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ORIGINAL ARTICLE

Serum-to-dialysate potassium gradient and its association with short-term outcomes in hemodialysis patients

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ABSTRACT

Background. A high serum-to-dialysate potassium (K^+) gradient at the start of dialysis leads to rapid lowering of serum K^+ and may confer a greater risk of adverse events. Here, we examined the near-term association of K^+ gradient with clinical outcomes.

Methods. This retrospective (2010–11) event-based study considered 830 741 patient-intervals, each defined by a pre-dialysis measurement of serum K^+ made among adult Medicare Parts A and B enrollees who received in-center hemodialysis on a Monday/Wednesday/Friday schedule at a large US dialysis organization. K^+ gradient was considered based on the difference in K^+ concentration (serum–dialysate) on the date of measurement; analyses accounted for multiple observations per patient. Outcomes considered were: all-cause and cardiovascular hospital admissions, emergency department (ED) visits and deaths.

Results. Higher K^+ gradient was associated with younger age, greater fistula use, lower comorbidity scores and better nutritional indices. Adjusting for patient differences, there was a dose–response relationship between higher K^+ gradient and greater risks of all-cause hospitalization and ED visit. A similar trend was seen for cardiovascular hospitalization but did not achieve statistical significance. No associations were observed with mortality, potentially due to a low number of events.

Conclusions. Higher K^+ gradient is independently associated with greater risk of all-cause hospitalizations and ED visits. Further research is needed to determine whether interventions that reduce the K^+ gradient ameliorate this risk.

Keywords: dialysate, epidemiology, ESRD, hemodialysis, potassium

INTRODUCTION

A major function of hemodialysis is to remove accumulated potassium (K^+), thereby maintaining or restoring serum K^+ levels to within the normal range. This is accomplished in large part by diffusion of K^+ down its concentration gradient from serum to dialysate [1]. The gradient is determined by the difference between two values: the patient's serum K^+ level and the K^+ concentration in the dialysate.

A steeper gradient, as results from the occurrence of high serum K^+, the use of low K^+ dialysate or both, facilitates more rapid removal of K^+ (and the removal of a larger mass of K^+ overall) than a shallower gradient generated by either lower serum K^+, higher dialysate K^+ concentration or both [2, 3]. A lower dialysate K^+ concentration can, therefore, serve an important role in the management of recurrent hyperkalemia among end-stage renal disease (ESRD) patients. However, the rapid removal of K^+ as occurs in the context of a steeper K^+ gradient may place patients at risk for adverse outcomes including cardiac arrhythmias [4–6] and rebound hypertension [7]. Further, patients requiring steeper gradients may be at increased risk of rebound hyperkalemia, especially those with short treatment times [1].

Many observational studies have examined associations of either serum K^+ or dialysate K^+ concentration with cardiac outcomes and/or mortality in hemodialysis patients. High serum K^+ is relatively common among patients with impaired kidney function [8–10] and has been consistently associated with increased risk of mortality compared with serum K^+ values in the normal range [9, 11–13]. Studies of dialysate K^+ and outcomes have yielded inconsistent results, with some studies suggesting an

increased risk of adverse outcomes at lower dialysate K^+ [14–16], and others finding no such associations [11, 17–20].

Whereas such studies are important and instructive, they tie into the biological concept of absolute level of ambient K^+ concentrations. By contrast, K^+ gradient ties into a separate (but complementary) biological concept: change (flux) in K^+ concentration that occurs during the course of the dialysis treatment. To our knowledge, there have not been any large, rigorous studies of the effect of K^+ gradient per se, leaving this as an important unanswered question.

In this study, we examined the association of K^+ gradient, defined as the difference between serum K^+ concentration (measured using blood drawn immediately prior to treatment) and the delivered (constant) dialysate K^+ concentration at a given hemodialysis treatment, with short-term outcomes including all-cause hospitalizations, emergency department (ED) visits, cardiovascular hospitalizations and mortality. By definition, because the goal of this study was to examine the risk associated with the gradient itself, neither the serum K^+ concentration nor the dialysate K^+ concentration was considered in isolation.

MATERIALS AND METHODS

Study design and data sources

This study was a retrospective, observational analysis of patients receiving in-center hemodialysis at a large dialysis organization (LDO) in the USA. This study used solely de-identified patient-level data. It was, therefore, deemed exempt from institutional review board or ethics committee approval by an independent Institutional Review Board (Quorum IRB, Seattle, WA, USA), in accordance with 45 Code of Federal Regulations (CFR) part 46 from the US Department of Health and Human Services. We adhered to the Declaration of Helsinki and informed consent was not required.

Data regarding serum K^+ levels (including dates), dialysate K^+ concentrations, covariates and deaths were derived from the electronic health records (EHR) of the LDO. Data regarding hospitalizations and ED visits were derived from the United States Renal Data System (USRDS) database, which contains final-action claims data for Medicare beneficiaries with ESRD. These two data sets were merged through direct linkage (secured prior to de-identification by USRDS), without the need for probabilistic matching.

Eligible patients were those who, between 1 January 2010 and 24 December 2011, were at least 18 years old, received in-center hemodialysis at the facilities of the participating LDO, were not US Veterans Administration beneficiaries (contractual stipulation), were Medicare Part A and Part B beneficiaries (to ensure visibility into claims data for outcomes ascertainment) and had serum K^+ measured on a Monday (M), Wednesday (W) or Friday (F) during routine dialysis. Blood is never drawn for routine laboratories on Saturday; therefore, patients dialyzing on a Tuesday/Thursday/Saturday schedule were not included.

Exposure

The exposure for this study was assigned based on the value of the K^+ gradient [(serum K^+) − (dialysate K^+)] and the day of the week (M/W/F) on which measurement occurred. Only those dialysis sessions at which a monthly blood draw for serum K^+ determination was obtained prior to the start of treatment were considered (to avoid misclassification stemming from unobserved changes in serum K^+ that occur between measurements). Gradient was categorized as <0, 0–<1, 1–<2, 2–<3, 3–<4, 4–<5 or ≥ 5 mEq/L. Laboratory blood draws are conducted prior to dialysis, and thus the value obtained represents the pre-dialysis value on that date. The results of these measurements (determined at a single central laboratory in DeLand, FL, USA) were not known to the dialysis facility on the day of treatment and thus did not influence choice of dialysate K^+ concentration. Dialysate K^+ concentration was identified through the EHR for each treatment. Individual patients could contribute one or more observations based upon the number of qualifying gradients observed.

Outcomes

Outcomes were assessed over two windows: same-day (i.e. the day of dialysis) and same-or-next day (the day of dialysis and the subsequent calendar day). Claims data record only the date of outcome events, and not the time of day that the events occurred, which is why calendar days were used to define the outcome windows. Although the data sources do not permit us to distinguish between outcome events that occur prior to or following dialysis on the index date, it is highly unlikely that a patient would have either a hospitalization or ED visit and then attend an in-center dialysis treatment later on the same calendar day. Thus, the risk of misclassification is small. The extended (same-or-next day) outcome window was designed to allow for capture of outcome events that, for administrative or other reasons, were not recorded on the same calendar date as the relevant dialysis treatment. Given the timing of clinical laboratory measurements and dialysis treatments, the outcome window was unique for each observation.

Deaths were identified from the LDO's EHR. Hospitalizations were identified from Medicare Part A claims in the USRDS data set. The primary International Classification of Diseases, Ninth Revision (ICD-9) code identified in the claim was used to define cardiovascular hospitalization, based on the Agency for Healthcare Research and Quality's Clinical Classification Software [21]. ED visits were identified from Medicare Part B (physician supplier) claims in the USRDS data set for which place of service is specified as the ED.

Statistical analysis

Patient demographics and baseline characteristics were considered as of index date and stratified by K^+ gradient category. They were summarized for each group as means, standard deviations, medians, interquartile ranges, counts and proportions, as dictated by data type.

Hospitalizations, ED visits and mortality were described in terms of risk (number of intervals affected divided by total number of intervals) and reported by K^+ gradient category. Formal comparisons were conducted using mixed linear models and reported as risk (probability of outcome occurring during outcome window) and odds ratios (ORs) [95% confidence

intervals (CI)] versus the referent K^+ gradient category (2–<3 mEq/L). Robust variance estimation was used to account for multiple observations within individual patients. Analyses were adjusted for age, sex, race, vintage, type of vascular access used, presumed cause of kidney disease, weight, reported presence of common comorbidities (diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease, malignancy), Charlson comorbidity index, albumin, creatinine, normalized protein catabolic rate (nPCR), pre-dialysis systolic blood pressure, intradialytic hypotension (defined using the Flythe criterion [22]), ultrafiltration volume, day of week, dialysis shift and total body water (calculated using the Watson formulae [23]).

All analyses were conducted with STATA version 10.0MP.

RESULTS

A total of 830 741 qualifying K^+ gradient measurements, contributed by 62 388 unique patients, were identified (Supplementary data, Tables S1 and S2, and Figure S1). Of these, 343 700 were observed on Monday, 445 781 on Wednesday, and 41 260 on Friday. Values of K^+ gradient were, in general, highest on Monday and lowest on Wednesday; however, differences were modest. Of the gradients observed, 98 095 (11.8%) fell into the highest two categories (4–<5 and ≥5 mEq/L). The vast majority of patients were prescribed dialysate potassium concentrations of 2–<4 mEq/L; none used dialysate of <1 mEq/L. In general, higher K^+ gradients were associated with younger age, greater frequency of arteriovenous fistulas, longer dialysis vintage, lower comorbidity scores, better nutritional indices (albumin, creatinine, nPCR) and greater ultrafiltration volume (Table 1).

There was an incremental and dose-dependent association between higher gradient and greater risk of same-day hospital admission (Table 2 and Figure 1). No statistically significant interaction was observed between gradient and day of week with respect to this or any other outcome (all P-interaction >0.05), and estimates were, therefore, pooled across the days of the week. When compared with the referent K^+ gradient category (2–<3 mEq/L), K^+ gradients in the highest two categories (4–<5 and ≥5 mEq/L) were associated with 30% and 51% higher multivariable-adjusted risks of same-day hospitalization, respectively. When the outcome window was extended to include the following day, a significantly higher risk of hospitalization was observed in the three highest gradient categories (3–<4, 4–<5 and ≥5 mEq/L) compared with the referent category (Table 3): the respective multivariable-adjusted risks were 8, 26 and 59% higher.

In an alternate approach, we considered the interaction between serum K^+ and dialysate K^+ with respect to hospitalization. We observed a significant interaction (P-interaction <0.001 for same-day hospitalization, and 0.006 for same-or-next-day hospitalization). However, when we examined stratum-specific estimates in these models, they were so imprecise that it was not possible to draw any conclusions using this approach (Supplementary data, Table S3).

There was an incremental and dose-dependent association between higher K^+ gradient and increased risk of same-day ED visit (Table 2 and Figure 2): K^+ gradients in the highest two categories (4–<5 and ≥5 mEq/L) were associated with 16% and 41% higher multivariable-adjusted risks, respectively, as compared with the referent category (2–<3 mEq/L). When the outcome window was extended to include the following day, a significantly higher risk of ED visit was observed in the three highest gradient categories (3–<4, 4–<5 and ≥5 mEq/L) compared with the referent category (Table 3): the respective multivariable-adjusted risks were 6%, 17% and 54% higher.

No associations were seen with cardiovascular hospitalizations or all-cause mortality (Tables 2 and 3). A trend towards higher risk of cardiovascular hospitalization was observed in the highest gradient category compared with the referent in both analyses; however, this did not achieve statistical significance. For all outcomes considered, the pattern of association with K^+ gradient was not modified based on the day of the week that the gradient was observed (P-interaction >0.05 for each).

DISCUSSION

We used the large, integrated EHR of a LDO linked to billing claims of patients insured by the Medicare program to investigate the relationship between K^+ gradient during hemodialysis and several short-term health outcomes. We observed that a steeper K^+ gradient was independently associated with increased risks of hospitalization and ED visit on the day of dialysis treatment or the next day. No statistically significant associations were observed with cardiovascular hospitalizations or mortality, although a paucity of outcome events in these categories may have limited our ability to detect associations. We can therefore neither confirm nor refute the previously reported associations between serum or dialysate K^+ concentrations and cardiovascular and mortality outcomes [9, 11–16]. However, our study complements these earlier analyses and provides a different angle on the topic of potassium dynamics in dialysis patients through direct examination of the K^+ gradient.

It seems possible that the observed associations between gradient and outcome may have been driven by cardiac arrhythmias and their immediate consequences (syncope, hypotension, etc.). These events cannot be directly assessed in our data set. Therefore, this study relied upon the use of surrogate outcomes (hospitalizations, ED visits) that are not specific to the posited mechanism. This lack of specificity and resulting inclusion of unrelated ED visits or hospitalizations in our analyses may have contributed to the relatively low unadjusted risk observed for each outcome, and likewise carries with it the potential for unmeasured confounding. However, our observation that patients in the higher gradient categories were, in general, younger and healthier than those in the lower gradient categories suggests that any residual confounding would lead to an underestimation of the association between higher gradients and adverse outcomes. Prospective studies, including those employing technologies such as rhythm monitors, will be needed to confirm and extend the findings reported here.

A prior study by Kovesdy *et al.* found that, among patients with higher monthly serum K^+, low dialysate K^+ (and, by implication, a steep K^+ gradient) was not associated with increased long-term mortality [11]. The study reported here, while not directly comparable to that of Kovesdy *et al.*,

Table 1. Patient characteristics by K^+ gradient category

Characteristic	K^+ gradient category (mEq/L)						
	<0 *n* = 1251	0–<1 *n* = 25 119	1–<2 *n* = 139 631	2–<3 *n* = 327 906	3–<4 *n* = 238 739	4–<5 *n* = 80 286	≥5 *n* = 17 809
Age (years)							
Mean ± SD	65.5 ± 14.4	67.9 ± 13.7	67.0 ± 13.9	64.1 ± 14.5	62.2 ± 14.5	60.3 ± 14.0	58.2 ± 13.7
Sex, %							
Female	45.5	48.2	46.4	44.6	44.2	43.0	40.9
Race, %							
White	52.7	50.7	46.8	41.0	44.2	46.0	46.9
Black	33.1	33.4	38.1	40.2	30.1	21.6	17.1
Hispanic	11.3	10.1	9.2	12.6	17.8	22.4	24.0
Other/unknown/missing	3.0	5.8	5.9	6.2	7.9	10.0	12.0
Vintage (months), %							
<12	37.8	42.3	32.6	18.3	10.8	8.1	8.4
12–<24	13.7	15.3	15.9	13.6	11.7	10.8	10.6
24–<48	28.1	19.2	21.6	24.8	26.2	27.2	26.9
≥48	19.2	20.1	27.2	41.1	49.1	51.7	52.1
Missing	1.3	3.1	2.7	2.2	2.2	2.1	2.0
Vascular access, %							
AVF	42.3	45.1	51.2	56.9	60.1	61.4	61.1
AVG	13.9	18.9	20.4	23.2	22.5	20.5	17.8
CVC	43.8	35.9	28.5	19.9	17.5	18.1	21.1
Etiology ESRD, %							
Diabetes	38.6	41.8	45.7	47.6	49.5	51.5	52.3
Hypertension	28.9	32.7	31.4	30.2	26.3	22.4	20.7
Other/unknown/missing	32.5	25.5	22.9	22.2	24.2	26.2	27.0
Target weight (kg), %							
<60	20.5	20.9	18.2	16.2	17.5	19.7	22.1
60–<70	24.0	21.4	20.4	19.7	20.6	21.6	22.0
70–<80	23.9	19.2	20.7	20.6	20.7	21.2	21.7
80–<90	17.2	14.2	15.4	16.1	15.5	14.6	13.6
90–<100	5.8	9.1	9.7	10.8	10.3	9.2	8.5
100–<110	3.8	6.4	6.2	6.5	6.1	5.6	5.6
≥110	3.4	7.6	8.4	9.4	8.8	7.7	6.3
Missing	1.4	1.3	0.9	0.6	0.4	0.3	0.4
Diabetes, %	62.5	66.1	70.5	72.4	73.2	74.2	75.6
CHF, %	13.9	12.6	14.0	15.1	15.5	15.4	15.7
CAD, %	13.2	16.9	17.7	19.1	19.8	20.1	20.7
CVD, %	1.0	1.8	1.5	1.2	0.9	0.7	0.6
PVD, %	11.2	7.4	8.3	9.6	10.2	10.2	10.7
Malignancy, %	3.6	3.1	2.7	2.6	2.2	2.0	2.0
CCI, %							
2	5.8	4.2	3.7	5.1	5.8	6.3	7.1
3	4.6	6.3	5.5	6.6	7.1	8.1	8.3
4	16.2	9.6	9.8	11.6	13.1	14.5	16.8
5	14.8	16.7	16.3	16.5	17.3	18.5	19.2
6	17.3	21.3	22.8	22.1	21.9	21.7	21.1
7	19.7	20.8	20.5	19.1	17.8	16.2	14.4
8	14.1	13.0	13.2	11.7	10.4	9.0	8.8
9	4.7	5.3	5.2	4.7	4.4	3.9	3.0
10+	2.9	2.8	3.0	2.6	2.2	1.7	1.4
Albumin (g/dL), %							
<3.0	26.1	15.1	7.9	3.6	2.1	1.6	1.8
3.0–<3.3	12.9	11.2	8.6	5.2	3.5	2.9	2.9
3.3–<3.6	14.1	18.3	16.6	13.0	10.0	8.8	8.1
3.6–<3.9	20.0	23.6	26.9	26.5	24.7	22.8	21.4
3.9–<4.2	15.8	20.7	25.6	30.7	33.2	34.7	34.8
≥4.2	11.2	11.1	14.4	21.0	26.5	29.3	31.1
Creatinine (mg/dL), %							
<4.0	28.9	27.2	15.3	5.7	2.1	0.9	0.7
4.0–<6.0	32.9	33.4	31.2	19.8	12.2	8.2	7.0
6.0–<8.0	23.3	22.1	26.3	28.3	27.0	24.6	22.7
8.0–<10.0	8.5	8.9	14.0	21.7	26.5	28.6	28.1
10.0–<12.0	0.6	2.9	5.9	12.1	15.9	18.8	20.4

Continued

Table 1. Continued

Characteristic	K^+ gradient category (mEq/L)						
	<0 $n = 1251$	0–<1 $n = 25\,119$	1–<2 $n = 139\,631$	2–<3 $n = 327\,906$	3–<4 $n = 238\,739$	4–<5 $n = 80\,286$	≥5 $n = 17\,809$
≥12.0	0.8	1.5	3.3	8.6	12.9	15.5	17.8
Missing	5.0	4.1	3.9	3.7	3.5	3.4	3.3
nPCR (g/kg/day), %							
<0.5	16.6	14.5	8.6	4.3	2.5	1.8	1.6
0.5–<0.7	28.8	25.8	21.8	13.1	7.4	5.5	5.2
0.7–<0.9	24.1	26.3	29.0	27.3	20.5	15.7	13.9
0.9–<1.1	13.2	17.2	21.3	27.2	28.2	25.7	22.5
1.1–<1.3	9.6	8.9	11.2	16.4	22.2	24.0	24.3
≥1.3	7.0	6.7	7.7	11.5	19.1	27.2	32.3
Missing	0.7	0.7	0.4	0.2	0.1	0.1	0.1
SBP, %							
<90	2.9	1.5	1.3	0.9	0.7	0.7	0.8
90–<110	17.7	11.1	8.4	6.7	5.7	5.1	4.6
110–<130	27.3	24.1	21.3	18.5	16.5	15.3	14.7
130–<150	28.1	28.2	28.4	27.7	27.0	26.1	24.5
150–<170	14.6	21.3	22.9	25.0	26.6	27.1	26.9
≥170	8.6	13.4	17.3	20.7	23.1	25.3	28.1
Missing	0.9	0.4	0.4	0.4	0.4	0.4	0.4
IDH, %	25.8	18.3	16.9	17.6	20.0	22.3	23.7
UF volume, %							
Mean ± SD	1.8 ± 1.4	2.0 ± 1.4	2.2 ± 1.4	2.6 ± 1.4	2.9 ± 1.4	3.2 ± 1.5	3.4 ± 1.5
Day of week, %							
Monday	52.1	39.8	37.2	37.1	44.6	52.9	59.9
Wednesday	38.9	53.8	57.6	58.2	50.7	41.9	33.8
Friday	9.0	6.4	5.3	4.7	4.8	5.2	6.4
Shift, %							
1	41.3	35.1	36.7	41.4	41.3	38.0	33.3
2	30.5	41.1	42.9	40.7	40.0	40.1	39.9
3	28.2	23.9	20.4	17.9	18.7	21.9	26.7
Tx time (min)[a]							
Mean ± SD	210.2 ± 25.9	212.0 ± 24.7	213.8 ± 24.9	215.7 ± 25.2	215.3 ± 25.3	214.9 ± 25.6	215.4 ± 25.8
Total body water (kg),							
Mean ± SD	26.1 ± 7.7	26.9 ± 8.0	27.5 ± 8.0	28.2 ± 8.2	28 ± 8.1	27.7 ± 7.9	27.4 ± 7.8
Serum K^+ (mEq/L)[a],							
Mean ± SD	3.3 ± 0.5	3.7 ± 0.3	4.1 ± 0.5	4.5 ± 0.4	5.2 ± 0.4	5.8 ± 0.5	6.5 ± 0.5
Dialysate K^+ (mEq/L)[a], %							
1	0.0	0.0	0.1	1.5	15.1	57.4	86.4
2	0.2	2.1	41.4	90.5	84.0	42.5	13.6
3	33.1	93.0	58.3	8.0	1.0	0.2	0.0
4	66.8	4.9	0.2	0.0	0.0	0.0	0.0

All comorbidities refer to any occurrence prior to or during the study period.
Distribution of patient characteristics across categories differed significantly by K^+ gradient category, $P < 0.001$ for each characteristic.
AVF, arteriovenous fistula; AVG, arteriovenous graft; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CVC, central venous catheter; CVD, cerebrovascular disease; IDH, intradialytic hypotension; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation; Tx time, treatment time; UF, ultrafiltration (expressed as a percent of body weight).
[a]Shown for informational purposes only. Analyses were not adjusted for this variable.

demonstrates that when the K^+ gradient itself is examined, a steeper gradient is associated with a substantially greater risk of short-term adverse outcomes (i.e. hospitalization, ED visit). The steepest gradients, by definition, can only be achieved by hyperkalemic patients dialyzing against a relatively low dialysate K^+. Thus, although this treatment strategy may not be associated with a greater long-term risk of all-cause mortality, it may still pose a significant short-term risk to patients' health.

Kovesdy *et al.* did observe a greater risk of long-term all-cause mortality in patients with high-average serum K^+ who used a higher dialysate K^+, implying a shallow K^+ gradient. A shallow gradient among patients with high serum K^+ may lead to inadequate K^+ removal during dialysis, resulting in a greater risk of hyperkalemia due to K^+ overload. Thus, patients with high serum K^+ may face a double-edged sword: on one hand, the use of a steep gradient enables better K^+ mass-balance over time, at the expense of increased risk of short-term complications (e.g. arrhythmias). On the other hand, although a shallow gradient may impose less risk of short-term complications, it carries a longer-term risk of mortality.

Taken together, the study by Kovesdy *et al.* and the results presented here underscore the flaws of the current thrice-weekly hemodialysis paradigm with respect to K^+ homeostasis. Ideal homeostasis requires both K^+ mass-balance over time

Table 2. Same-day outcomes by K^+ gradient category

Outcomes	K^+ gradient category (mEq/L)						
	<0 $n = 1251$	0–<1 $n = 25\,119$	1–<2 $n = 139\,631$	2–<3 $n = 327\,906$	3–<4 $n = 238\,739$	4–<5 $n = 80\,286$	≥5 $n = 17\,809$
Hospitalization							
Events	<10	109	562	1080	707	281	71
Crude risk[a]	0.799	4.339	4.025	3.294	2.961	3.500	3.987
Unadjusted OR	0.24	1.32	1.22	1 (ref)	0.90	1.06	1.21
(95% CI)	(0.03–1.73)	(1.08–1.61)	(1.10–1.35)		(0.82–0.99)	(0.93–1.21)	(0.95–1.55)
Adjusted OR[b]	0.12	0.87	0.98	1 (ref)	1.02	1.30	1.51
(95% CI)	(0.02–0.90)	(0.70–1.08)	(0.87–1.09)		(0.92–1.13)	(1.13–1.51)	(1.16–1.97)
ED visit							
Events	<10	227	1331	2793	1944	697	192
Crude risk[a]	7.194	9.037	9.532	8.518	8.412	8.682	10.781
Unadjusted OR	0.84	1.06	1.12	1 (ref)	0.96	1.02	1.27
(95% CI)	(0.43–1.67)	(0.92–1.22)	(1.05–1.20)		(0.90–1.01)	(0.93–1.11)	(1.09–1.48)
Adjusted OR[b]	0.36	0.80	0.98	1 (ref)	1.06	1.16	1.41
(95% CI)	(0.16–0.82)	(0.69–0.93)	(0.91–1.05)		(0.99–1.13)	(1.06–1.28)	(1.20–1.67)
Cardiovascular hospitalization							
Events	0	24	134	299	209	69	21
Crude risk[a]	0	0.956	0.960	0.912	0.875	0.859	1.179
Unadjusted OR	N/E[c]	1.05	1.05	1 (ref)	0.96	0.94	1.29
(95% CI)		(0.69–1.59)	(0.86–1.29)		(0.80–1.15)	(0.72–1.23)	(0.82–2.05)
Adjusted OR[b]	N/E[c]	0.73	0.93	1 (ref)	1.07	1.13	1.36
(95% CI)		(0.45–1.18)	(0.74–1.16)		(0.88–1.30)	(0.84–1.52)	(0.80–2.31)
Death							
Events	0	<10	21	34	16	<10	<10
Crude risk[a]	0	0.159	0.150	0.104	0.067	0.100	0.112
Unadjusted OR	N/E[c]	1.54	1.45	1 (ref)	0.65	0.96	1.08
(95% CI)		(0.54–4.33)	(0.84–2.50)		(0.36–1.17)	(0.44–2.08)	(0.26–4.51)
Adjusted OR[b]	N/E[c]	0.92	1.05	1 (ref)	0.74	1.13	1.71
(95% CI)		(0.30–2.85)	(0.58–1.93)		(0.39–1.43)	(0.45–2.85)	(0.38–7.68)

CI, confidence interval; N/E, non-estimable, OR, odds ratio.

[a]Given the short duration of the outcome windows, multiple outcome events are not a relevant consideration. Therefore, analyses are presented in terms of risk (per 1000 intervals) rather than rate.

[b]Adjusted for age, sex, race, vintage, access, etiology, weight, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease, malignancy, Charlson comorbidity index, albumin, creatinine, normalized protein catabolic rate, pre-dialysis systolic blood pressure, intradialytic hypotension, ultrafiltration volume, day of week, shift and total body water.

[c]Non-estimable due to a paucity of outcome events.

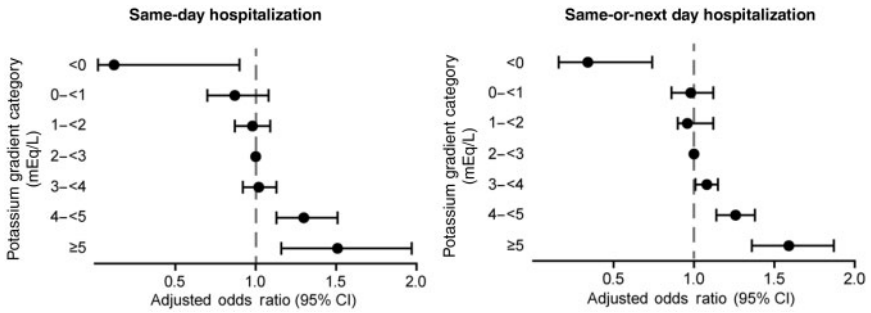

FIGURE 1: Odds ratios for hospitalization by K^+ gradient category. The adjusted odds ratios (circles) and 95% confidence intervals (horizontal error bars) for same day (left panel) or same-or-next day (right panel) hospitalization for each of the indicated K^+ gradient categories (referent to 2–<3 mEq/L) are presented.

and the avoidance of large fluctuations in K^+ concentration. Modifications to the current system, such as more frequent dialysis or more severe dietary K^+ restrictions, are unlikely to be widely accepted by patients. K^+ profiling, in which the K^+ concentration of the dialysate is gradually reduced over the course of the treatment to enable adequate K^+ removal across a relatively small gradient, has been found to reduce arrhythmias [24], but it is unclear if this is practicable at scale. Pharmacologic approaches to K^+ management may present a more tractable alternative, but this will require high-level evidence from well-designed and adequately-powered prospective trials on surrogate outcomes (e.g. arrhythmia) or, preferably, endpoints that are specific to the proposed mechanisms of action.

This study needs to be interpreted in light of its limitations. Derived from an observational study, the associations described

Table 3. Same-or-next day outcomes by K^+ gradient category

Outcomes	K^+ gradient category (mEq/L)						
	<0 $n = 1251$	0–<1 $n = 25\,119$	1–<2 $n = 139\,631$	2–<3 $n = 327\,906$	3–<4 $n = 238\,739$	4–<5 $n = 80\,286$	≥5 $n = 17\,809$
Hospitalization							
Events	11	313	1399	2734	1865	688	191
Crude risk[a]	8.793	12.461	10.019	8.338	7.812	8.569	10.725
Unadjusted OR	1.06	1.50	1.20	1 (ref)	0.94	1.03	1.29
(95% CI)	(0.57–1.95)	(1.33–1.70)	(1.13–1.29)		(0.88–0.99)	(0.94–1.12)	(1.11–1.50)
Adjusted OR[b]	0.34	0.98	0.96	1 (ref)	1.08	1.26	1.59
(95% CI)	(0.16–0.74)	(0.86–1.12)	(0.90–1.03)		(1.01–1.15)	(1.14–1.38)	(1.36–1.87)
ED visit							
Events	18	459	2459	5129	3535	1255	372
Crude risk[a]	14.389	18.273	17.611	15.642	14.807	15.632	20.888
Unadjusted OR	0.92	1.17	1.13	1 (ref)	0.95	1.00	1.34
(95% CI)	(0.56–1.51)	(1.06–1.30)	(1.07–1.19)		(0.90–0.99)	(0.93–1.07)	(1.20–1.50)
Adjusted OR[b]	0.34	0.85	0.96	1 (ref)	1.06	1.17	1.54
(95% CI)	(0.19–0.63)	(0.76–0.94)	(0.91–1.01)		(1.01–1.11)	(1.08–1.25)	(1.36–1.74)
Cardiovascular hospitalization							
Events	<10	49	240	490	351	103	30
Crude risk[a]	0.799	1.951	1.719	1.494	1.470	1.282	1.685
Unadjusted OR	0.53	1.31	1.15	1 (ref)	0.98	0.86	1.13
(95% CI)	(0.07–3.85)	(0.97–1.76)	(0.99–1.34)		(0.86–1.13)	(0.69–1.06)	(0.78–1.63)
Adjusted OR[b]	N/E[c]	1.02	1.01	1 (ref)	1.11	1.03	1.37
(95% CI)		(0.75–1.41)	(0.86–1.19)		(0.96–1.28)	(0.83–1.28)	(0.94–2.00)
Death							
Events	0	16	65	99	62	24	<10
Crude risk[a]	0	0.637	0.466	0.302	0.260	0.299	0.169
Unadjusted OR	N/E[c]	2.11	1.54	1 (ref)	0.86	0.99	0.56
(95% CI)		(1.24–3.58)	(1.13–2.11)		(0.63–1.18)	(0.63–1.55)	(0.18–1.76)
Adjusted OR[b]	N/E[c]	1.05	1.11	1 (ref)	1.15	1.47	0.94
(95% CI)		(0.59–1.88)	(0.79–1.57)		(0.82–1.61)	(0.90–2.39)	(0.29–3.03)

[a]CI, confidence interval; N/E, non-estimable, OR, odds ratio. Given the short duration of the outcome windows, multiple outcome events are not a relevant consideration. Therefore analyses are presented in terms of risk (per 1000 intervals) rather than rate.
[b]Adjusted for age, sex, race, vintage, access, etiology, weight, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease, malignancy, Charlson comorbidity index, albumin, creatinine, normalized protein catabolic rate, pre-dialysis systolic blood pressure, intradialytic hypotension, ultrafiltration volume, day of week, shift, and total body water.
[c]Non-estimable due to a paucity of outcome events.

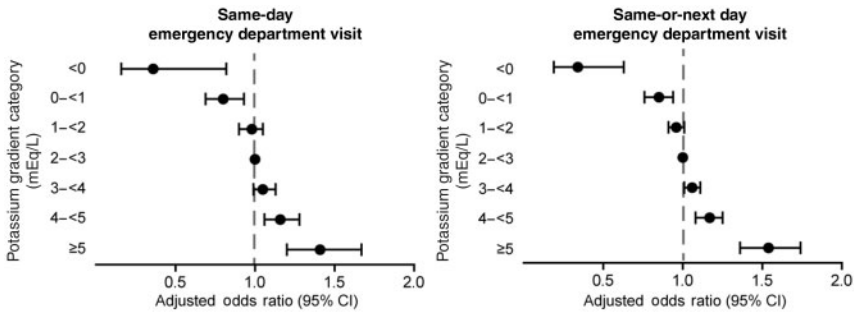

FIGURE 2: Odds ratios of ED visit by K^+ gradient category. The adjusted odds ratios (circles) and 95% confidence intervals (horizontal error bars) for same-day (left panel) or same-or-next day (right panel) ED visit for each of the indicated K^+ gradient categories (referent to 2–<3 mEq/L) are presented.

may not reflect causality. In addition, residual confounding may be present. Our focus on short-term outcomes led to relatively low numbers of some outcomes of interest and reduced power to detect associations that may have existed, especially with cardiovascular events or mortality. Further, our reliance on routinely collected, retrospective data precluded the analysis of outcome events that might be more directly linked to the proposed mechanism of action, such as arrhythmias. The source data contained records of the calendar date of exposure and outcome events, but not the time of day at which they occurred. Thus, while we presume that the majority of outcome events occurring on the same calendar day as the relevant dialysis treatment occurred following the treatment as opposed to prior, we cannot test this empirically and caution should be used when interpreting these findings. Our study analyzed patients who dialyzed on a Monday/Wednesday/Friday

schedule only; it is plausible, but not certain that these findings would generalize to patients dialyzing on a Tuesday/Thursday/Saturday schedule. Finally, it is unclear whether these findings from a large US dialysis organization can be generalized to other settings or countries with different types of patients or dialysis practice patterns.

In conclusion, we provide novel evidence linking a large gradient between pre-dialysis serum K^+ concentration and prescribed dialysate K^+ concentration with untoward short-term outcomes in patients undergoing hemodialysis. Determining whether these associations are causal will require randomized trials.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

S.M.B. is an employee of DaVita Clinical Research. His spouse is an employee of AstraZeneca. C.D.M., N.O. and D.M.S. are employees of Relypsa Inc. W.C.W. has served as a scientific adviser or consultant to AstraZeneca, Relypsa and Vifor Fresenius Medical Care Renal Pharma. C.P.K. has received consulting fees from Astra Zeneca, Relypsa and ZS Pharma. The results presented in this article have not been published previously in whole or part.

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