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Association of Dyskalemias with Ischemic Stroke in Advanced Chronic Kidney Disease Patients Transitioning to Dialysis

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Keywords
Potassium · Chronic kidney disease · Ischemic stroke · Dialysis

Abstract
Introduction: Hypo- and hyperkalemia are associated with a higher risk of ischemic stroke. However, this association has not been examined in an advanced chronic kidney disease (CKD) population. ***Methods:*** From among 102,477 US veterans transitioning to dialysis between 2007 and 2015, 21,357 patients with 2 pre-dialysis outpatient estimated glomerular filtration rates <30 mL/min/1.73 m^2 90–365 days apart and at least 1 potassium (K) each in the baseline and follow-up period were identified. We separately examined the association of both baseline time-averaged K (chronic exposure) and time-updated K (acute exposure) treated as categorized (hypokalemia [K <3.5 mEq/L] and hyperkalemia [K >5.5 mEq/L] vs. referent [3.5–5.5 mEq/L]) and continuous exposure with time to the first ischemic stroke event prior to dialysis initiation using multivariable-adjusted Cox regression models. ***Results:*** A total of 2,638 (12.4%) ischemic stroke events (crude event rate 41.9 per 1,000 patient years; 95% confidence interval [CI] 40.4–43.6) over a median (Q_1–Q_3) follow-up time of 2.56 (1.59–3.89) years were observed. The baseline time-averaged K category of hypokalemia (adjusted hazard ratio [aHR], 95% CI: 1.35, 1.01–1.81) was marginally associated with a significantly higher risk of ischemic stroke. However, time-updated hyperkalemia was associated with a significantly lower risk of ischemic stroke (aHR, 95% CI: 0.82, 0.68–0.98). The exposure-outcome relationship remained consistent when using continuous K levels for both the exposures. ***Discussion/Conclusion:*** In patients with advanced CKD, hypokalemia (chronic exposure) was associat-

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ed with a higher risk of ischemic stroke, whereas hyperkalemia (acute exposure) was associated with a lower risk of ischemic stroke. Further studies in this population are needed to explore the mechanisms underlying these associations.

Introduction

The kidneys play a critical role in serum potassium (K) homeostasis; thus, patients with chronic kidney disease (CKD) are prone to dyskalemias (hypo- and hyperkalemia, especially the latter) [1, 2]. Dyskalemias in CKD occur due to various factors including lower estimated glomerular filtration rate (eGFR), prevalence of diabetes mellitus (DM) and/or cardiovascular disease, and use of medications such as renin-angiotensin-aldosterone system inhibitors (RAASi) and diuretics, and reduced dietary intake of K [1–4] and are associated with adverse outcomes, including higher mortality and cardiovascular events, and health-care burden [4–11].

Previous studies suggested that dyskalemias (especially hypokalemia) are associated with a higher risk of ischemic stroke [12–15]. Among the general population [14], diuretics users [12] and treated hypertensive patients [15], hypokalemia was associated with a higher risk of ischemic stroke. Conversely, a study in the general population [13] showed that higher levels of K were associated with a higher risk of ischemic stroke. Patients with advanced CKD are at higher risk of dyskalemias [4, 16] and ischemic stroke [17, 18]. However, the association between dyskalemias and ischemic stroke has not been examined in an advanced CKD population. The aim of our study was to assess this association in a large population of patients with advanced CKD prior to their transition to dialysis.

Materials and Methods

Study Population

Longitudinal data from a historical cohort of US veterans transitioning to dialysis (Transition of Care in Chronic Kidney Disease [TC-CKD] cohort [n = 102,477]) from October 1, 2007 to March 31, 2015 identified from the US Renal Data System were used for this study [16, 19, 20]. An initial sample of 60,520 US veterans with pre-dialysis outpatient eGFR data was identified. Among these, 36,644 patients with 2 outpatient eGFRs <30 mL/min/1.73 m^2 measured 90–365 days apart were identified, with the second eGFR serving as the index. Further, the sample was restricted to 23,363 patients with at least 1 year each of the look-back period (baseline) and follow-up period (prior to dialysis initiation) from the index. Among these, 21,669 patients had at least 1 outpatient or inpatient K value each in the baseline and follow-up period. Finally, we excluded 312 patients (age <18 years at index [n = 1], without medication data [n = 235], and with ischemic stroke event at the index [n = 76]) to yield a final sample size of 21,357 patients (see online suppl. Fig. 1; see www.karger.com/doi/10.1159/000516902 for all online suppl. material).

Exposure

The exposures of interest were (a) baseline time-averaged K levels (average of all K measurements over the 1-year baseline) and (b) time-updated K levels to the end of follow-up, categorized as hypokalemia (K <3.5 mEq/L), hyperkalemia (K >5.5 mEq/L), and referent (3.5 ≤ K ≤ 5.5 mEq/L) [19], and also treated as a continuous exposure.

Covariates

Patient demographic characteristics were extracted from the US Renal Data System Patient and Medical Evidence file. Data on marital and smoking status were obtained from VA records [21, 22]. Pre-existing comorbidities as of the index were identified from the VA Inpatient and Outpatient Medical SAS, and the VA/Centers for Medicare and Medicaid Services databases with a diagnosis defined as the presence of 2 outpatient or 1 inpatient claims for the condition according to the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic and *Current Procedural Terminology* codes. The Charlson Comorbidity Index (CCI) score was calculated using the Deyo modification for administrative datasets with kidney disease excluded from the algorithm [23]. Data on prescribed medications were collected both in the baseline period and as a time-varying covariate for the follow-up period from inpatient and outpatient VA pharmacy dispensation records and VA/Centers for Medicare and Medicaid Services Medicare Part D. For the baseline period, patients were considered to be users if they had at least one 30-day supply dispensation for medications used for chronic therapy (RAASi, loop diuretics, K sparing diuretics, thiazide diuretics, nonsteroidal anti-inflammatory drugs, antiplatelet agents, aspirin, anticoagulants, lipid-lowering medications, anti-arrhythmics, digoxin, beta-blockers, calcium channel blockers, insulin, oral hypoglycemic drugs, beta-2 agonist, and calcineurin inhibitors) and at least 1 dispensation of any day supply for sodium polystyrene sulfonate (SPS), trimethoprim, azole antifungals, and laxatives. For the time-updated K level exposure, medications were treated as a time-varying covariate and were deemed to be present if the prescription date was the same as the K measurement date or if the K measurement fell within the time period covered by the day supply of the medication. Laboratory measurements and vital signs data were captured over the baseline period and were obtained from VA research databases, as previously described [24, 25]. The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26]. Further, sodium (Na) and eGFR levels were treated as time-varying covariates and captured on the same date as each individual time-updated K level, when K levels were treated as a time-updated exposure.

Outcomes

The outcome of interest was time to the first ischemic stroke event over the follow-up period. Ischemic stroke was ascertained based on ICD-9-CM diagnosis codes (433.01, 433.11, 433.21,

Table 1. Baseline characteristics

Characteristic	All (*N* = 21,357)	K <3.5 mEq/L (*N* = 402)	K 3.5–5.5 mEq/L (*N* = 20,287)	K >5.5 mEq/L (*N* = 668)	*p* value
Age at index, years	68.6 (10.4)	65.6 (10.2)	68.6 (10.4)	70.6 (10.2)	<0.0001*
Males	20,963 (98.2)	395 (98.3)	19,912 (98.2)	656 (98.2)	0.98†
Race					
White	14,712 (68.9)	190 (47.3)	13,392 (68.9)	530 (79.3)	
Black	6,044 (28.3)	203 (50.5)	5,725 (28.2)	116 (17.4)	<0.0001†
Other	601 (2.8)	9 (2.2)	570 (2.8)	22 (3.3)	
Married	12,309 (57.7)	216 (54.0)	11,670 (57.6)	423 (63.3)	0.008†
Region					
Northeast	3,155 (14.8)	36 (8.9)	3,007 (14.8)	112 (16.8)	
Midwest	4,776 (22.4)	87 (21.6)	4,562 (22.5)	127 (19.0)	
South	9,648 (45.2)	229 (56.9)	9,105 (44.9)	314 (47.0)	<0.0001†
West	3,459 (16.2)	46 (11.4)	3,332 (16.4)	81 (12.1)	
Other	305 (1.4)	4 (1.0)	267 (1.3)	34 (5.1)	
Income ($)	18,036 (6,492–34,662)	17,734 (4,524–34,992)	18,036 (6,684–34,675)	18,042 (1,722–33,876)	0.58‡
Smoking status					
Current	6,928 (32.5)	122 (30.4)	6,610 (32.6)	196 (29.3)	
Past	7,524 (35.3)	134 (33.3)	7,147 (35.3)	243 (36.4)	0.18†
Never	6,892 (32.3)	146 (36.3)	6,517 (32.1)	229 (34.3)	
Comorbidities					
DM	14,752 (69.1)	284 (70.7)	14,004 (69.0)	464 (69.5)	0.77†
Congestive heart failure	7,466 (34.9)	153 (38.1)	7,097 (34.9)	216 (32.3)	0.16†
Hypertension	20,678 (96.8)	392 (97.5)	19,649 (96.9)	637 (95.4)	0.07†
Hyperlipidemia	16,669 (78.1)	289 (71.9)	15,842 (78.1)	538 (80.5)	0.004†
Peripheral vascular disease	6,579 (30.8)	96 (23.9)	6,257 (30.8)	226 (33.8)	0.003†
Cerebrovascular disease	5,359 (25.1)	87 (21.6)	5,095 (25.1)	177 (26.5)	0.19†
Chronic lung disease	6,308 (29.5)	107 (26.6)	6,013 (29.6)	188 (28.1)	0.31†
Peptic ulcer disease	1,001 (4.7)	14 (3.5)	948 (4.7)	39 (5.8)	0.19†
Ischemic heart disease	10,573 (49.5)	195 (48.5)	10,032 (49.5)	346 (51.8)	0.45†
Paraplegia/hemiplegia	507 (2.4)	8 (1.9)	489 (2.4)	10 (1.5)	0.27†
Anemia	10,145 (47.5)	167 (41.5)	9,624 (47.4)	354 (52.9)	0.001†
Atrial fibrillation	2,456 (11.5)	55 (13.7)	2,321 (11.4)	80 (11.9)	0.35†
Liver disease	1,563 (7.3)	33 (8.2)	1,491 (7.4)	39 (5.8)	0.26†
Malignancies	4,238 (19.8)	71 (17.7)	4,044 (19.9)	123 (18.4)	0.34†
Ischemic stroke/transient ischemic stroke	3,261 (15.3)	64 (15.9)	3,109 (15.3)	88 (13.2)	0.29†
Charlson comorbidity index	4 (2–6)	3 (2–5)	4 (2–6)	4 (2–6)	0.22‡
Utilization measures					
Outpatient visits	16 (9–28)	17 (10–28)	17 (9–28)	12 (7–20)	<0.0001‡
Hospital visits	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	<0.0001‡
Emergency room visits	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0.009‡
Nephrology visits	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	<0.0001‡
Medications					
RAASi	15,892 (74.4)	292 (72.6)	15,114 (74.5)	486 (72.8)	0.42†
Loop diuretics	11,986 (56.1)	253 (62.9)	11,428 (56.3)	305 (45.7)	<0.0001†
K sparing diuretics	1,955 (9.2)	76 (18.9)	1,840 (9.1)	39 (5.8)	<0.0001†
Thiazide diuretics	6,969 (32.6)	228 (56.7)	6,547 (32.3)	194 (29.0)	<0.0001†
Sodium polystyrene sulfonate	1,684 (7.9)	2 (0.5)	1,496 (7.4)	186 (27.8)	<0.0001†
NSAIDs	7,188 (33.7)	137 (34.1)	6,892 (33.9)	159 (23.8)	<0.0001†
Digoxin	1,007 (4.7)	22 (5.5)	961 (4.7)	24 (3.6)	0.30†
Beta-blockers	14,650 (68.6)	303 (75.4)	13,931 (68.7)	416 (62.3)	<0.0001†
Calcium channel blockers	14,089 (65.9)	307 (76.4)	13,414 (66.1)	368 (55.1)	<0.0001†
Anticoagulants	1,839 (8.6)	42 (10.5)	1,757 (8.7)	40 (5.9)	0.02†
Antiplatelets	3,300 (15.5)	41 (10.2)	3,157 (15.6)	102 (15.3)	0.01†
Antihyperlipidemic	16,441 (76.9)	297 (73.9)	15,638 (77.1)	506 (75.8)	0.24†
Anti-arrhythmics	499 (2.3)	16 (3.9)	468 (2.3)	15 (2.3)	0.09†

Table 1 (continued)

Characteristic	All (N = 21,357)	K <3.5 mEq/L (N = 402)	K 3.5–5.5 mEq/L (N = 20,287)	K >5.5 mEq/L (N = 668)	p value
Aspirin	6,004 (28.1)	106 (26.4)	5,783 (28.5)	115 (17.2)	<0.0001†
Insulin	8,698 (40.7)	177 (44.0)	8,291 (40.9)	230 (34.4)	0.002†
Oral hypoglycemics	7,506 (35.2)	153 (38.1)	7,103 (35.0)	250 (37.4)	0.20†
Calcineurin inhibitors	227 (1.1)	4 (1.0)	215 (1.1)	8 (1.2)	0.93†
Trimethoprim	392 (1.8)	9 (2.2)	368 (1.8)	15 (2.3)	0.59†
Azole antifungals	2,304 (10.8)	34 (8.5)	2,225 (10.9)	45 (6.7)	0.0009†
Beta-2 agonists	3,224 (15.1)	57 (14.2)	3,095 (15.3)	72 (10.8)	0.006†
Laxatives	5,881 (27.5)	101 (25.1)	5,674 (27.9)	106 (15.9)	<0.0001†
Vitals					
BMI, kg/m^2	29.9 (6.1)	31.4 (6.3)	29.9 (6.1)	29.0 (5.8)	<0.0001*
SBP, mm Hg	143.6 (16.3)	147.7 (18.8)	143.5 (16.2)	143.8 (17.6)	<0.0001*
DBP, mm Hg	74.9 (10.8)	80.1 (13.2)	74.9 (10.8)	72.9 (11.0)	<0.0001*
Low-density lipoprotein, mg/dL	94.5 (36.6)	96.8 (40.1)	94.5 (36.6)	93.5 (35.2)	0.41*
High-density lipoprotein, mg/dL	40.0 (13.1)	40.7 (13.2)	39.9 (13.1)	40.4 (11.8)	0.48*
Total cholesterol, mg/dL	172.1 (47.1)	174.5 (50.1)	172.1 (47.1)	169.9 (43.7)	0.35*
Triglycerides, mg/dL	188.5 (145.3)	184.6 (136.6)	188.9 (146.0)	177.7 (127.3)	0.17*
Laboratory measures					
Index eGFR, mL/min/1.73 m^2	24.8 (20.9–27.6)	24.1 (20.3–27.4)	24.9 (20.9–27.6)	23.4 (19.2–27.3)	<0.0001‡
Average K, mEq/L	4.5 (0.5)	3.3 (0.2)	4.5 (0.5)	5.7 (0.2)	<0.0001*
Number of K measurements	3 (2–6)	3 (2–6)	3 (2–7)	2 (1–4)	<0.0001‡
Bicarbonate, mEq/L	24.9 (3.2)	27.9 (3.9)	24.9 (3.2)	22.8 (3.1)	<0.0001*
Sodium, mEq/L	139.5 (2.7)	139.9 (2.8)	139.5 (2.7)	139.4 (2.7)	0.0009*
At least 1 dyskalemia event					
K >5.5, mEq/L	3,709 (17.4)	2 (0.5)	3,309 (14.9)	668 (100)	<0.0001†
K <3.5, mEq/L	2,431 (11.4)	402 (100)	2,029 (10.0)	0	<0.0001†
Both K <3.5 and K >5.5, mEq/L	371 (1.7)	2 (0.5)	369 (1.8)	0	0.0003†

Data are presented as n (%), mean (SD), and median (Q_1–Q_3), unless otherwise needed. eGFR, estimated glomerular filtration rate; K, potassium; DM, diabetes mellitus; BMI, body mass index; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation. * One-way analysis of variance. † χ^2 test. ‡ Kruskal-Wallis test.

433.31, 433.81, 433.91, 434.00–434.91, and 436) [27] captured as the primary diagnosis at an outpatient or inpatient visit. The follow-up started from the index eGFR and patients were followed up through first ischemic stroke or censored at dialysis initiation for those who did not experience the stroke event, whichever occurred first.

Statistical Analysis

Patient characteristics were summarized for the entire sample and by hypokalemia (K <3.5 mEq/L), hyperkalemia (K >5.5 mEq/L), and referent (3.5 ≤ K ≤ 5.5 mEq/L) categories based on baseline time-averaged K levels. Data were presented as counts (percentages), mean (SD) or median (25–75th percentile), and the differences between the K categories were assessed using χ^2 tests, one-way analysis of variance, and the Kruskal-Wallis test, as appropriate. The association of baseline time-averaged K categories with time to ischemic stroke was assessed using multivariable-adjusted Cox regression models (models 1–4) which incrementally accounted for confounders based on theoretical considerations and availability in the database (shown in online suppl. Table 1). We also conducted an additional exploratory model (model 5) which adjusted for systolic blood pressure (SBP) and diastolic blood pressure (DBP) due to their potential mediatory effects. Similarly, the association of categorized time-updated K levels and ischemic stroke was assessed in incrementally multivariable-adjusted models, as described in online suppl. Table 1, with additionally accounting for time-varying medications, eGFR, and Na and baseline average K levels in models 4 and 5. Cox regressions using cubic splines and fractional polynomials by treating the K levels as a continuous exposure were used to assess nonlinearity in exposure-outcome relationship.

Missingness was observed for marital status (0.05%), smoking status and region of residence (0.07% each), Na (0.4%), SBP and DBP (0.7% each), body mass index (BMI) (10.8%), total cholesterol (12.3%), triglycerides (13.5%), high-density lipoprotein (14.5%), low-density lipoprotein (17.2%), bicarbonate (22.3%), time-varying Na (2.3%), and eGFR (6.5%). The main analysis (models 1–4 and model 5) for the exposure-outcome relationship was conducted using singly imputed data for missing baseline covariates derived from regression imputation. In the time-updated K level exposure models, time-varying Na and eGFR at each K were imputed using the last observation carried forward method. We conducted subgroup analyses after categorizing patients by age; race; region of residence; prevalent DM; congestive heart fail-

ure; ischemic heart disease; ischemic stroke/transient ischemic stroke (TIA); baseline use of SPS, RAASi, loop diuretics, and antiplatelet agents; BMI; and index eGFR using singly imputed data. Potential interactions between dyskalemia categories and selected subgroups were tested by including interaction terms. We conducted several sensitivity analyses. The exposure-outcome association was assessed by categorizing the K levels into granular categorizes as K <3.5 mEq/L, 3.5–<4.0 mEq/L, 4.0–<4.5 mEq/L (reference), 4.5–<5.0 mEq/L, 5.0–<5.5 mEq/L, 5.5–<6.0 mEq/L, and ≥6.0 mEq/L. Further, the exposure-outcome association was assessed among those without baseline history of ischemic stroke/TIA (n = 18,096). Finally, analyses were repeated using multiple imputation (imputation, n = 25) and complete case analyses (n = 12,388 for baseline K exposure [after excluding missing baseline covariates]; n = 6,542 for time-updated K exposure [after excluding missing baseline and time-varying covariates]). A 2-sided p value of <0.05 was used as a threshold of statistical significance. Analyses were conducted in SAS Enterprise guide v8.2 (SAS Institute; Cary, NC, USA) and STATA/MP version 15 (STATA Corporation, College Station, TX, USA). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical centers, with exemption from informed consent.

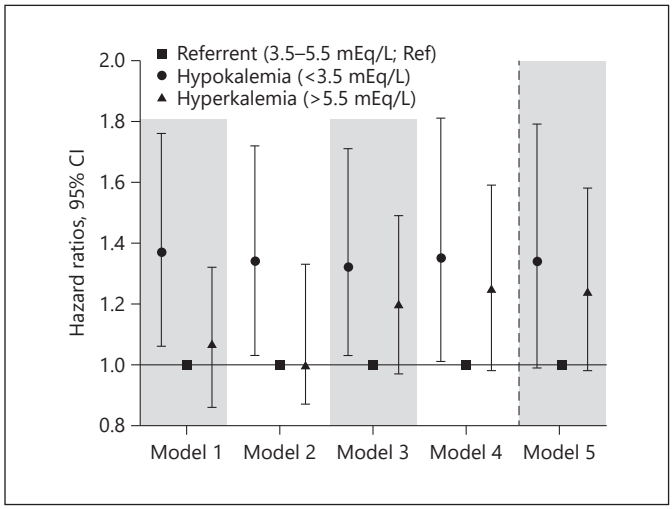

Fig. 1. Association of baseline time-averaged K categories with time to ischemic stroke (n = 21,357). Models 1–5 account for confounders described in online suppl. Table 1. CI, confidence interval; K, potassium.

Results

Baseline Characteristics

The mean (SD) age of the sample was 68.6 (10.4) years; 98.2% were male; 28.3% were black; and 68.1% had DM (shown in Table 1). The most commonly used medications were lipid-lowering agents (76.9%), RAASi (74.4%), and beta-blockers (68.6%). Approximately 8% of the patients used SPS. The median (25–75th) index eGFR was 24.8 (20.9–27.6) mL/min/1.73 m^2. Patients had a median (25–75th) of 3 (2–6) K measurements, with a mean (SD) K of 4.5 (0.5) mEq/L in the baseline. Approximately 3 and 1.9% of the sample had average baseline K levels >5.5 and <3.5 mEq/L, respectively. Those with average baseline K levels >5.5 mEq/L were more likely to be older, to be white, have prevalent hyperlipidemia and anemia, to be SPS users, and have lower eGFR, bicarbonate, SBP, DBP, and BMI levels. Conversely, those with average baseline K levels <3.5 mEq/L were more likely to be younger; black; users of loop, K sparing, and thiazide diuretics and insulin; and have higher eGFR, bicarbonate, SBP, DBP, and BMI levels.

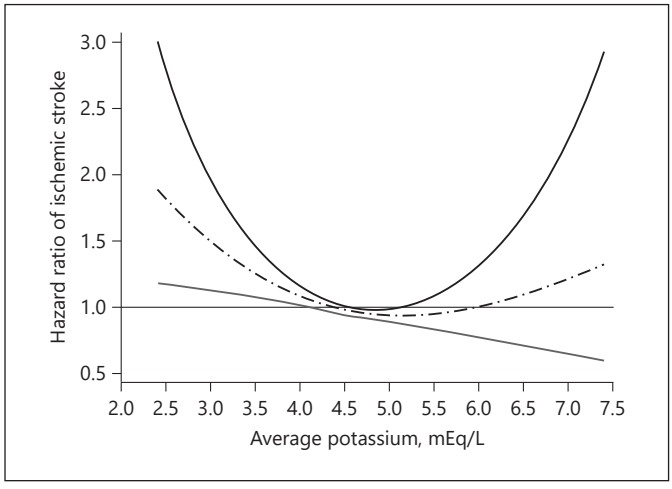

Fig. 2. Association of baseline continuous time-averaged K with time to ischemic stroke (n = 21,357) Dashed and solid lines represent HR and 95% CI, respectively. Model adjusted for confounders accounted in model 4 (fully adjusted) as described in online suppl. Table 1. K, potassium; HR, hazard ratio; CI, confidence interval.

Association of Baseline Time-Averaged Dyskalemia Categories with Ischemic Stroke

A total of 2,638 (12.4%) ischemic stroke events (crude event rate 41.9 per 1,000 patient years; 95% confidence interval [CI] 40.4–43.6) occurred over a median (Q_1–Q_3) follow-up time of 2.56 (1.59–3.89) years. Crude event rates for the overall cohort and by baseline time-averaged K categories are shown in online suppl. Table 2. In the unadjusted analysis, only hypokalemia was associated with a higher risk of ischemic stroke (hazard ratio [HR], 95% CI: 1.37, 1.06–1.76) (shown in Fig. 1 [model 1]). Similarly, in the multivariable-adjusted model, only hypokalemia (HR, 95% CI: 1.35, 1.01–1.81) was associated with a higher risk of ischemic stroke (shown in Fig. 1 [model

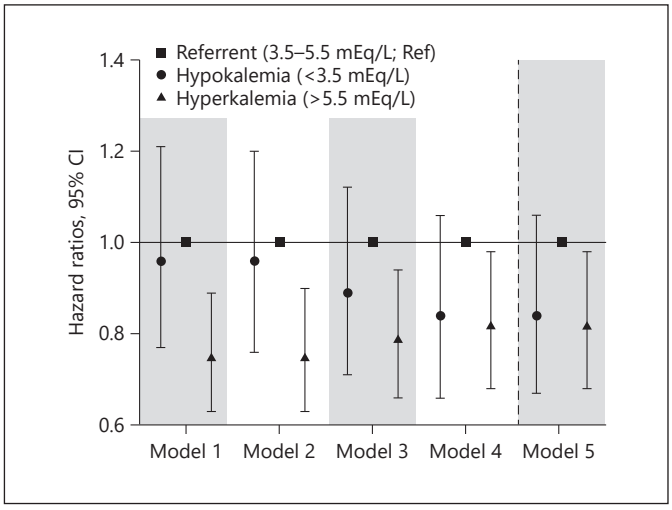

Fig. 3. Association of time-updated K categories with time to ischemic stroke (n = 21,357) Models conducted as described in online suppl. Table 1 with further accounting for baseline averaged K levels and time-varying medications, eGFR, and Na levels. CI, confidence interval; K, potassium; eGFR, estimated glomerular filtration rate; Na, sodium.

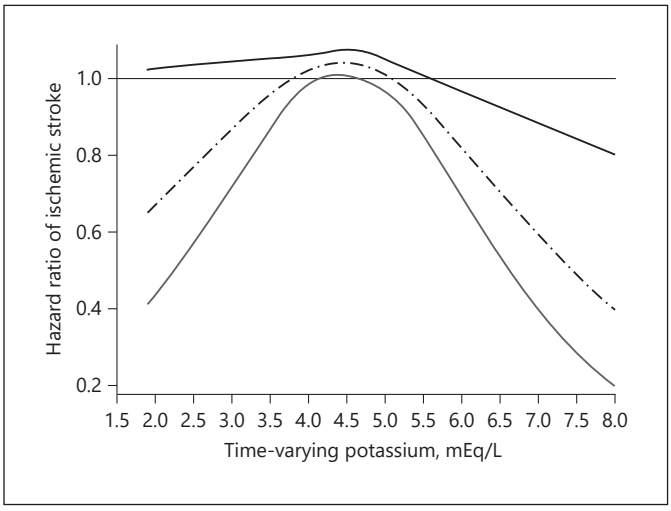

Fig. 4. Association of continuous time-updated K with time to ischemic stroke (n = 21,357) Dashed and solid lines represent HR and 95% CI, respectively. Model adjusted for confounders accounted in model 4 (fully adjusted), as described in online suppl. Table 1 with further accounting for baseline averaged K levels and time-varying medications, eGFR, and Na levels. HR, hazard ratio; CI, confidence interval; K, potassium; eGFR, estimated glomerular filtration rate; Na, sodium.

4]). The association for hypokalemia (HR, 95% CI: 1.34, 0.99–1.79) was attenuated after adjustment for SBP and DBP (shown in Fig. 1 [model 5]). Continuous K levels showed a nonlinear association (p value for quadratic term: 0.002), with lower K levels associated with a higher risk of ischemic stroke (shown in Fig. 2).

Associations for the categorized K levels were robust to multiple imputation and complete case analyses (data not shown). In the multivariable-adjusted model, the association of granular K level categories showed a lower risk (vs. K 4.0–<4.5 mEq/L) of ischemic stroke associated with K 4.5–<5.0 and K 5.0–<5.5 mEq/L (shown in online suppl. Table 3 [model 4]). No significant differences were observed across subgroups (shown in online suppl. Table 4). In the sensitivity analysis, among the 84.7% without baseline history of stroke, hypokalemia was associated with a higher risk of ischemic stroke (shown in online suppl. Table 5 [model 4]).

Association of Time-Updated Dyskalemia Categories with Ischemic Stroke

Over the follow-up time (median [Q_1–Q_3]: 2.56 [1.59–3.89] years), there were a total of 489,486 K measurements with a median (Q_1–Q_3) of 15 (6–30) K measurements per patient, of which 21,382 (4.5%) and 27,318 (5.6%) patients were categorized as hypokalemia and hyperkalemia, respectively. Online suppl. Table 6 shows the distribution of the K categories using the last time-updated K level prior to ischemic stroke by the baseline time-averaged K categories among those who experienced a stroke event. Online suppl. Table 7 shows the distribution of time-updated K categories across all K measurements during follow-up by baseline time-averaged K categories. In the unadjusted analysis, hyperkalemia was associated with a lower risk of ischemic stroke (HR, 95% CI: 0.75, 0.63–0.89; shown in Fig. 3 [model 1]). The results were similar in the multivariable-adjusted model (HR, 95% CI: 0.82, 0.68–0.98; shown in Fig. 3 [model 4]). Results were similar after adjusting for SBP and DBP (HR, 95% CI: 0.82, 0.68–0.98; shown in Fig. 3 [model 5]). Continuous K levels showed a nonlinear association (p value for quadratic term: 0.009), with higher K levels associated with a lower risk of ischemic stroke (shown in Fig. 4).

Association of time-updated K categories with time to the first ischemic stroke event was similar to the main analysis when using multiple imputation and complete case analyses (data not shown). In the multivariable-adjusted model, the association of granular K level categories showed a lower risk (vs. K 4.0–<4.5 mEq/L) of ischemic stroke associated with K 5.5–<6.0 mEq/L (shown in online suppl. Table 8 [model 4]). In the subgroup analysis, significant differences were observed by region of res-

idence (shown in online suppl. Table 9). In the sensitivity analysis, among the 84.7% without baseline history of stroke, lower risk of ischemic stroke associated with hyperkalemia could no longer be established (shown in online suppl. Table 10).

Discussion/Conclusion

In a nationally representative cohort of US veterans with advanced CKD who transitioned to dialysis, hypokalemia (chronic exposure) was associated with a higher risk of ischemic stroke irrespective of baseline history of ischemic stroke/TIA. Conversely, hyperkalemia (time-updated and acute exposure) was associated with a lower risk of ischemic stroke. Our results were robust to various other sensitivity analyses including granular K categories, complete case analysis, and multiple imputation.

Our results align with existing research that suggests that hypokalemia (chronic exposure) is associated with a higher risk of ischemic stroke. Among diuretic users [12], general population [14], and a treated hypertensive population [15], hypokalemia was associated with a 2.5-, 2.1-, and 2-fold higher risk of ischemic stroke, respectively. On the other hand, in a general population [13], both K levels between 4.3-8.4 mmol/L and a per mmol/L increase in K levels were associated with 1.3-fold higher risk of ischemic stroke. However, all these studies are characterized by the use of baseline K levels (chronic exposure) to define dyskalemias and long follow-up times for outcome assessment (minimum follow-up of 1 year and maximum median follow-up of 26.9 years) [12–15].

To determine the short-term risk associated with dyskalemias, we also assessed the association of time-updated dyskalemias (acute exposure) with ischemic stroke where we observed that hyperkalemia (and higher levels of K) was associated with a lower risk of ischemic stroke. Previous studies have hypothesized that hypokalemia might be a marker of increased RAAS activity [28], and an increased activity in systemic and cerebral RAAS system could potentiate the effect of a stroke, by resulting in more extensive neurologic damage and neurologic deficits [14]. This may explain the association of hypokalemia (chronic exposure) with a higher risk of ischemic stroke. Further, a number of studies (animal models and epidemiological research) [29–37] suggested that higher levels of K lead to vasodilation, whereas lower levels of K lead to vasoconstriction by exerting effects through Na^+/K^+ATPase in the vascular smooth muscle cell. A recent study by Li et al. [38] in a rat model observed that elevated serum K levels alleviated cerebral ischemia-reperfusion injury. A lower risk of ischemic stroke associated with time-updated hyperkalemia levels could be explained by these biological changes exerted by higher levels of K, especially in the acute setting. Patients with advanced CKD are at higher risk of hyperkalemia [4, 16], and the hemodynamic effects exerted by repeated hyperkalemia events may acutely potentiate lower blood pressure levels and hence lower the risk of stroke. It is also noteworthy that in our cohort, we observed that those in the hyperkalemia group (vs. hypokalemia group) based on the baseline time-averaged K levels had lower SBP (143.8 vs. 147.7 mm Hg) and DBP (72.9 vs. 80.1 mm Hg) levels, which supports the hypothesis that vasodilatory effects of hyperkalemia could lower the risk of ischemic stroke. Further, higher dietary intake of K is associated with better blood pressure control and lower risk of ischemic stroke [39–41]. However, current guidelines recommend restriction of dietary intake of K due to the risk of hyperkalemia [42], despite the lack of association between dietary K intake and serum K levels or hyperkalemia [43] and the known health benefits of high dietary K intake [2]. However, lack of dietary K intake data did not allow us to assess the association of dietary intake of K (in concurrence with serum K) with ischemic stroke.

Our study results need to be interpreted in light of several limitations. First, our cohort consisted of predominantly male US veterans, thus limiting generalizability to women or to a broader general population. Second, we cannot infer causality due to the observational nature of the study. Third, we cannot eliminate the possibility of unmeasured confounding due to lack of access to dietary intake of K. Several studies have noted the beneficial effects of dietary K intake and lowering of blood pressure and stroke risk [39–41]. Finally, our source cohort is designed such that outcomes such as mortality are only observed following dialysis initiation, but for this study, we assessed dyskalemia-ischemic stroke association in the pre-dialysis period. Thus, caution should be exercised when interpreting the association of time-updated hyperkalemia and lower risk of ischemic stroke as dyskalemias are associated with a short-term risk of death [10, 44], which could not be ascertained due to the nature of our cohort.

In conclusion, in patients with advanced CKD transitioning to dialysis, hypokalemia as a chronic exposure was associated with a higher risk of ischemic stroke, while hyperkalemia as an acute exposure was associated with a lower risk of ischemic stroke. Further studies are needed to explore this association and shed light on the possible mechanisms driving this relationship.

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C.P.K., K.K.Z., and E.S. are employees of the Department of Veterans Affairs. Opinions expressed in this article are those of the authors and do not necessarily represent the opinion of the Department of Veterans Affairs.

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 Statement

C.P.K. received honoraria from Akebia, Ardelyx, AstraZeneca, Bayer, Boehringer-Ingelheim, Cara Therapeutics, Reata, and Tricida. K.K.Z. has received honoraria and/or support from Abbott, AbbVie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, American Society of Nephrology, AstraZeneca, Aveo, B. Braun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition and Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Kissei, Novartis, OPKO, National Institutes of Health (NIH), National Kidney Foundations, Pfizer, Regulus, Relypsa, Resverlogix, Dr. Schaer, Sandoz, Sanofi, Shire, Veterans' Affairs, Vifor, UpToDate, and ZS Pharma. J.G. has received research support from AstraZeneca, Merck & Co., and GlaxoSmithKline. Y.O. has received research support from Relypsa/Vifor Pharma Inc. The remaining authors declare that they have no relevant financial interests.

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Author Contributions

Research idea: C.P.K. and A.A.D.; study design: A.A.D., K.S., J.G., F.T., O.A., and C.P.K.; data acquisition: A.A.D., P.K.P., E.S., M.Z.M., K.K.Z., and C.P.K.; data analysis/interpretation: A.A.D., K.S., J.G., F.T., O.A., and C.P.K.; statistical analysis: A.A.D., F.T., and C.P.K.; supervision or mentorship: C.P.K. Each author contributed important intellectual content during the manuscript drafting or revision, accepted personal accountability for the authors own contributions, and agreed to ensure that questions pertaining to the accuracy or integrity of any portion of the work were appropriately investigated and resolved. Funders of this study had no role in study design; collection, analysis, and interpretation of the data; writing the report; and the decision to submit the report for publication.

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