Temporal changes in dialysate $[\text{Na}^+]$ prescription from 1996 to 2018 and their clinical significance as judged from a meta-regression of clinical trials

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Abstract

Over the last two decades, the clinical care of dialysis patients has refocused sharply on fluid volume control. Dialysate $[\text{Na}^+]$ is a key, albeit under-investigated, clinical tool for manipulation of fluid volume on dialysis. In the article, we firstly use data from the Dialysis Outcomes and Practice Patterns Study to document the global decrease in dialysate $[\text{Na}^+]$ that has occurred from 1996 to 2018, and demonstrate the virtual disappearance of $[\text{Na}^+]$ profiling from routine dialysis practice over the same period. Second, we used data from previously synthesized randomized clinical trial evidence combined with that of a more recently published trial to assess the clinical significance of these changes, estimating the effects of different levels of low dialysate $[\text{Na}^+]$ on key clinical outcomes. Our analyses suggest that current levels of dialysate $[\text{Na}^+]$ in some health jurisdictions are possibly causing harm to many patients, especially given that real world populations are significantly less robust and more vulnerable than clinical trial ones. To quote a recent editorial, "more evidence needed before lower dialysate sodium concentrations can be recommended." That evidence is coming, and no further changes should be made to default customary practice until it is available.

1 INTRODUCTION

There is ample evidence supporting a causal link between fluid overload and the development of morbidity and mortality in dialysis populations. Although there have always been proponents of aggressive fluid volume control as a means of improving patient outcomes,$^3$ it has only been more recently that there has been a more systematic focus in this area.$^2,3$

Recently, there has been renewed interest in lower dialysate $[\text{Na}^+]$ as a means for controlling fluid volume, supported by positive qualitative and quantitative reviews of cumulative clinical experience.$^4,5$ This has provided a much needed evidence base to support the various "calls to action" from clinical governance groups that have made specific clinical recommendations in this area. Nonetheless, definitive clinical trials of lower dialysate $[\text{Na}^+]$ are still needed to ascertain the effect of this intervention on harder clinical outcomes, such as hospitalization and mortality.

In this report, we used data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to document secular change in the landscape of dialysate $[\text{Na}^+]$ prescription, examining multiple health jurisdictions over all phases of the study spanning 1996 to 2018. In an effort to determine the clinical significance of these changes, we use data from clinical trials of low dialysate $[\text{Na}^+]$ to estimate the effects of different levels of low dialysate $[\text{Na}^+]$ on key clinical outcomes.
2 | METHODS

2.1 | Secular change analysis

For the documentation of prescription changes over time, we included data from DOPPS Phase 1 (1996-2001), Phase 2 (2002-2004), Phase 3 (2005-2008), Phase 4 (2009-2011), Phase 5 (2012-2015), and Phase 6 (2015-2018) cohorts of HD populations from 14 countries across 4 regions: North America (ie Canada and US); Europe (ie Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom [UK]); Australia and New Zealand (ANZ) and Japan. The study population comprised all patients on HD enrolled in the DOPPS and dialyzing 3 to 5 times per week. We performed a descriptive analysis rather than an inferential one, describing practice patterns around dialysate [Na+] in each phase of the DOPPS as designated follow-up periods.

For each patient, we utilized their recorded dialysate [Na+] at the baseline of each DOPPS phase. Mean values for dialysate [Na+] in each country and region were calculated among all HD patients, combining ANZ and Europe into a single region. Linear mixed models were used to estimate the slope in each country over the course of their participation in the DOPPS, accounting for within-facility clustering. These analyses were performed using SAS software (version 9.4; SAS Institute).

2.2 | Clinical significance analysis

To estimate dose-response relationships in relation to different levels of low dialysate [Na+], we examined effect modification of treatment effectiveness using meta-regression of data from published randomized clinical trials. We extracted data from a recent Cochrane systematic review on the subject,4 which made comparisons between control groups receiving conventional dialysate [Na+] (the weighted average being 140.8 mmol/L) and intervention groups receiving a lower concentration (the weighted average being 133.9 mmol/L). We combined these data with that from a clinical trial that has been published since the Cochrane review (the SoLID trial), which compares a variety outcomes over one year between patients randomized to dialysate [Na+] of 140 vs 135 mmol/L.6-9

In these 13 clinical trials, a range of lower dialysate [Na+] were trialed, spanning from 130 to 137 mmol/L. In addition, a range of conventional dialysate [Na+] were used in the trials, meaning overall differences in dialysate [Na+] between the control and intervention groups spanned 3 to 15 mmol/L across the different studies. We therefore modeled the effect of these two treatments (the first being level of low dialysate [Na+], the second the level of difference in dialysate [Na+] between groups) on key clinical outcomes using meta-regression.

The outcomes we used as efficacy and safety measures are limited by what is actually available in the literature, and there are no clinical trials reporting effects of low dialysate [Na+] on outcomes such as mortality or major adverse clinical events. We therefore used inter-dialytic weight gain and pre-dialysis mean arterial blood pressure (MAP) as efficacy measures. These variables are excellent markers of fluid status in clinical trials—unlike the case in observational studies, since dissociation of these variables from fluid status by dysnutrition, cardiac dysfunction, dialysis prescription misspecifications etc is abrogated by randomization. In terms of treatment safety measures, we used intra-dialytic hypotension and cramps as markers for adverse effects from the intervention.

We created meta-regression linear prediction (and 95% confidence interval) graphs by plotting the treatment variable (dialysate [Na+] in the low dialysate [Na+] group, or difference in dialysate

| TABLE 1 | Patients included in the analysis, by country and region, over the six Phases of the DOPPS |
|----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| Region | Phase of DOPPS | 2 | 3 | 4 | 5 | 6 |
| Europe/ANZ | ANZ | 3998 | 5032 | 5464 | 6322 | 5352 | 2879 |
| Bel | . | 535 | 709 | 739 | 437 | . |
| Fra | 909 | 641 | 729 | 695 | 298 | . |
| Ger | 826 | 675 | 719 | 811 | 905 | 463 |
| Ita | 794 | 737 | 661 | 871 | 784 | 334 |
| Spa | 795 | 811 | 846 | 1005 | 954 | 677 |
| Swe | . | 635 | 702 | 793 | 794 | 663 |
| UK | 674 | 421 | 520 | 655 | 512 | 420 |
| Japan | Jpn | 2592 | 2183 | 2257 | 2111 | 2277 | 2228 |
| North America | Can | 4472 | 2111 | 1815 | 1858 | 2777 | 2283 |
| US | 4472 | 1642 | 1381 | 1398 | 2090 | 1664 |
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[Na+] between groups) on the x-axis and treatment effect measure on the y-axis. The bubbles were plotted in proportion to the contribution of each study to the regression model. These analyses were performed using Stata software (version IC/14.2; StataCorp).

3 | RESULTS

A total of 58,011 patients from 1,699 facilities with values for dialysate [Na+] were included for analysis over the 6 phases of the DOPPS. The distribution of patients by health jurisdiction is Table 1.

Over the course of this analysis, mean dialysate [Na+] decreased in all countries and regions over the course of the study, from an overall mean dialysate [Na+] of 140.06 mmol/L in phase 1 (1996-2001) to 138.90 in phase 6 (2015-2018). The fastest decrease in dialysate [Na+] was seen in the United States at 0.53 mmol/L (95% CI: −0.65, −0.41) per phase of the DOPPS, and the slowest was in Spain at 0.05 mmol/L (95% CI: −0.13, 0.02) per phase of the DOPPS. Over this period of observation, the utilization of [Na+] profiling decreased to less than 10% of patients overall, with a particularly marked fall in North America, which has always been the bastion of this technique.

The use of a facility-level default dialysate [Na+] (defined as ≥90% of non-profiled patients having the same dialysate sodium in a given facility) appears to be constant overall, although there are isolated changes in certain countries. Approximately half of patients are treated in dialysis facilities with a default dialysate [Na+], with the exception of Japan where this proportion is higher due to the widespread use of central dialysate delivery. Of note, the sampling
The frame of this study did not include a separate analysis of incident patients due to power concerns. The assessment of this characteristic in dominantly prevalent patients will underestimate, since there will always be a proportion of patients initially treated with initially default setting, before such as their dialysate [Na⁺] is individualized according the their response to therapy.
These data are illustrated graphically in Figures 1 and 2, and provided in Tables S1-S3.

The meta-regression of data from the Cochrane review and the recently published SoLID trial are illustrated in Figures 3-6. Figure 3 illustrates dose-response for the treatment efficacy measure of inter-dialytic weight gain. In those trials reporting this measure, there is a progressive decrease over the entire span of lower dialysate [Na+] and reduction in dialysate sodium, indicating a monotonic dose-response relationship. Figure 4 illustrates the corresponding relationship for pre-dialysis MAP, where there is also a progressive decrease as degree of any decrease in dialysate [Na+] becomes greater.

The dose-response relationships for treatment safety measures are illustrated in Figures 5 and 6. In terms of intra-dialytic hypotension, there appears at first glance to be only a modest increase in the relative risk of events as dialysate [Na+] becomes lower or progressively reduced. However, many of the studies are from an older era, with likely under-reporting of this outcome—no definitions and taxonomy existed in those times, and a reactive rather than proactive approach was taken to ascertainment, which is evident in the reading of the publications. Accordingly, removing all studies performed before 1990 and including only modern ones, there is a progressive increase in the relative risk of intra-dialytic hypotension over the entire span of lower dialysate [Na+] and reduction in dialysate [Na+], indicating a monotonic dose-response relationship. The second treatment safety measure of intra-dialytic cramps shows a
similar dose-response relationship to intra-dialytic hypotension (Figure 6).

4 | DISCUSSION

The mortality risk of dialysis patients has improved over the last 10 years, although their survival in absolute terms remains similar or worse than many common cancers. The dominant cause of death in this population is cardiovascular in nature; approximately half of modern end-stage kidney disease patients start dialysis with a diagnosis of cardiovascular (CV) disease, and the majority of naïve patients develop it over their remaining lifetime. The most common modality of demise is sudden cardiac death due to bradyarrhythmia, and a panacea for this appears some way off given our limited understanding of specific risk factors and casual pathways.

Against this background, one of the most accepted surrogate markers of CV risk is left ventricular (LV) hypertrophy. One of the strongest predictors of LV mass is fluid overload, and one of the axiomatic causes of fluid overload is salt loading either through dialysate, diet, and/or inadequate ultrafiltration. The possibility that lower dialysate [Na+] might benefit LV mass has been studied in two recent and randomized clinical trials. Both demonstrated an improvement in inter-dialytic weight gain and blood pressure with lower dialysate [Na+], but only one found that lower dialysate [Na+] reduced LV mass. As such, the impact of lower dialysate [Na+] upon CV risk must still be viewed as moot.
The data in this study show that the world is moving on the basis of heuristics rather than waiting for definitive data. We show that dialysate [Na+] prescriptions are lower than previously, likely resulting in neutral—at least—or negative—at most—sodium balance in patients during HD. While this seems laudable, lower dialysate [Na+] is not without its hazards, the most obvious of which is intra-dialytic hypotension (IDH). For instance, the Cochrane meta-analysis of this intervention showed that risk of IDH with lower dialysate [Na+] was 1.52 (96% CI 1.14, 2.02) compared to conventional dialysate [Na+].

It is important too to recognize that measures of central tendency do not reflect distribution. For example, in Phase 6 of the DOPPS in the United States, the mean (standard deviation) of dialysate [Na+], was 137.5 (0.8). This indicates that 95% of the population are dialyzing at a dialysate [Na+] of between 135.9 to 139.1 mmol/L, with significant numbers of patients exposed to what must be regarded as truly low dialysate [Na+].

So the two key questions are (a) how low should we go with dialysate [Na+] to optimize fluid status without risking adverse events? (b) will any improvements achieved in this way translate to better patient survival? As to the first question, it would appear from the meta-regression that there is no particular threshold or limit around a benefit for our chosen markers of fluid balance, and the edict of “the lower the better” applies. However, for the adverse treatment effects of intra-dialytic hypotension and cramps, there is a fairly steady increase as dialysate [Na+] becomes progressively lower. From the point of view of safety, then, it would appear there is indeed a threshold for harm in relation to a weighted average dialysate [Na+] of 140.8 mmol/L, which starts at about 136 mmol/L.

It is absolutely critical to note that these estimates of treatment effect in clinical trials will misestimate corresponding effect in real world populations. This likelihood is illustrated as follows. An recent systematic review showed that 186 dialysis-related randomized clinical trials (excluding smaller ones with <100 participants) have been published globally from 1 January 2007 to 31 December 2016, enrolling a total of 79 104 participants on dialysis. In this analysis, participants were younger, more likely to be male, and less likely to have diabetes than “real life” patients. The mortality rate in the studies was approximately half of that in the registry data to which it was compared (8.9 versus 18.6 deaths per 100 patient years). Such selection bias favoring “healthy patients” is not unique to dialysis-related clinical trials—entirely concordant findings are seen in clinical trials within other medical subspecialties. However, to illustrate the impact of this situation in the real world, an exercise can be undertaken using the dialysis registry data from New Zealand from 1 January 1998 to 31 December 2017. The median (interquartile range) mortality rate in this sample was 15.9 deaths per 100 patients. The sub-sample with a mortality rate was 7.6 deaths per 100 patients amounts to between only 50 and 70% of the population, depending on sampling frame, with the most death-prone patients being excluded of course.

Therefore, when applying the results of the meta-regression of clinical trials to real world populations, the following generalizations are reasonable to make. It is reasonable to conclude that the lower the dialysate [Na+], the better the fluid status. It is also reasonable to conclude that there is an increase in clinical and patient-centered adverse events in these relatively health dialysis populations at a dialysate [Na+] of less than 136 mmol/L, although it is possible or even likely that vulnerable patients with impaired compensatory mechanisms will experience these events more easily and at a higher dialysate [Na+]. It can be speculated that this latter situation is the basis for the seminal observation that hyponatremic hemodialysis patients (hyponatremia being a powerful marker for general and especially cardiovascular comorbidity)
### TABLE 2
Unpublished and recruiting or completed randomized clinical trials with an intervention of lower dialysate [Na+] from the WHO Registry Network of primary and partner clinical trials registries

| Registration number | Estimated enrolment, study duration | Key inclusions | Key exclusions | Intervention | Control | Primary outcome |
|---------------------|-------------------------------------|----------------|---------------|--------------|---------|-----------------|
| NCT03144817 (Dialysate Sodium Lowering Trial (DeSaLT)) | 44 patients, 6 mo | Adults on facility hemodialysis, currently dialyzing at a dialysate [Na+] ≥ 137 mmol/L, pre-dialysis BP of >140/90 or treatment with 1 or more antihypertensives | Prone to intra-dialytic hypotension (occurring in > 10% of treatments in the past 3 mo), defined in terms of either symptoms, blood pressure, or need for intervention | Dialysate [Na+] 135 mmol/L | Dialysate [Na+] 138 mmol/L | Intra-dialytic hypotension, patient tolerance, frequency of emergency room visits and hospitalization, adherence to allocation |
| NCT02145260 (Trial of Dialysate Sodium in Chronic Hospitalized Hemodialysis Patients) | 200 patients | Adults on facility hemodialysis admitted to hospital | Use of pressors, pre-dialysis serum sodium <128 or >145 mmol/L, pre-dialysis systolic BP > 180, acute coronary syndrome within 7 d, acute stroke | Dialysate [Na+] 138 mmol/L | Dialysate [Na+] 142 mmol/L | Intra-dialytic blood pressure |
| NCT00724633 (Effect of Lowering Dialysate Sodium on Blood Pressure in Hemodialysis Patients: a Randomized Controlled Trial) | 35 participants, 3 mo | Adults on 3 times/wk hemodialysis >3 mo, hypertension, dialysate sodium [Na+] 140 mmol/L, mean pre-dialysis serum [Na+] <140 mmol/L | Frequent intra-dialytic hypotension, significant residual renal function, life expectancy <1 y | Dialysate [Na+] equal to patient’s pre-HD serum [Na+] OR Dialysate [Na+] lower than patient’s pre-dialysis serum [Na+] | Dialysate [Na+] 140 mmol/L | Change in blood pressure (ambulatory monitoring) |
| NCT02823821 (Randomised Evaluation of Sodium Dialysate Levels on Vascular Events (RESOLVE)) | 51520 participants (duration event driven) | Adults on facility hemodialysis | None | Default facility dialysate [Na+] 137 mmol/L | Default facility dialysate [Na+] 140 mmol/L | Composite of major cardiovascular events (hospitalised acute myocardial infarction, hospitalised stroke) and all-cause death |
| NCT02621450 (Low Sodium Dialysate and Ambulatory Blood Pressure Measurement Parameters) | 50 participants, 6 mo | Hemodialysis for more than 1 y, creatinine clearance less than 10 mL/min/1.73 m² | Frequent intra-dialytic hypotension, masking or white coat hypertension, heart failure, cardiomyopathies, acute coronary syndromes, chronic ischemic heart disease, acute or chronic liver disease, endocrine or pulmonary diseases, valvular heart diseases, malignancies, active urinary tract infections, hemoglobin levels below 8 g/dL | Dialysate [Na+] 137 mmol/L | Dialysate [Na+] 140 mmol/L | Change in blood pressure (ambulatory monitoring) |
have an increased risk with lower dialysate [Na+] in real world settings.\textsuperscript{27}

The second of the two key questions posited above is something that cannot be answered at present—we do not know if optimizing fluid status (without adverse events) using lower dialysate [Na+] improves patient survival. There are several randomized clinical trials forthcoming evaluating lower dialysate [Na+] (Table 2), the most important of which is the Randomised Evaluation of Sodium Dialysate Levels on Vascular Events (RESOLVE) study. RESOLVE is a cluster randomized pragmatic clinical trial, allocating participating dialysis facilities to a default facility-level dialysate [Na+] 137 versus 140 mmol/L (ClinicalTrials.gov Identifier: NCT02823821). The outcome is major adverse cardiac events, and the trial is proceeding well with now 95 facilities randomized in four countries, aiming for a final sample of 414 facilities to provide a total of 26,000 events. The final result of this study is still coming years away, but should be definitive as to answering the following question: what is the best default facility-level dialysate [Na+] that patients should start on, before it is modified according to their individual response to therapy.

While further evidence is awaited, what is the optimal approach for patients? It seems reasonable that if the patient has a high blood pressure, fluid overload, or high inter-dialytic weight gain, then it is probably helpful to consider a lower dialysate [Na+] so long as the patient does not have significant comorbidity putting them at undue risk from adverse effects. If these problems are not an issue, then perhaps it is better to place priority on avoiding intra-dialytic hypotension, and advise a higher dialysate [Na+].

As importantly, what is the optimal approach for hemodialysis providers? The overall picture suggests that they should not be continuing to decrease default dialysate [Na+] without further evidence or assessment for benefit and harm. Intradialytic hypotension—despite its clinical importance—is possibly the most poorly collected adverse event and clinical performance indicator for providers, impeding granularity of research and precision of patient care.\textsuperscript{28} At the present time, given the current levels dialysate [Na+] around the world and the ongoing downward trend, it is possible or even likely that some patients are already experiencing harm from this prescribing pattern. However, we will only be certain about the presence and extent of that harm once the RESOLVE trial is reported. In essence, Dr Hecking and colleagues are correct—“More Evidence Needed Before Lower Dialysate Sodium Concentrations Can Be Recommended”\textsuperscript{29}

**DISCLOSURES**

MRM was an employee of Baxter Healthcare (Asia) Pte Ltd, Singapore 2013-2020.

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**REFERENCES**

1. Charra B, Calemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. Kidney Int. 1992;41(5):1286-1291.
2. Weiner DE, Brunelli SM, Hunt A. Improving clinical outcomes among hemodialysis patients: a proposal for a “volume first” approach from the chief medical officers of US dialysis providers. Am J Kidney Dis. 2014;64(5):685-695.
3. Flythe JE, Mc Causland FR. Dialysate sodium: rationale for evolution over time. Semin Dial. 2017;30(2):99-111.
4. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. Cochrane Database Syst Rev. 2019;1:p.CD011204.
5. Basile C, Pisano A, Lisi P, et al. High versus low dialysate sodium concentration in chronic haemodialysis patients: a systematic review of 23 studies. Nephrol Dial Transplant. 2016;31(4):548-563.
6. Dunlop JL, Vandal AC, de Zoyza JR, et al. Rationale and design of the myocardial microinjury and cardiac remodeling extension study in the sodium lowering in dialysate trial (Mac-SoLID study). BMC Nephrol. 2014;15:120.
7. Dunlop JL, Vandal AC, de Zoyza JR, et al. Rationale and design of the Sodium Lowering In Dialysate (SoLID) trial: a randomised controlled trial of low versus standard dialysate sodium concentration during hemodialysis for regression of left ventricular mass. BMC Nephrol. 2013;14:149.
8. Dunlop JL, Vandal AC, de Zoyza JR, et al. Update: Rationale and design of the Sodium Lowering In Dialysate (SoLID) trial: a randomised controlled trial of low versus standard dialysate sodium concentration during hemodialysis for regression of left ventricular mass. BMC Nephrol. 2015;16:120.
9. Marshall MR, Vandal AC, de Zoyza JR, et al. Effect of low-sodium versus conventional sodium dialysate on left ventricular mass in home and self-care satellite facility hemodialysis patients: a randomised clinical trial. J Am Soc Nephrol. 2020;31(5):1078-1091.
10. Naylor KL, Kim SJ, Mc Arthur E, et al. Mortality in incident maintenance dialysis patients versus incident solid organ cancer patients: a population-based cohort. Am J Kidney Dis. 2019;73(6):765-776.
11. Marshall MR, Chan CT. The evolution of home HD – meeting modern patient needs. Contrib Nephrol. 2017;189:36-45.
12. Roy-Chaudhury P, Tumlin J, Koplan BA, et al. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. Kidney Int. 2018;93(4):941-951.
13. Roberts PR, Zachariah D, Morgan JM, et al. Monitoring of arrhythmia and sudden death in a hemodialysis population: The CRASH-ILR Study. PLoS One. 2017;12(12):e0188713.
14. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. Semin Dial. 2008;21(4):300-307.
15. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998;98(21):2334-2351.
16. Herzog CA, Strief JW, Collins AJ, Gilbertson DT. Cause-specific mortality of dialysis patients after coronary revascularization: why don’t dialysis patients have better survival after coronary intervention? Nephrol Dial Transplant. 2008;23(8):2629-2633.
17. Ritz E, Wanner C. The challenge of sudden death in dialysis patients. Clin J Am Soc Nephrol. 2008;3(3):920–9.
18. Liu J, Sun Fang, Ma Li-jie et al. Increasing dialysis sodium removal on arterial stiffness and left ventricular hypertrophy in hemodialysis patients. J Ren Nutr. 2016;26(1):38-44.
19. Smyth B, Haber A, Trongtrakul K, et al. Representativeness of randomized clinical trial cohorts in end-stage kidney disease: a meta-analysis. JAMA Intern Med. 2019;179(10):1316-1324.
20. Smyth B, Trongtrakul K, Haber A, et al. Inequities in the global representation of sites participating in large, multicentre dialysis trials: a systematic review. BMJ Glob Health. 2019;4(6):e001940.
21. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003;21(12):2268-2275.
22. Ridda I, MacIntyre CR, Lindley RI, Tan TC. Difficulties in recruiting older people in clinical trials: an examination of barriers and solutions. Vaccine. 2010;28(4):901-906.
23. Saunders DC, Twycross R. Why are trials in palliative care so difficult? Palliat Med. 2000;14(5):435.
24. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL, Straus SE. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer. 2006;6:34.
25. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol. 2005;23(13):3112-3124.
26. Witham MD, McMurdo ME. How to get older people included in clinical studies. Drugs Aging. 2007;24(3):187-196.
27. Hecking M, Karaboyas A, Saran R, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2012;59(2):238-248.
28. Flythe JE, Xue H, Lynch KE, et al. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol. 2015;26(3):724-734.
29. Hecking M, Rayner H, Port FK. More evidence needed before lower dialysate sodium concentrations can be recommended. American Journal of Kidney Diseases. 2015;65(3):519-520.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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