AJKD

Original Investigation

# Serum Potassium and Short-term Clinical Outcomes Among Hemodialysis Patients: Impact of the Long Interdialytic Interval

*Steven M. Brunelli, MD, MSCE,[1] Charles Du Mond, PhD,[2] Nina Oestreicher, PhD,[2,3] Viatcheslav Rakov, MD,[4] and David M. Spiegel, MD[2]*

**Background:** Hyperkalemia is common among hemodialysis patients and is associated with morbidity and mortality. The long interdialytic interval is likewise associated with adverse outcomes. However, the interplay among serum potassium, dialysis cycle phase, and clinical outcomes has not been examined.

**Study Design:** Retrospective observational study.

**Setting & Participants:** 52,734 patients receiving in-center hemodialysis at a large dialysis organization during 2010 and 2011 contributed 533,889 potassium measurements (230,634 on Monday; 285,522 on Wednesday; 17,733 on Friday).

**Predictor:** Serum potassium concentration, day of the week of potassium measurement.

**Outcomes:** Death, hospitalization, emergency department (ED) visit.

**Results:** There was a significant association between higher serum potassium and risk of hospitalization within 96 hours that was of greater magnitude on Fridays (389 hospitalizations) than Mondays or Wednesdays (4,582 and 4,629 hospitalizations, respectively; *P* for interaction = 0.008). Serum potassium of 5.5 to <6.0 (vs the referent category of 4.0-<4.5 mEq/L) was associated with increased risk of hospitalization on Fridays, with an adjusted OR of 1.68 (95% CI, 1.22-2.30). However, serum potassium of 5.5 to <6.0 mEq/L was associated with only mild elevation of risk on Mondays and no significantly increased risk on Wednesdays (adjusted ORs of 1.12 [95% CI, 1.00-1.24] and 1.04 [95% CI, 0.94-1.16], respectively). Associations of elevated serum potassium (6.0-<6.5 mEq/L or greater) with death and ED visit were significant, but did not differ based on day of the week.

**Limitations:** There were insufficient observations to detect effect modification by day of the week for deaths, ED visits, and specific causes of hospitalizations. Confounding may have influenced results.

**Conclusions:** Higher serum potassium is associated with increased short-term risk of hospitalization, ED visit, and death. The association between serum potassium and hospitalization risk is modified by day of the week, consistent with a contribution of accumulated potassium to adverse outcomes following the long interdialytic interval. Further work is needed to determine whether directed interventions ameliorate this risk.


***INDEX WORDS:*** Hyperkalemia; serum potassium; hemodialysis; hospitalization; mortality; emergency department visit; long interdialytic interval; phase of dialytic cycle; potassium gradient; end-stage renal disease (ESRD).

**Editorial, p. 4**

In states of health, serum potassium is typically maintained between 3.5 to 5.0 mEq/L.[1] Tight control is necessary because serum potassium is a crucial determinant of resting membrane potential, and homeostasis is necessary for proper neurologic and cardiac conduction.[2]

Excessively high serum potassium has long been known to promote ventricular arrhythmias and cardiac death. However, extreme elevations in serum potassium are comparatively rare among nonhospitalized patients. Recent evidence has shown that more modest elevations in serum potassium are common, particularly among patients with end-stage renal disease (ESRD) and earlier stages of chronic kidney disease (CKD),[3,4] despite widespread recommendation for dietary potassium restriction among the former.[5] The effects of serum potassium are therefore particularly relevant in these populations. An emerging literature has documented that such modest elevations

*From [1]DaVita Clinical Research, Minneapolis, MN; [2]Relypsa Inc, Redwood City; [3]Department of Clinical Pharmacy, University of California San Francisco, San Francisco, CA; and [4]Vifor Pharma, Glattbrugg, Switzerland.*

*Received July 7, 2016. Accepted in revised form October 9, 2016. Originally published online January 19, 2017.*

*Address correspondence to Steven M. Brunelli, MD, MSCE, 825 S 8th St, Minneapolis, MN 55404. E-mail: steven.brunelli@davita.com*



*0272-6386*

*http://dx.doi.org/10.1053/j.ajkd.2016.10.024*

in serum potassium are associated with death, hospitalization, and cardiovascular events,[6-8] but there has been little study of effects on other indices of morbidity or on health resource use, particularly in patients with ESRD, for whom only all-cause and cardiovascular mortality have been investigated.[6]

In the United States and elsewhere, patients with ESRD treated with in-center hemodialysis (HD) are typically dialyzed on a thrice-weekly basis. This paradigm creates a clinical scenario in which there are interspersed short (1-day) and long (2-day) interdialytic breaks. It has been shown that risk of mortality and hospitalization peaks at the end of the long interdialytic interval[9-11] and speculated that potassium accumulation may play a role. Nonetheless, an independent association of serum potassium concentration with outcomes following the long interdialytic interval has not been empirically confirmed or quantified.

The purpose of this study was 2-fold. First, we sought to estimate the independent association between serum potassium and short-term hospitalization risk, hospital costs, mortality risk, and risk for emergency department (ED) visit among patients with ESRD treated with thrice-weekly in-center HD. To the extent possible, we isolated the effect of serum potassium from the potential effects of fluid removal and clearance of other small molecules by adjusting our analyses for interdialytic weight gain, dialysis session length, and Kt/V. Second, we sought to estimate whether and to what degree associations between serum potassium and the outcomes listed above were affected by the phase of the dialytic cycle.

## METHODS

### Data and Patient Cohort

This was a retrospective observational study that considered a cohort of patients who were receiving thrice-weekly in-center HD at a large dialysis organization between January 1, 2010 and December 24, 2011. We conducted our study using deidentified patient data; therefore, according to title 45, part 46 of the US Department of Health and Human Services' Code of Federal Regulations, this study was deemed exempt from institutional review board (IRB) or ethics committee approval (Quorum IRB, Seattle, WA, identification number QR30707). We adhered to the Declaration of Helsinki and informed consent was not required.

At the large dialysis organization, routine serum potassium measurement is generally performed monthly. Routine laboratory measurements, including serum potassium, are processed at a central clinical laboratory (Deland, FL), typically within 24 hours of blood draw, and are recorded in automated fashion in the electronic health record. Blood draws occur immediately prior to HD, most often on the first or second treatment day of the week (eg, Monday or Wednesday for a Monday/Wednesday/Friday patient). Routine measurements may occasionally occur on Fridays for Monday/Wednesday/Friday patients for one of 2 reasons: (1) the patient missed dialysis on the regularly scheduled draw date, or (2) the facility rescheduled all its routine laboratory draws due to an extenuating circumstance (eg, weather). In the former case, there is a strong likelihood of confounding because factors that affected timing of the serum potassium measurement plausibly relate to outcome. In the latter case, the timing of serum potassium measurements is essentially independent of the health circumstances of the corresponding patient and therefore provide an opportunity to study the respective roles of serum potassium, day of the week, and health outcomes. Therefore, primary analyses were restricted to serum potassium measurements in which the corresponding patient had not missed dialysis in the 7-day period leading up to the serum potassium measurement (ie, patients for whom the timing of serum potassium measurement was not dictated by dialysis absenteeism). Otherwise analogous sensitivity analyses considered serum potassium measurements irrespective of antecedent dialysis attendance. When routine laboratory draws for Tuesday/Thursday/Saturday patients are disrupted by extenuating circumstances, they are not rescheduled to Saturdays, but instead to the following week; therefore, Tuesday/Thursday/Saturday patients were not considered in these analyses.

Separately, emergency ("stat") laboratory measurements may be ordered by clinicians at any time for any patient. Such measurements are processed in local clinical laboratories, rather than the central laboratory, and recorded separately in the electronic health record. Given that the circumstance surrounding the need for stat serum potassium measurements may engender confounding, they were not considered in these analyses.

In total, eligibility for this study required that (see diagram in Fig S1) patients: (1) were 18 years or older, enrolled at the large dialysis organization, and receiving thrice-weekly in-center HD on a Monday/Wednesday/Friday schedule; (2) had at least 1 routine serum potassium measurement made between January 1, 2010 and December 24, 2011; (3) were enrolled in Medicare Parts A and B at the time of serum potassium measurement (necessary to ensure visibility to outcomes); and (4) had not missed HD in the 7 days preceding serum potassium measurement (primary analyses only).

### Exposure and Outcomes

Data were considered on a patient-interval level. Patients were eligible to contribute multiple intervals provided that each interval met the eligibility criteria. Each interval began at the time of a qualifying serum potassium measurement (index date). Outcomes for the interval were considered for the 4-day period consisting of index date and the next 3 calendar days (see study schema, Fig 1). The 4-day window was chosen to allow observation for events that occurred during the ensuing interdialytic interval, as well as those that might be precipitated by the subsequent dialysis treatment (ie, due to high implied serum to dialysate potassium gradient). For events that occurred on the index date, records did not permit us to distinguish between those that occurred before or after dialysis. However, because the likelihood of patients reporting to their ambulatory dialysis centers later in the day following an outcome event (eg, hospitalization) was deemed low and interest in day 0 outcomes was high, all day 0 outcomes were considered. Exposure was assigned based on the value of the serum potassium measurement and the day of the week (Monday, Wednesday, or Friday) on which the measurement occurred. Serum potassium was categorized as 4.0 to $<$4.5, 4.5 to $<$5.0, 5.0 to $<$5.5, 5.5 to $<$6.0, 6.0 to $<$6.5, 6.5 to $<$7.0, or $\geq$7.0 mEq/L. Interest in this study was on the effects of high serum potassium. Considering this and the high likelihood of confounding (eg, on the basis of nutritional status), serum potassium values $<$ 4.0 mEq/L were not considered.

Outcomes of interest were death, hospitalization, ED visits, and hospital costs. Deaths were identified from the large dialysis organization's electronic health record. Hospitalizations were identified from Medicare Part A claims in the US Renal Data System (USRDS) data set. Causes of hospitalization were ascribed on the basis of the primary *International Classification of Diseases, Ninth Revision* (*ICD-9*) code identified in the claim, applying the Agency