Effect of Low-Sodium versus Conventional Sodium Dialysate on Left Ventricular Mass in Home and Self-Care Satellite Facility Hemodialysis Patients: A Randomized Clinical Trial

Mark R. Marshall,1,2,3 Alain C. Vandal,4 Janak R. de Zoysa,5,6 Ruvin S. Gabriel,7 Imad A. Haloob,8 Christopher J. Hood,1 John H. Irvine,9 Philip J. Matheson,10 David O.R. McGregor,9 Kannaiyan S. Rabindranath,11 John B.W. Schollum,12 David J. Semple,13 Zhengxiu Xie,14 Tian Min Ma,1 Rose Sisk,15 and Joanna L. Dunlop1

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Fluid overload in patients undergoing hemodialysis contributes to cardiovascular morbidity and mortality. There is a global trend to lower dialysate sodium with the goal of reducing fluid overload.

Methods To investigate whether lower dialysate sodium during hemodialysis reduces left ventricular mass, we conducted a randomized trial in which patients received either low-sodium dialysate (135 mM) or conventional dialysate (140 mM) for 12 months. We included participants who were aged >18 years old, had a predialysis serum sodium ≥135 mM, and were receiving hemodialysis at home or a self-care satellite facility. Exclusion criteria included hemodialysis frequency ≥3.5 times per week and use of sodium profiling or hemodiafiltration. The main outcome was left ventricular mass index by cardiac magnetic resonance imaging.

Results The 99 participants had a median age of 51 years old; 67 were men, 31 had diabetes mellitus, and 59 had left ventricular hypertrophy. Over 12 months of follow-up, relative to control, a dialysate sodium concentration of 135 mmol/L did not change the left ventricular mass index, despite significant reductions at 6 and 12 months in interdialytic weight gain, in extracellular fluid volume, and in plasma B-type natriuretic peptide concentration (ratio of intervention to control). The intervention increased intradialytic hypotension (odds ratio [OR], 7.5; 95% confidence interval [95% CI], 1.1 to 49.8 at 6 months and OR, 3.6; 95% CI, 0.5 to 28.8 at 12 months). Five participants in the intervention arm could not complete the trial because of hypotension. We found no effect on health-related quality of life measures, perceived thirst or xerostomia, or dietary sodium intake.

Conclusions Dialysate sodium of 135 mmol/L did not reduce left ventricular mass relative to control, despite improving fluid status.

Clinical Trial registry name and registration number: The Australian New Zealand Clinical Trials Registry, ACTRN12611000975998.

JASN 31: 1078–1091, 2020. doi: https://doi.org/10.1681/ASN.2019090877

Although outcomes are improving, patients on dialysis have an annual mortality rate many-fold greater than the general population; bradyarrhythmias and progressive vascular disease are responsible for most deaths.1,2 The majority of elevated risk is attributable to kidney failure–related factors...
(fluid overload, toxicity from uremic solutes, and chronic inflammation) and treatment-related factors (sodium loading during dialysis and intradialytic hypotension [IDH]).\textsuperscript{3–6} Taken together, these factors culminate in defective left ventricular (LV) structure and function that are the basis for premature cardiovascular death.\textsuperscript{7,8}

The most potent intervention to improve LV structure and function in such patients is “intensive hemodialysis” (HD) implemented through frequent and/or extended-hour treatments. Intensive HD acts through greater control of fluid balance and/or greater removal of retained uremic solutes.\textsuperscript{9–11} However, the large majority of world’s patients are treated in HD facilities with constrained schedules of 3- to 6-hour treatments on a thrice-weekly basis. The intervention with the greatest effectiveness at a population level will be one providing the benefits of intensive HD but for patients on facility HD on constrained schedules. Lower dialysate $[\text{Na}^+]$ is a treatment that improves fluid overload and can be applied without any additional expense.\textsuperscript{12,13} We, therefore, sought to determine the effects of lower dialysate $[\text{Na}^+]$ compared with conventional practice, examining efficacy in terms of LV mass and function, patient-centered outcomes, and markers of fluid overload, such as interdialytic weight gain (IDWG) and BP, and safety in terms of IDH, dietary $\text{Na}^+$ intake, and plasma $[\text{Na}^+]$.

**METHODS**

**Study Participants**

Participants were recruited from HD providers across New Zealand. Eligible patients were $\geqslant18$ years old, were receiving home or self-care satellite facility HD, with a predialysis serum $[\text{Na}^+] \geqslant 135$ mM at enrolment. Home HD in New Zealand is logistically similar to that practiced elsewhere, with the exception that there are several assisted home HD programs in the country,\textsuperscript{14} although these patients did not participate in this study. In general, the definition of home HD in New Zealand includes community house HD where shared domestic facilities are used instead of individual domiciles.\textsuperscript{15,16} Self-care satellite facility HD in New Zealand is practiced in standalone or hospital-based HD facilities, where patients perform some or all of the dialysis procedure with less than full or no staff assistance. Such models of care are common elsewhere and reasonably well defined in published health technology assessments.\textsuperscript{17–22}

Patients were excluded from participation if they met the following conditions at enrolment: HD at a frequency $>3.5$ times per week, treatment with maintenance hemodialfiltration, life expectancy $<12$ months, enrolment in clinical studies involving antihypertensive medications, sodium profiling during HD, scheduled live donor kidney transplantation within 12 months, documented infiltrative or hereditary cardiomyopathies, at least moderate aortic valve disease, or considered by their treating nephrologist to have conditions limiting or contraindicating study procedures. All participants provided written informed consent.

**Significance Statement**

Because fluid overload in patients undergoing hemodialysis contributes to cardiovascular morbidity and mortality, there is a global trend to use low-sodium dialysate in hemodialysis with the goal of reducing fluid overload. To investigate whether lower dialysate sodium during hemodialysis improves left ventricular mass, the authors conducted a randomized clinical trial of 99 adults that compared use of low-sodium dialysate (135 mM) with conventional dialysate (140 mM) for 12 months. Although participants with lower dialysate sodium showed significant improvement in fluid status, the intervention had no effect on left ventricular mass index. The intervention also increased intradialytic hypotension. Given these findings, the current trend to lower dialysate sodium should be reassessed, pending the results of large trials with hard clinical end points.

**Study Protocol**

This was a two-group, parallel-design study, with a protocol and update that have been published.\textsuperscript{23,24} Eligible patients were randomly allocated 1:1 to either intervention (lower dialysate $[\text{Na}^+]$ at 135 mmol/L) or control (conventional dialysate $[\text{Na}^+]$ at 140 mmol/L) groups. Randomization was through the National Health Medical Research Council, Sydney, Australia, using a computer-generated sequence with permuted blocks with random block sizes (15% blocks of size 6 and 85% blocks of size 4) stratified by (1) study site and (2) conventional ($\leqslant18$ h/wk) versus extended-hour ($>18$ h/wk) HD; the allocation itself was by an interactive voice response system. Allocation was not accessible to study personnel except to receive a treatment assignment for a specific participant. Randomization was performed after baseline study assessments and measurements.

HD procedures and medical cares were performed as per usual practice as defined by the Caring for Australasians with Renal Impairment guidelines (www.cari.org.au). HD products are detailed in Supplemental Table 1, and were identical within the centers forming randomization strata. All home HD machines were maintained and calibrated as per manufacturers’ instructions, with the same cadence as per in-center machines. Dietary salt intake was managed by dietitians according to local clinical practice guidelines.\textsuperscript{25} Participants with IDH1 or who were found to have a systolic BP $<95$ mm Hg at any time were managed to a standard protocol, with adjustment of antihypertensive medications as was considered safe in the judgement of the treating physician. Ethnicity was self-declared. Comorbidity data were collected by chart review and direct participant interview.

Study measurements other than for LV mass were for the most part taken in the participants’ homes for those on home HD and at their dialysis facility for those on self-care satellite facility HD, although all participants were offered both options where feasible. All study measurements were performed by the same observer for a given participant.
Study Outcomes

The primary outcome was LV mass index, with an end point 12 months after baseline assessment. Prespecified secondary efficacy outcomes included LV volume (0 and 12 months); IDWG (0, 3, 6, 9, and 12 months); intra- and interdialytic BP (0, 3, 6, 9, and 12 months and 0, 6, and 12 months, respectively); number and dose of antihypertensives (0, 3, 6, 9, and 12 months); plasma B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels (0, 3, 6, 9, and 12 months); extracellular fluid volume (0, 3, 6, 9, and 12 months); health-related quality of life (HRQoL; 0 and 12 months); and xerostomia and thirst (0 and 12 months). Prespecified secondary safety outcomes included IDH (0, 3, 6, 9, and 12 months); dietary Na⁺ intake (0, 6, and 12 months); and predialysis serum osmolality and [Na⁺] (0, 3, 6, 9, and 12 months).

LV mass index was measured by cardiac magnetic resonance imaging (CMR). It is known that, when fluid accumulates between HD sessions, this results in myocardial edema. During ultrafiltration with HD, there is redistribution of this fluid from the myocardium back onto the intravascular compartment. Therefore, CMR was performed immediately (as practicable) predialysis to ensure within-participant and between-group comparability of repeated measures. The timing of CMR was after a “long break” for thrice-weekly participants and after a midweek break for participants with fixed interdialytic intervals. All imaging was performed on 1.5-Tesla scanners (various vendors) using a phased array surface coil during mild expiration and electrocardiographic triggering. Cine images in four-, three-, and two-chamber views and short axis views with a 6-mm slice thickness and 12-mm slice gap with 20–30 phases depending on heart rate were acquired according to a prespecified standardized protocol using steady-state free precession (sequences). Quantitative assessments of LV mass, end diastolic/end systolic volumes, and ejection fraction were analyzed at a core laboratory using validated Cardiac Image Modeler (Auckland MRI Research Group) software. The analysis was performed in duplicate by two independent and blinded analysts, and it was regularly monitored for drift. Measurements obtained from analysts were averaged.

Secondary efficacy outcomes were assessed as follows. IDWG was measured as gain in weight during dialysis treatments modeled as the time-averaged value over 2 weeks of HD treatments before each study visit. Intradialytic BP was measured using the Omron HEM-7911T BP Monitor (Omron Healthcare Inc., Lake Forest, IL) and modeled as the time-averaged value over 2 weeks of dialysis treatments before each study visit. Interdialytic BP was measured as ambulatory measurements at 30-minute intervals over the “long break” using Oscar 2 ambulatory BP monitors (Suntech Medical Instruments, Raleigh, NC). For those unable or unwilling to perform ambulatory BP measurements, interdialytic BP was determined as the weekly average of home BP readings made three times per day (on waking up, between 12:00 PM and 7:00 PM, and before bed) as the best approximation of ambulatory BP. The number and dose of antihypertensives were recorded as the aggregated percentage of maximum recommended daily dose [\( \sum \text{antihypertensives} / \text{prescribed daily dose/maximum recommended daily dose} \)] for intervention, and it was recorded as the number of treatments affected by IDH from treatment records over 2 weeks of dialysis treatments before each study visit. Predialysis plasma [Na⁺] was assessed by indirect ion-specific ionometry using the Abbott Architect system. Serum osmolality was assessed by freezing point depression using the Advanced Model 3250 (Advanced Instruments Inc., Norwood, MA). Dietary sodium intake was assessed by 3-day weighed food diaries using standardized measuring scales and measuring cups/spoons computed by Foodworks 8 professional (http://www.xyris.com.au/) supplemented with the Nutritrack database (www.nutriweb.org.nz) as well packages from retail outlets.

Bioimpedance spectroscopy and all blood samples were performed or drawn immediately (as practicable) predialysis after a “long break” for thrice-weekly participants and after a midweek break for participants with fixed interdialytic intervals. All laboratory tests were undertaken a central laboratory on a single batch and machine.

Study Oversight

The study was designed by a steering committee, and the study protocol was approved through the National (New Zealand) Multi-Region Ethics Committee (IRB00004663) of the New Zealand Ministry of Health (JORG0000895) and institutional review boards from participating centers. Study data were entered and managed centrally by the data coordinating center, and they were analyzed by study statisticians blinded to allocation. An external advisory committee selected by the New Zealand Health Research Council reviewed the protocol and served as the data and safety monitoring board. All of the authors vouch for the accuracy and completeness of reported data and the fidelity of this report to the study protocol, and they jointly agreed to submit for publication. The results have not been published before except in abstract form as a conference proceeding.
Statistical Analyses

Power calculations were on the basis of the primary outcome measure of LV mass index, and they assumed a baseline mean (SD) LV mass index of 110 (40) g/m² on the basis of published data in HD populations using CMR. Correlation between base-line and follow-up measurements of LV mass index was conservatively estimated at 0.75 in the original study design in the absence of any available published data at the time reporting repeated measures CMR in patients on dialysis. This was subsequently revised to 0.8 on the basis of reported values of 0.81 and 0.87 in cohorts with repeated measures at least 6 months apart, with the change published prospectively in a protocol update. Modeling these data using repeated measures analysis of covariance and allowing for 25% for drop-outs, it was determined that 48 participants should be enrolled in each arm (power of 0.8, \( \alpha = 0.05 \)). Plans for all analyses were finalized in an analysis plan prior to unblinding of allocation to study analysts. A blind review was conducted to assess the plausibility of assuming normality in the residuals, to explore the correlation structure between repeatedly measured outcomes, and to determine which covariates should remain in the final adjusted models. No models fitted during the blind review stage included the allocation variable, and models were fitted using only complete data.

All continuous outcomes were initially modeled using a normal linear mode adjusted for baseline. Where the assumption of normality in the residuals was not plausible, then an alternative generalized linear model was sought. A \( \gamma \)-generalized linear model was fit to the primary outcome with identity link function. For those outcomes that were measured repeatedly, nested random effects for center and participant were included to capture the correlation between observations on the same individual.

The partial coefficient of determination was used to assess the set of candidate covariates to include in the final adjusted model. A model including only baseline outcome value, assessment time (where relevant), and the set of candidate predictors was fit to each outcome. Predictors considered for inclusion in each adjusted model were albumin, presence of diabetes mellitus, sex, age, prerandomization dialysis frequency, years on dialysis, baseline intradialytic weight gain, baseline predialysis mean arterial pressure, and residual renal function. All continuous predictors were dichotomized into high versus low groups at the observed median value.

Missing values in the primary and secondary outcomes were handled differently according to whether they were observed at one or multiple time points postbaseline. Missing values in outcomes observed only at 12 months were multiply imputed ten times. The analysis model was then applied to the multiply imputed data, and the results were combined using Rubin rules. Missingness in outcomes observed at multiple time points postbaseline was handled by selecting an appropriate correlation structure for the dependence between the repeated measures because this has been shown to produce unbiased effect estimates under a missing at random assumption.

For all outcomes, the primary analyses used the intention to treat approach. Four sensitivity analyses were also performed for the primary outcome defined as follows: return to baseline—all missing outcome data were imputed with the baseline value; intention to treat extended—all missing outcome data from participants who had withdrawn or ceased treatment were imputed with a random draw from the control group, and all missing outcome data from other participants were imputed with a random draw from their own group; worst case for intervention—all missing outcome data were imputed with a random draw from the control group; and best case for intervention—all missing outcome data in the intervention group were imputed with a random draw from the control group shifted by \( -15 \) (the detectable difference in the sample size calculation). Statistical analyses were performed with R for Windows, v3.6.0 (The R Foundation for Statistical Computing).

RESULTS

Flow of the Participants and Their Baseline Characteristics

The first participant was enrolled on March 20th, 2012, and the follow-up was completed on July 6th, 2016. Eligibility was assessed in 633 patients, and 99 patients from 11 dialysis centers were enrolled and randomized (Figure 1). Over the course of the study, there were 33 instances of incorrect dialysate administration among participants, none lasting for >2 weeks, and almost all were during the titration phase or when the participant was on holiday. There were 13 participants who did not complete the study.

Table 1 shows the baseline characteristics of the participants. Most received home HD and 4–6 hours of dialysis per treatment. Participant characteristics were similar to the source home HD population in New Zealand, although different from the facility HD population. There was a greater proportion of men and patients were younger, more likely to be New Zealand European, and less likely to have diabetes mellitus compared with their counterparts on facility HD. Antihypertensive use at baseline by class of agent is shown in Supplemental Table 2.

There were minor differences in the study sample between allocated groups. Participants allocated to lower dialysate \([\text{Na}^+]\) tended to have a slightly higher frequency and duration of HD sessions at baseline and slightly higher serum phosphate at baseline.

Table 2 shows baseline values for study outcomes, by allocation. The presence and extent of LV hypertrophy were similar between groups at baseline and similar to (or somewhat greater than) those reported by other studies of cardiac structure and function that have used CMR.
Primary and Secondary Efficacy Outcomes

Table 3 shows the effects of lower dialysate [Na\(^+\)] on study outcomes. The intervention did not result in a change in LV mass index over the duration of follow-up. In terms of secondary outcomes, lower dialysate [Na\(^+\)] resulted in a sustained decrease in IDWG accompanied by an early decrease in extracellular fluid volume and a sustained decrease in BNP but not NT-pro-BNP.

There was a trend to reduced antihypertensive medication burden with lower dialysate [Na\(^+\)], possibly reflecting down titration of antihypertensive medication in response to IDH. This did not, however, reach statistical significance.

There were no differences in LV size and volume between groups, measures of thirst and xerostomia, or HRQoL.

Secondary Safety Outcomes

Lower dialysate [Na\(^+\)] resulted in a directional increase in frequency of IDH over the course of the study, which was statistically significant at 6 months and a trend at 12 months. There was no difference between predialysis serum [Na\(^+\)] and osmolality between groups and no difference in dietary Na\(^+\) intake. Adverse events are presented in Supplemental Table 3, and they were not different between groups.

Other Analyses

The results of the preplanned sensitivity and interaction analyses are shown in Figure 2. The effect of the intervention on the primary outcome was nonsignificant in sensitivity analyses. The effect of the intervention on the primary outcome was also nonsignificant in subgroups separated by median LV mass index at baseline and median intradialysis and interdialysis mean arterial pressures. Although not a preplanned analyses, the effect of the intervention was also not different in subgroups defined by vintage (<1 year on dialysis versus ≥1 year on dialysis, \(P=0.40\)) or in subgroups defined by HD machine manufacturer (Gambro versus Fresenius, \(P=0.76\)).

Although not preplanned outcomes, lower dialysate [Na\(^+\)] did not result in change in residual urine volume or presence of anuria.

DISCUSSION

ESKD is an important cause of patient life-years lost and impaired patient-centered outcomes. Treating ESKD accounts for as much as 1%–7% of the total health expenditure in any
given country, despite ESKD representing only 0.02%–0.03% of the population. Despite this expenditure, survival on dialysis remains relatively poor and comparable with (or worse than) many common cancers. Accelerated cardiovascular disease is arguably the most important priority for advancement, being responsible for the majority of patient
deaths\textsuperscript{52} and being among the most prioritized patient-centered outcomes.\textsuperscript{53,54}

Within this landscape, lower dialysate [Na\textsuperscript{+}] has appealing potential to improve outcomes. It directly addresses fluid overload, an important risk factor for cardiovascular morbidity and mortality.\textsuperscript{55,56} It is also easy to implement and free of additional cost. This appeal has led to a global trend toward reduced dialysate [Na\textsuperscript{+}]\textsuperscript{57,58} (Supplemental Figure 1). However, there are some effects of lower dialysate [Na\textsuperscript{+}] that are potentially harmful. For instance, there is

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Characteristics} & \textbf{135 mM} & \textbf{140 mM} & \textbf{Total} \\
\hline
Participants with data & 49 (100) & 50 (100) & 99 (100) \\
\hline
CMR parameters & & & \\
LV mass index, g/m\textsuperscript{2} & 91.9 (25) & 96.1 (27.4) & 94.0 (26.2) \\
LV mass, g & 184.4 (56.7) & 194.8 (60.2) & 189.6 (58.5) \\
LV end diastolic volume, ml & 190.5 (54.6) & 196.2 (57.3) & 193.4 (55.8) \\
LV end systolic volume, ml & 83.8 (33.5) & 88.3 (48.1) & 86.1 (41.4) \\
Stroke volume, ml & 106.6 (28.9) & 107.9 (26.0) & 107.3 (27.3) \\
Ejection fraction, % & 56.9 (8.2) & 56.9 (11.4) & 56.9 (9.9) \\
LV hypertrophy, %\textsuperscript{a} & 27 (55) & 32 (64) & 59 (60) \\
IDWG, kg & 1.8 (0.9) & 1.7 (0.8) & 1.8 (0.8) \\
IDWG, % of predialysis weight & 2.2 (1.1) & 1.9 (0.8) & 2.0 (1.0) \\
\hline
Bioimpedance analysis parameters & & & \\
Extracellular fluid, L & 19.6 (4.7) & 19.7 (3.8) & 19.6 (4.2) \\
Intracellular fluid, L & 21.5 (5.6) & 21.4 (5.8) & 21.4 (5.6) \\
\hline
Systolic BP, mm Hg & & & \\
Interdialysis & 144.3 (24.2) & 146.9 (20.7) & 145.6 (22.4) \\
Predialysis & 144.6 (23.5) & 149.3 (19.9) & 146.9 (21.8) \\
Intradialysis & 139.8 (23.2) & 140.3 (18.6) & 140.1 (20.9) \\
Postdialysis & 140.1 (24.4) & 142.4 (16.6) & 141.3 (20.8) \\
\hline
Diastolic BP, mm Hg & & & \\
Interdialysis & 86.4 (14.8) & 87.2 (10.4) & 86.8 (12.7) \\
Predialysis & 80.2 (13.5) & 82.7 (13.3) & 81.5 (31.4) \\
Intradialysis & 79.7 (13.1) & 78.5 (11.6) & 79.1 (12.3) \\
Postdialysis & 79.3 (15.5) & 80.2 (11.4) & 79.7 (13.5) \\
\hline
Mean arterial pressure, mm Hg & & & \\
Interdialysis & 105.7 (16.9) & 107.1 (12.9) & 106.4 (14.9) \\
Predialysis & 108.8 (15.0) & 105.2 (13.8) & 103.5 (14.4) \\
Intradialysis & 99.7 (14.8) & 99.2 (12.6) & 99.4 (13.7) \\
Postdialysis & 100 (17.1) & 101.2 (11.4) & 100.6 (14.5) \\
\hline
Dietary sodium intake, mg/d & & & \\
& 2475 (901) & 2531 (1024) & 2502 (957) \\
\hline
KDQOL & & & \\
Burden of kidney disease & 41 (28.2) & 46.5 (27.3) & 43.8 (27.7) \\
Effect of kidney disease & 60 (24.9) & 67.2 (20.4) & 63.6 (22.9) \\
Symptoms of kidney disease & 73.1 (16.1) & 77.8 (16.5) & 75.5 (16.4) \\
\hline
SF-36 & & & \\
Mental Health Component & 48.3 (10.8) & 52.2 (8.8) & 50.3 (10) \\
Physical Health Component & 41.9 (8.1) & 42.9 (9.3) & 42.4 (8.7) \\
EQ5D, score of 100 & 68.5 (17.9) & 70.3 (19.6) & 69.4 (18.7) \\
Xerostomia Inventory, score 5–25 & 11 (4.6) & 10.6 (5) & 10.8 (4.8) \\
Dialysis Thirst Inventory, score 7–35 & 18.2 (7.5) & 17.4 (5.2) & 17.8 (6.4) \\
IDH, no. of sessions (%) & 16 (5.5) & 7 (2.4) & 23 (4.0) \\
Predialysis plasma [Na\textsuperscript{+}], mmol/L & 138 (2.6) & 138.3 (2.9) & 138.2 (2.8) \\
Serum osmolality, mOsm/L & 307.9 (10.9) & 309.1 (8.6) & 308.5 (9.8) \\
Plasma NT-pro-BNP, pmol/L, median (25%–75% quartiles) & 412 (101–1020) & 405 (109–1580) & 412 (106–1082) \\
Plasma BNP, pmol/L, median (25%–75% quartiles) & 22 (50–109) & 78 (29–233) & 66 (23–185) \\
Serum C-reactive protein, mg/L, median (25%–75% quartiles) & 3.2 (1.6–7.2) & 3.7 (1.6–9.1) & 3.5 (1.6–7.9) \\
Antihypertensive medications (aggregated % of maximum recommended daily dose), N with no medications (median) & 27 (0) & 17 (24.4) & 44 (11.9) \\
\hline
\end{tabular}
\caption{Baseline values of study outcomes, by allocation}
\end{table}
known to be less hemodynamic stability and reduced treatment tolerability. The lack of evidence defining optimal dialysate [Na\(^+\)] underpins the high degree of clinical equipoise that currently exists—despite the overall trend to lower dialysate [Na\(^+\)], there is still wide variation in prescribing both between HD programs, enriching our sample with patients with

In our study, lower dialysate [Na\(^+\)] did not affect LV mass index in patients on home or self-care satellite facility HD, despite convincingly improving indicators of fluid status. Moreover, the intervention worsened intradialytic hemodynamic instability. These findings align with recent systematic reviews.\(^\text{12,13}\) Notably, however, they are at odds with a previous smaller single-center trial showing lower dialysate [Na\(^+\)] to regress LV mass on echocardiography.\(^\text{59}\) Our results can be regarded as having a higher degree of internal validity due to the greater accuracy of outcome ascertainment and superior trial design and execution. On the basis of our findings, we believe that further assessments of this intervention are needed before lower dialysate [Na\(^+\)] is accepted as standard. Importantly, our study participants were recruited from home or self-care satellite facility HD programs, enriching our sample with patients with

| Table 3. Effect of intervention on predetermined study outcomes relative to control |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Follow-Up       | 3 mo           | 6 mo           | 9 mo           |
| Primary outcome                 |                 |                |                |                |
| LV mass index, g/m\(^2\)        |                 |                |                |                |
| Secondary outcomes—efficacy     |                 |                |                |                |
| CMR parameters                  |                 |                |                |                |
| LV end diastolic volume, ml     |                 |                |                |                |
| LV end systolic volume, ml      |                 |                |                |                |
| Stroke volume, ml               |                 |                |                |                |
| Ejection fraction, %            |                 |                |                |                |
| IDWG, kg                        | -0.47 (-0.80 to -0.15)* | -0.56 (-0.90 to -0.22)* | -0.90 (-1.26 to -0.54)* | -0.57 (-0.86 to -0.27)* |
| IDWG, % of predialysis body     | -0.52 (-0.87 to -0.17)* | -0.59 (-0.95 to -0.23)* | -0.93 (-1.38 to -0.52)* | -0.61 (-0.96 to -0.27)* |
| Extracellular fluid, L          | -1.05 (-1.81 to -0.30)* | -0.90 (-1.63 to -0.18)* | 0.08 (-0.70 to 0.86) | -0.60 (-1.48 to 0.26) |
| Plasma BNP, ratio I/C           | 0.74 (0.40 to 1.36) | 0.43 (0.23 to 0.78)* | 0.51 (0.28 to 0.94)* | 0.49 (0.27 to 0.90)* |
| Plasma NT-pro-BNP, ratio I/C    | 0.81 (0.41 to 1.61) | 0.70 (0.35 to 1.39) | 0.90 (0.45 to 1.80) | 0.84 (0.42 to 1.68) |
| Xerostomia Index                | -0.59 (-1.56 to 2.39) | -0.38 (-2.55 to 1.35) |                               |                               |
| Dialysis Thirst Index           | -1.22 (-3.93 to 1.49) | 0.70 (-2.15 to 4.68) |                               |                               |
| Mean arterial pressure, mm Hg   | -1.11 (-5.76 to 3.52) | -2.94 (-7.49 to 1.61) | -0.71 (-5.56 to 4.14) | -0.92 (-6.51 to 4.68) |
| Intradialysis                   | -2.82 (-8.24 to 2.60) | -4.98 (-10.03 to 0.06) | -1.90 (-7.29 to 3.48) | 1.08 (-5.02 to 7.18) |
| Postdialysis                    | -0.23 (-4.77 to 4.31) | -4.96 (-9.54 to -0.39)* | -0.70 (-5.69 to 4.28) | -1.23 (-7.04 to 4.59) |
| Interdialysis                   | 0.89 (-4.35 to 6.14) |                               |                               |                               |
| Antihypertensive medications    | (aggregated fraction of maximum recommended daily dose) |                               |                               |                               |
| KDQOL—kidney disease domains   |                 |                |                |                |
| Burden                          | -0.52 (-11.7 to 10.6) | -1.67 (-9.45 to 6.11) | -1.24 (-7.6 to 5.07) |                               |
| Effects                         | -0.52 (-11.7 to 10.6) | -1.67 (-9.45 to 6.11) | -1.24 (-7.6 to 5.07) |                               |
| Symptoms                        | -1.24 (-7.6 to 5.07) |                               |                               |                               |
| KDQOL—SF-36 domains             |                 |                |                |                |
| Mental health                   | 1.77 (-1.66 to 5.20) |                               |                               |                               |
| Physical health                 | 1.13 (-3.76 to 4.01) |                               |                               |                               |
| EQSD                            | -0.07 (-6.71 to 6.57) |                               |                               |                               |
| C-reactive protein, ratio I/C   | 2.1 (1.2 to 3.7) | 1.4 (0.8 to 2.5) | 1.20 (0.7 to 2.1) | 0.99 (0.6 to 1.7) |
| Secondary outcomes—safety       |                 |                |                |                |
| IDH (OR)                        | 1.5 (0.2 to 10.2) | 7.5 (1.1 to 49.8)* | 3.44 (0.5 to 23.6) | 3.6 (0.5 to 28.8) |
| Predialysis plasma [Na\(^+\)], mmol/L | -1.2 (-2.4 to 0.1) | 0.0 (-1.2 to 1.2) | -0.7 (-2.0 to 0.5) | 0.4 (-0.8 to 1.6) |
| Serum osmolality, mOsm/L        | -2.1 (-5.9 to 1.7) | 0.1 (-2.9 to 4.7) | 1.5 (-2.4 to 5.4) | -3.3 (-7.1 to 0.6) |
| Dietary Na\(^+\) intake, mg/d   | 474 (-94 to 1042) |                               |                               |                               |
| Exploratory outcomes            |                 |                |                |                |
| Residual urine volume, ratio I/C| 0.9 (0.3 to 3.0) | 0.9 (0.3 to 3.0) |                               |                               |
| Anuria, OR                      | 2.92 (0.09 to 99.4) | 3.51 (0.1 to 122) |                               |                               |

I/C, intervention/control; KDQOL, Kidney Disease Quality of Life; SF-36, short form 36; EQSD, name of the instrument; OR, odds ratio. *P<0.05.
comparatively little comorbidity and arguably relatively intact hemodynamic regulatory mechanisms. As a result, there is under-representation of frail and vulnerable patients in our study, even more so than is usual for clinical trials. As such, there may be greater potential for (and harm from) intradialytic hemodynamic instability from lower dialysate [Na⁺] in real-world settings, especially in frailler facility-based HD cohorts. Our definition of IDH is on the basis of the older Disease Outcomes Quality Initiative syndromic definition rather than the recent and more potent BP nadir definition. Notwithstanding, IDH as per the Disease Outcomes Quality Initiative is still a strong predictor of death, and the risk that we demonstrate from exacerbated IDH should not be discounted. We recommend that future observational studies of dialysate [Na⁺] should carefully identify and analyze data around adverse events, such as deterioration in residual kidney function, vascular access complications, myocardial stunning, and other end organ effects of microischemia.

In the general population, LV mass is an independent predictor of cardiovascular outcomes. Regression of LV mass improves cardiovascular risk independent of confounders, such as BP. In dialysis populations, LV hypertrophy affects the majority of patients, with both the presence and extent being independent predictors of cardiovascular morbidity and mortality. Progression of LV hypertrophy is typical in patients on dialysis, and regression of LV mass is associated with improved outcomes. The most potent intervention for LV hypertrophy in this population is intensive HD. The mechanisms responsible for improvement are uncertain but mainly attributed to better control of extracellular fluid. In our study, lower dialysate [Na⁺] improved indicators of extracellular fluid control as much as intensive HD when applied over a similar or greater duration of exposure. However, there were no resulting changes in LV mass. There are three possible explanations. The most likely explanation, in our opinion, is that the effects of intensive HD on LV mass are as much related to enhanced removal of uremic toxins as they are to better control of extracellular fluid. Of course, other unassessed neurohormonal factors, such as the sympathetic nervous and renin-angiotensin systems, may also be intermediary variables affecting this causal pathway.

The second and in our opinion, a less likely explanation may be that degree of LV hypertrophy of our participants was insufficient to show an effect from the intervention. This is suggested by the nonsignificant trend to a greater reduction in LV mass in participants who had marked LV hypertrophy at baseline (Fig. 2). Notwithstanding, the presence and extent of LV hypertrophy in our study were similar to those seen in other studies of interventions to reduce LV mass in patients on dialysis, and the trend to effect modification across subgroups defined by LV mass has also been seen in studies of intensive HD.

A final explanation might be that a longer follow-up is needed to show a significant effect of lower dialysate [Na⁺] on LV mass. We feel that this is also less likely. Badwe et al. recently reviewed clinical trials of various interventions to reduce LV mass in the setting of CKD. Of the 50 performed in patients on dialysis, only 3 had a follow-up duration >12 months. None of these three used CMR to assess LV mass, and moreover, none showed any effect after 12 months that was not already present at 12 months. Without exception, all of the 4 trials of the 50 that used CMR had a follow-up duration of 12 months, with most showing an effect of the intervention at the end of that follow-up. Overall, our study shows the effect of lower dialysate [Na⁺] on LV mass to be less than that of intensive HD when applied in similar populations and in a similar manner.

Figure 2. Preplanned sensitivity and predetermined subgroup analyses showing the effect of the intervention (dialysate [Na⁺] = 135 mmol/L) relative to control (dialysate [Na⁺] = 140 mmol/L) on the primary outcome (LV mass index). Subgroups are all specified according to the observed median. MAP, mean arterial pressure.
Our study provides three additional notable insights. First, despite lower dialysate [Na\(^{+}\)] reducing IDWG and therefore, water intake, there was no associated change in perceived thirst. In the absence of external constraint on access to water (and noting no change in other sources of loss), anyone who drinks less must desire to do so (i.e., their thirst must have been reduced). We can conclude that a better instrument than the Dialysis Thirst Inventory is, therefore, needed to assess thirst in patients on dialysis. Lower dialysate [Na\(^{+}\)] also did not reduce xerostomia. In contrast to the situation with thirst, this situation may indeed be true because we did not have an objective measure of dryness of the mouth in our study. Alternatively, the Xerostomia Inventory may not have performed as well in prospective settings as it has done in cross-sectional ones. We suspect that many participants in our study normalized their current symptoms, making it difficult for them to assess change over time. Whatever the explanation, definitive studies of xerostomia probably need a more objective measure alongside the Xerostomia Inventory to assess the effect of interventions.

Second, another insight is that lower dialysate [Na\(^{+}\)] resulted in different magnitude of change in BNP and NT-pro-BNP, although the direction was the same. There is no consensus as to which is more sensitive or specific, but it is known that the effect of kidney function on NT-pro-BNP is more pronounced than that on BNP.\(^{86}\) Given the directional reduction in residual kidney function in the lower dialysate [Na\(^{+}\)] group, it is possible that there was an increase in NT-pro-BNP in this group for this reason, partially obscuring any decreases from better extracellular fluid status. Whatever the explanation, BNP rather than NT-pro-BNP would seem more suitable for patients on dialysis.

Third, despite lower dialysate [Na\(^{+}\)] improving indicators of fluid status, there was little if any effect on LV chamber size. It is known that right-sided cardiac chamber size is more responsive to (and reflective of) changes in intravascular volume, and our study supports the tenet that bioimpedance-measured extracellular fluid is potentially more reliable in estimating plasma volume expansion than changes in left atrium and ventricle size.\(^{87}\)

Our study has two major limitations and several smaller ones. First of the major limitations is that there is some uncertainty around the validity of LV mass as a surrogate outcome in dialysis populations.\(^{82}\) This is compounded (or even driven) by the lack of positive trials in such patients with which to validate the outcome (individual/trial-level association, Prentice criteria, etc.).\(^{88}\)

The second major limitation is that our study sample (as discussed above) does not completely represent the entire interdialytic cycle. Also, the study was well powered for the primary end point using CMR to measure LV mass. However, it was underpowered to detect differences in mortality, hospitalization, and HRQoL. Finally, we did not check delivered dialysate [Na\(^{+}\)] using laboratory methods and relied instead on HD machines to measure and model dialysate conductivity to achieve prescribed dialysate [Na\(^{+}\)]. This is a potential concern because published papers have consistently shown prescribed dialysate [Na\(^{+}\)] to be lower than measured dialysate [Na\(^{+}\)]. Some show a small difference,\(^{92}\) others show a large one,\(^{93}\) and yet others are in between.\(^{94}\) These studies all have limitations, and the true extent of any difference is still unknown. Irrespective, our study is concerned primarily with assessing clinical outcomes with different models of routine clinical care. In real-world settings, dialysate [Na\(^{+}\)] is prescribed using dialysate conductivity, not measured dialysate [Na\(^{+}\)]. Accordingly, our trial (and most clinical trials with similar aims to our trial\(^{59,95,96}\)) was designed and implemented with this in mind. Of course, the veracity of dialysate [Na\(^{+}\)] that is prescribed in this manner remains a high priority for further study, which should be performed using gold standard laboratory measurements of dialysate ionic activity (not concentration) over the entire course of HD across multiple sessions, with interpretation that takes due account of laboratory testing variability (H.-D. Polaschegg, personal communication).

In conclusion, despite the appeal of lower dialysate [Na\(^{+}\)], our study showed no improvement in LV mass index with this intervention, although there was strong evidence of better extracellular fluid control. Taken together, the results of our study suggest that the “volume first” paradigm may be necessary but not sufficient to improve cardiovascular outcomes in patients on dialysis and that future research should place equal emphasis on the potential role of greater removal of uremic toxins. These findings should give pause to the wider adoption of lower dialysate [Na\(^{+}\)], reorienting researchers and clinicians to larger trials with “hard” clinical end points, such as the ongoing Randomized Evaluation of Sodium Dialysate Levels on Vascular Events study (ClinicalTrials.gov: NCT02823821),
while motivating further inquiry into alternative strategies for improving cardiovascular outcomes, such as enhanced uremic solute clearance. On a final practical note, in the setting of home and self-care satellite facility HD, more intensive dialysis seems to have greater benefits than lower dialysate [Na+] for our studied outcomes.

ACKNOWLEDGMENTS

The investigators acknowledge Brenda Luey, Jenny Han, Xiaodong He, Jerred George, Grace Muyoma, Tess Ostapowicz, Jenny Usher, Deborah Peek, and Amanda West for their contribution to data collection and management; Dr. Angela Yee Moon Wang for her advice on the draft of the manuscript; and Middlemore Clinical Trials and the Australasian Kidney Trials Network for their operational support.

This work was previously reported in abstract form (Marshall et al., J Am Soc Nephrol 27: 1B, 2016).

The Health Research Council of New Zealand had no role in the design of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Individual participant data that underlie the results reported in this article as well as the study protocol and statistical analysis plan will be shared after deidentification (text, tables, figures, and appendices) beginning 12 months and ending 36 months following article publication for individual participant data meta-analysis. Investigators who propose to use the data will be evaluated by an independent review committee identified for this purpose. Proposals should be directed to markrogermarshall@icloud.com. To gain access, data requestors will need to sign a data access agreement.

Dr. Dunlop, Dr. Marshall, Dr. Vandal, and Ms. Xie conceptualized and designed the study. Dr. de Zoysa, Dr. Dunlop, Dr. Halooob, Dr. Hood, Dr. Irvine, Dr. Ma, Dr. Marshall, Dr. Matheson, Dr. McGregor, Dr. Rabindranath, Dr. Schollum, Dr. Semple, and Ms. Xie acquired the data. Dr. Gabriel, Dr. Marshall, Ms. Sisk, and Dr. Vandal drafted the manuscript. Dr. de Zoysa, Dr. Dunlop, Dr. Halooob, Dr. Hood, Dr. Irvine, Dr. Ma, Dr. Matheson, Dr. McGregor, Dr. Rabindranath, Dr. Schollum, Dr. Semple, and Ms. Xie performed critical revision of the manuscript for important intellectual content. Dr. Sisk and Dr. Vandal performed statistical analysis. Dr. Dunlop, Dr. Marshall, Dr. Vandal, and Ms. Xie obtained funding. Dr. Gabriel and Dr. Ma provided administrative, technical, or material support. Dr. Dunlop, Dr. Gabriel, Dr. Ma, Dr. Marshall, and Dr. Vandal provided study supervision. Dr. Marshall, Ms. Sisk, Dr. Vandal, and Ms. Xie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of analyses.

DISCLOSURES

After the protocol was approved and funded, Dr. Marshall became an employee of Baxter Healthcare (Asia) Pte Ltd. Baxter Healthcare (Asia) Pte Ltd. provided no funding for the study, no input into the analysis or interpretation of the results, and no input into the drafting of the manuscript. Dr. Marshall reports grants from the Health Research Council of New Zealand, grants from the Maurice and Phyllis Paykel Trust, grants from the Royal Australasian College of Physicians, grants from the Royal Australasian College of Physicians, Jacquot Research Establishment Fellowship 2013-2015, Unilever New Zealand, and Fresenius Medical Care Australia Ltd.

FUNDING

The study was sponsored and funded by the Health Research Council of New Zealand, grants 11/583 and 13/442 and cofunded by the Maurice and Phyllis Paykel Trust, Grant-in-Aid 2010, on behalf of the Kwok Family, and nonfinancial support from Fresenius Medical Care Australia Ltd. during the conduct of the study and other from Baxter Healthcare (Asia Pacific) Pte Ltd. outside the submitted work. Dr. Xie reports funding from a Unilever New Zealand postgraduate scholarship during the conduct of the study.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019090877/-/DCSupplemental.

Supplemental Figure 1. Dialysate [Na+] prescription patterns by country over the six phases of the Dialysis Outcomes and Practice Patterns Study.

Supplemental Table 1. Hemodialysis equipment and dialysate temperature within sites.

Supplemental Table 2. Antihypertensive drug class dosing at baseline by allocation.

Supplemental Table 3. Adverse event frequencies.

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**AFFILIATIONS**

1Department of Renal Medicine, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand

2School of Medicine, University of Auckland, Auckland, New Zealand

3Medical Affairs, Baxter Healthcare (Asia) Pte Ltd., Singapore

4Department of Statistics, Faculty of Science, University of Auckland, Auckland, New Zealand

5Department of Renal Medicine, North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand

6Waitemata Clinical School, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

7Department of Cardiology, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand

8Department of Renal Medicine, Bathurst Base Hospital, New South Wales, Bathurst, Australia

9Department of Nephrology, Christchurch Hospital, Canterbury District Health Board, Christchurch, New Zealand

10Department of Nephrology, Wellington Hospital, Capital & Coast District Health Board, Wellington, New Zealand

11Department of Nephrology, Waikato Hospital, Waikato District Health Board, Hamilton, New Zealand

12Nephrology Service, Dunedin Hospital, Southern District Health Board, Dunedin, New Zealand

13Department of Renal Medicine, Auckland City Hospital, Auckland District Health Board, Auckland, New Zealand

14Middlemore Clinical Trials, Auckland, New Zealand

15Division of Informatics, Imaging & Data Sciences, School of Health Sciences, University of Manchester, Manchester, United Kingdom
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Supplementary Figure 1: Dialysate [Na+] prescription patterns, by country, over the six Phases of the Dialysis Outcomes and Practice Patterns Study (DOPPS).

**Supplementary Table 1: Hemodialysis equipment and dialysate temperature within sites**

Hemodialysis equipment and dialysate temperature within sites, where each sites’ patients share the same technology platform. All dialysate concentrates used with machinery was proprietary to the manufacturer, and of the same brand and sub-brand within sites. The study sites, as defined below, form one of the strata used for randomization.

<table>
<thead>
<tr>
<th>Sites</th>
<th>Dialysate temperature</th>
<th>Hemodialysis Machines</th>
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</thead>
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<td>Gambro AK96, Gambro AK200S</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>Gambro AK96, Gambro AK200S</td>
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<td>3</td>
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<td>Fresenius 4008B, Fresenius 4008NSG</td>
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Supplementary Table 2: Antihypertensive drug class dosing at baseline, by allocation

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<th>Antihypertensive drug class</th>
<th>135 mM (n=49)</th>
<th>140 mM (n=50)</th>
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<td>Participants on antihypertensive drug class (%)</td>
<td>Mean aggregated % of maximum recommended daily dose (SD)</td>
<td>Participants on antihypertensive drug class (%)</td>
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<td>Angiotensin-converting enzyme (ACE) inhibitor / Angiotensin receptor blocker</td>
<td>7 (14)</td>
<td>0.27 (0.17)</td>
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<tr>
<td>β-blocker</td>
<td>15 (31)</td>
<td>0.25 (0.23)</td>
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<tr>
<td>α-blocker</td>
<td>5 (10)</td>
<td>0.28 (0.16)</td>
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<tr>
<td>Calcium channel blocker</td>
<td>7 (14)</td>
<td>0.39 (0.27)</td>
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Supplementary Table 3: Adverse event frequencies

Adverse event frequencies by Common Terminology Criteria for Adverse Events (CTCAE) category, allocation arm, relationship to intervention, outcome and severity

<table>
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<th>CTCAE v. 4 Category</th>
<th>Arm</th>
<th>Number of events</th>
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<th>Unlikely</th>
<th>Possible</th>
<th>Probable</th>
<th>Definite</th>
<th>Death</th>
<th>Ongoing</th>
<th>Sequelae</th>
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Abbreviations: I, intervention; C, control