Nutrition* and *CJASN* editorial board. F. Thomas reports being a scientific advisor or member as an associate editor for *Journal of Statistical Computation and Simulation*, Taylor and Francis (no reimbursement). All remaining authors have nothing to disclose.

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A.A. Dashputre, C.P. Kovesdy, P.K. Potukuchi, and K. Sumida were responsible for the research idea and study design; A.A. Dashputre, K. Kalantar-Zadeh, C.P. Kovesdy, P.K. Potukuchi, E. Streja, and K. Sumida were responsible for data acquisition; A.A. Dashputre, J.D. Gatwood, C.P. Kovesdy, M.Z. Molnar, Y. Obi, P.K. Potukuchi, K. Sumida, and F. Thomas were responsible for data analysis/interpretation; A.A. Dashputre and P.K. Potukuchi were responsible for statistical analysis; K. Kalantar-Zadeh and C.P. Kovesdy provided supervision or mentorship; all authors contributed important intellectual content during manuscript drafting or revision, accept personal accountability for their own contributions, and agree to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved; and all authors reviewed and approved the final version of this manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020081120/-/DCSupplemental.

Supplemental Table 1. Drug names used to identify laxative types.

Supplemental Table 2. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (versus nonuse of laxatives) during the last 1-year pre-ESKD period (n=36,116).

Supplemental Table 3. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (versus nonuse of laxatives) during the last 1-year pre-ESKD period after including patients with missing covariates and imputing missing data (n=44,642).

Supplemental Table 4. Adjusted hazard ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (versus nonuse of laxatives) during the last 1-year pre-ESKD period using repeated events survival analysis (n=36,116).

Supplemental Table 5. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with laxative use (versus nonuse of laxatives) on the basis of data at the first K^+ measurement during the last 1-year pre-ESKD period (n=42,420).

Supplemental Table 6. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (versus nonuse of laxatives) during the last 1-year pre-ESKD period using more granular K^+ categories (n=36,116).

Supplemental Figure 1. Algorithm used to define the analytical cohort.

Supplemental Figure 2. The number of K^+ measurements per patient during the last 1-year pre-ESKD period.

Supplemental Figure 3. The time interval between each K^+ measurement and dialysis initiation during the last 1-year pre-ESKD period.

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Supplementary Online Contents

Supplementary Table 1. Drug names used to identify laxative types

Laxative tyes	Generic names
Stool softener laxative	Docusate sodium
	Docusate calcium
Stimulant laxatives	Bisacodyl
	Castor oil
	Senna
	Sennosides
Hyperosmotics laxatives	Lactulose
	Magnesium citrate
	Magnesium sulphate
	Sodium Biphosphate
	Polyethylene glycol 3350
	Sorbitol
	Glycerin
Bulk laxatives	Calcium polycarbophil
	Cellulose powder
	Methylcellulose
	Psyllium
	Wheat dextrin
Chloride channel blockers	Lubiprostone
Lubricant laxatives	Mineral oil (heavy)

Supplementary Table 2. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (vs. non-use of laxatives) during the last 1-year pre-ESRD period (n=36,116)

	K^+ concentration (mEq/L)		
	<3.5 (hypokalemia)	3.5 to 5.5 (normokalemia)	>5.5 (hyperkalemia)
% of all repeated K^+ values	4.0%	91.0%	5.0%
Model 1	0.99 (0.95-1.06)	1 [reference]	0.68 (0.65-0.72)
Model 2	0.99 (0.94-1.05)	1 [reference]	0.68 (0.65-0.72)
Model 3	1.03 (0.98-1.09)	1 [reference]	0.82 (0.78-0.86)
Model 4	1.01 (0.96-1.07)	1 [reference]	0.79 (0.76-0.84)
Model 5	1.01 (0.95-1.07)	1 [reference]	0.79 (0.76-0.84)

Note: Model 1 is unadjusted; model 2 is adjusted for age, sex, race, and marital status; model 3 is adjusted for the variables in model 2 plus smoking status, body mass index averaged over the 1-year pre-ESRD period, comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders*, and constipation), Charlson Comorbidity Index, and cumulative length of hospital stay, in-hospital acute kidney injury, number of medical visits, and number of K^+ measurements during the 1-year pre-ESRD period; model 4 is adjusted for the variables in model 3 plus time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium sparing diuretics, calcium channel blockers, beta blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and beta-2 agonists); and model 5 is adjusted for the variables in model 4 plus time-varying eGFR. *Bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea.

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; K^+ = plasma potassium

Supplementary Table 3. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (vs. non-use of laxatives) during the last 1-year pre-ESRD period after including patients with missing covariates and imputing missing data (n=44,642)

	K^+ concentration (mEq/L)		
	<3.5 (hypokalemia)	3.5 to 5.5 (normokalemia)	>5.5 (hyperkalemia)
% of all repeated K^+ values	4.1%	90.8%	5.1%
Model 1	0.99 (0.95-1.05)	1 [reference]	0.67 (0.64-0.70)
Model 2	0.99 (0.95-1.05)	1 [reference]	0.67 (0.65-0.70)
Model 3	1.04 (0.99-1.09)	1 [reference]	0.81 (0.78-0.85)
Model 4	1.02 (0.97-1.07)	1 [reference]	0.79 (0.76-0.84)
Model 5	1.01 (0.96-1.06)	1 [reference]	0.80 (0.77-0.84)

Note: Model 1 is unadjusted; model 2 is adjusted for age, sex, race, and marital status; model 3 is adjusted for the variables in model 2 plus smoking status, body mass index averaged over the 1-year pre-ESRD period, comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders*, and constipation), Charlson Comorbidity Index, and cumulative length of hospital stay, in-hospital acute kidney injury, number of medical visits, and number of K^+ measurements during the 1-year pre-ESRD period; model 4 is adjusted for the variables in model 3 plus time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium sparing diuretics, calcium channel blockers, beta blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and beta-2 agonists); and model 5 is adjusted for the variables in model 4 plus time-varying eGFR. *Bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea.

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; K^+ = plasma potassium

Supplementary Table 4. Adjusted hazard ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (vs. non-use of laxatives) during the last 1-year pre-ESRD period using repeated events survival analysis (n=36,116)

	K^+ concentration (mEq/L)		
	<3.5 (hypokalemia)	3.5 to 5.5 (normokalemia)	>5.5 (hyperkalemia)
Model 1	0.83 (0.79-0.86)	1 [reference]	0.86 (0.82-0.89)
Model 2	0.83 (0.80-0.87)	1 [reference]	0.86 (0.82-0.89)
Model 3	0.87 (0.83-0.91)	1 [reference]	0.88 (0.85-0.92)
Model 4	0.91 (0.87-0.95)	1 [reference]	0.93 (0.89-0.97)
Model 5	0.88 (0.84-0.93)	1 [reference]	0.92 (0.87-0.96)

Note: Model 1 is unadjusted; model 2 is adjusted for age, sex, race, and marital status; model 3 is adjusted for the variables in model 2 plus smoking status, body mass index averaged over the 1-year pre-ESRD period, comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders*, and constipation), Charlson Comorbidity Index, and cumulative length of hospital stay, in-hospital acute kidney injury, number of medical visits, and number of K^+ measurements during the 1-year pre-ESRD period; model 4 is adjusted for the variables in model 3 plus time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium sparing diuretics, calcium channel blockers, beta blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and beta-2 agonists); and model 5 is adjusted for the variables in model 4 plus time-varying eGFR.
*Bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea.

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; K^+ = plasma potassium

Supplementary Table 5. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with laxative use (vs. non-use of laxatives) based on data at the first K^+ measurement during the last 1-year pre-ESRD period (n=42,420)

	K^+ concentration (mEq/L)		
	<3.5 (hypokalemia)	3.5 to 5.5 (normokalemia)	>5.5 (hyperkalemia)
Model 1	1.17 (0.98-1.41)	1 [reference]	0.83 (0.69-0.98)
Model 2	1.13 (0.94-1.36)	1 [reference]	0.82 (0.69-0.97)
Model 3	1.11 (0.92-1.34)	1 [reference]	0.85 (0.72-1.01)
Model 4	1.05 (0.87-1.28)	1 [reference]	0.80 (0.67-0.96)
Model 5	1.05 (0.87-1.27)	1 [reference]	0.83 (0.69-0.99)

Note: Dyskalemia and laxative use status were assessed at the time of the first K^+ measurement during the last 1-year pre-ESRD and the risk was estimated using logistic regression models. Model 1 is unadjusted; model 2 is adjusted for age, sex, race, and marital status; model 3 is adjusted for the variables in model 2 plus smoking status, body mass index averaged over the 1-year pre-ESRD period, comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders*, and constipation), and Charlson Comorbidity Index; model 4 is adjusted for the variables in model 3 plus medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium sparing diuretics, calcium channel blockers, beta blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and beta-2 agonists) at the first K^+ measurement during the last 1-year pre-ESRD; and model 5 is adjusted for the variables in model 4 plus eGFR at the first K^+ measurement during the last 1-year pre-ESRD. The absolute risks for hyperkalemia were 5.9% and 7.1% in patients with and without laxative use, respectively; while, the respective absolute risks for hypokalemia were 5.1% and 4.4%.
*Bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea.

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; K^+ = plasma potassium

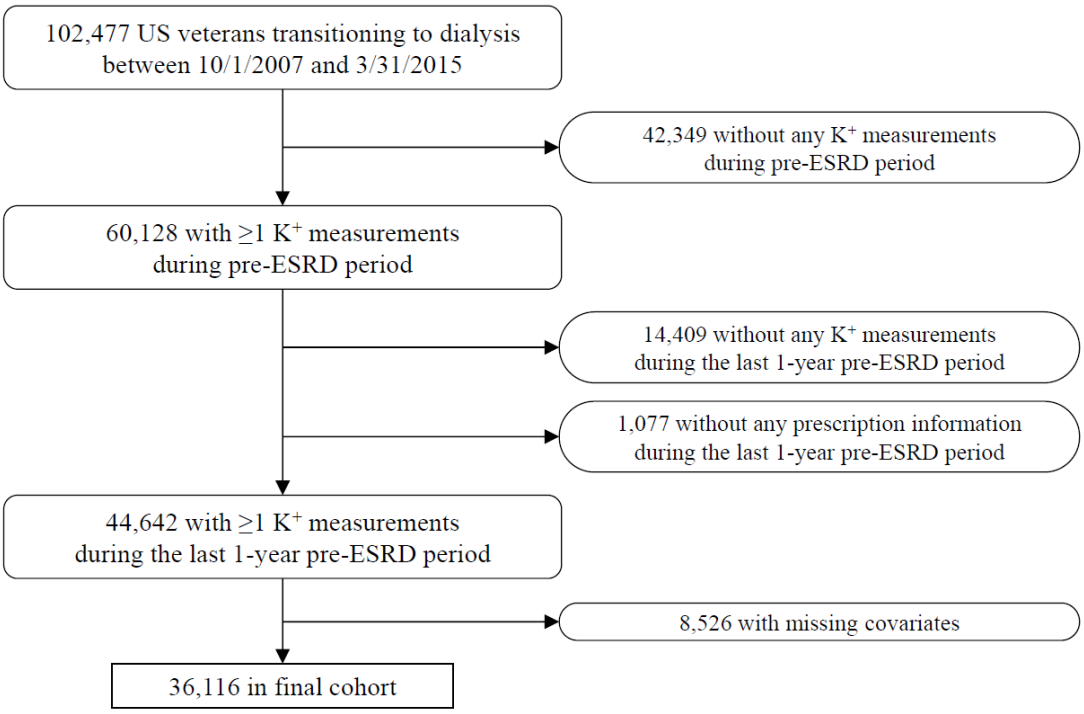
Supplementary Table 6. Adjusted odds ratios and 95% confidence intervals of dyskalemia associated with time-varying laxative use (vs. non-use of laxatives) during the last 1-year pre-ESRD period using more granular K^+ categories (n=36,116)

	K^+ concentration (mEq/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
% of all repeated K^+ values	4.0%	17.0%	30.9%	27.6%	14.1%	4.7%	1.7%
Model 1	1.07 (1.01-1.13)	1.25 (1.19-1.29)	1.16 (1.12-1.19)	1 [reference]	0.86 (0.83-0.88)	0.73 (0.69-0.77)	0.74 (0.68-0.79)
Model 2	1.06 (1.00-1.13)	1.24 (1.19-1.29)	1.16 (1.12-1.19)	1 [reference]	0.86 (0.83-0.88)	0.73 (0.69-0.77)	0.74 (0.68-0.79)
Model 3	1.07 (1.00-1.14)	1.13 (1.08-1.19)	1.08 (1.05-1.11)	1 [reference]	0.90 (0.87-0.93)	0.82 (0.78-0.87)	0.85 (0.79-0.92)
Model 4	1.04 (0.98-1.11)	1.10 (1.06-1.15)	1.07 (1.04-1.10)	1 [reference]	0.91 (0.88-0.94)	0.80 (0.76-0.85)	0.79 (0.73-0.86)
Model 5	1.04 (0.97-1.10)	1.09 (1.05-1.15)	1.07 (1.03-1.09)	1 [reference]	0.91 (0.88-0.94)	0.81 (0.76-0.85)	0.79 (0.73-0.86)

Note: Model 1 is unadjusted; model 2 is adjusted for age, sex, race, and marital status; model 3 is adjusted for the variables in model 2 plus smoking status, body mass index averaged over the 1-year pre-ESRD period, comorbidities (diabetes mellitus, congestive heart failure, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, lung disease, liver disease, peptic ulcer disease, atrial fibrillation, malignancies, bowel disorders*, and constipation), Charlson Comorbidity Index, and cumulative length of hospital stay, in-hospital acute kidney injury, number of medical visits, and number of K^+ measurements during the 1-year pre-ESRD period; model 4 is adjusted for the variables in model 3 plus time-varying medications (renin-angiotensin system inhibitors, sodium polystyrene sulfonate, loop diuretics, thiazide diuretics, potassium sparing diuretics, calcium channel blockers, beta blockers, phosphate binders, digoxin, insulin, oral hypoglycemics, calcineurin inhibitors, azole antifungals, opioid analgesics, and beta-2 agonists); and model 5 is adjusted for the variables in model 4 plus time-varying eGFR.
*Bowel disorders include inflammatory bowel disease, irritable bowel syndrome, and diarrhea.

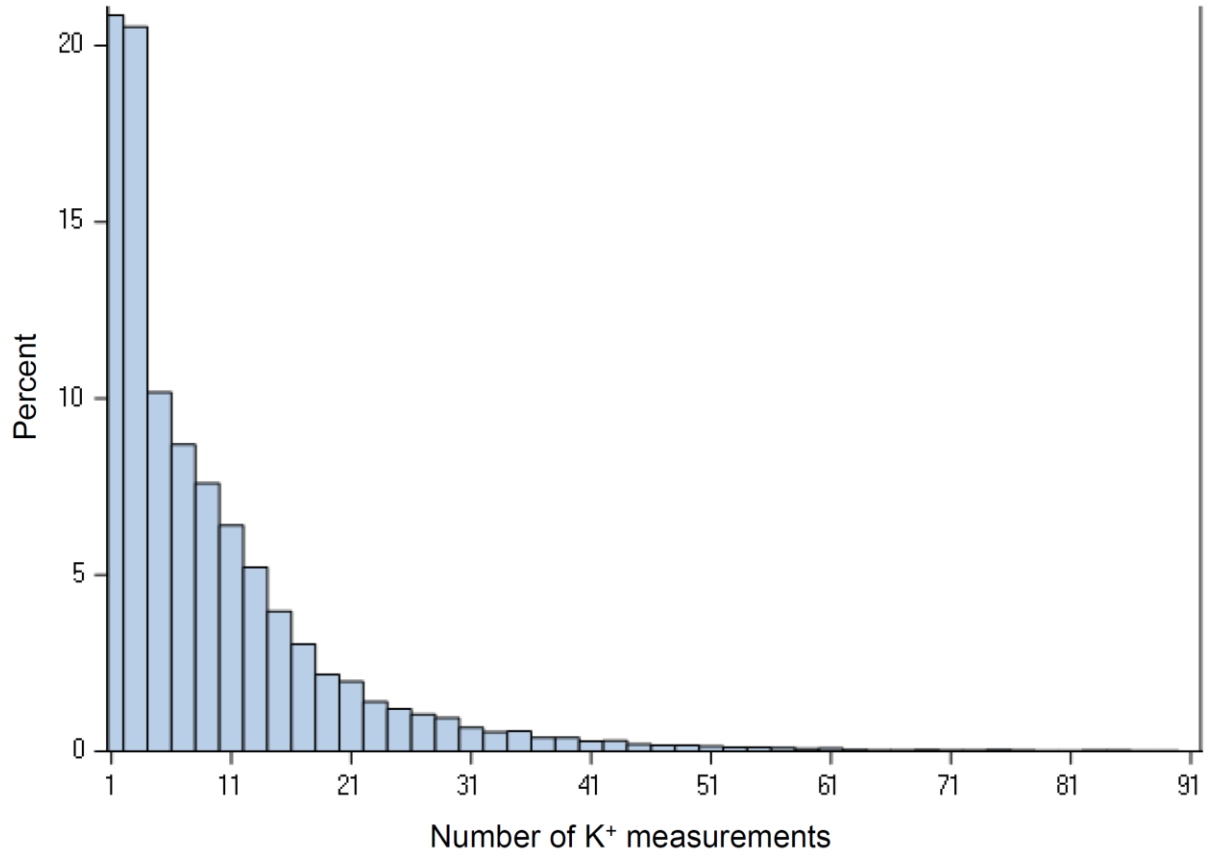
Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; K^+ = plasma potassium

Supplementary Figure 1. Algorithm used to define the analytical cohort



Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; K^+ = plasma potassium

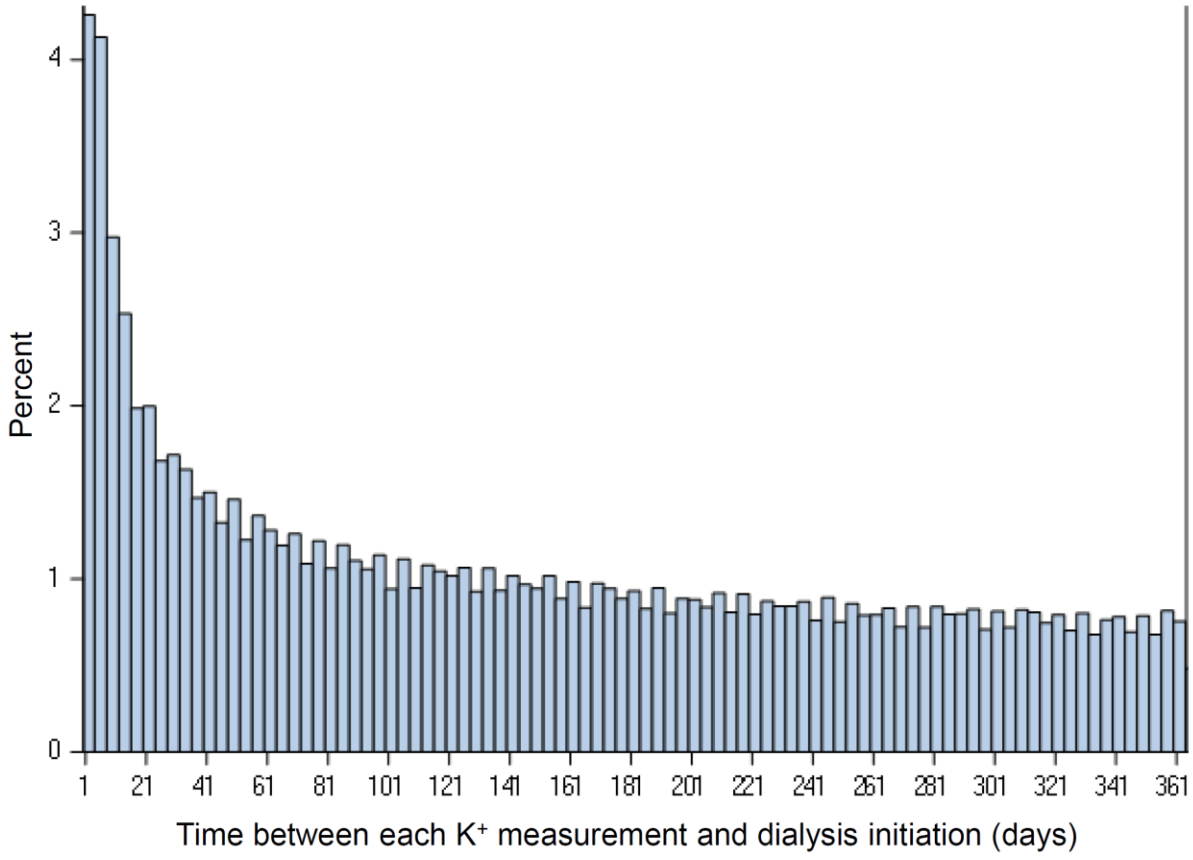
Supplementary Figure 2. The number of K^+ measurements per patient during the last 1-year pre-ESRD period



Note: The histogram was trimmed at 100 K^+ measurements (at ~99.9%).

Abbreviations: ESRD = end-stage renal disease; K^+ = plasma potassium

Supplementary Figure 3. The time interval between each K^+ measurement and dialysis initiation during the last 1-year pre-ESRD period



Abbreviations: ESRD = end-stage renal disease; K^+ = plasma potassium