

## Research Article

# Course of Hyperkalemia in Patients on Hemodialysis

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**Background.** Evidence of longitudinal serum potassium ( $sK^+$ ) concentrations in hyperkalemic hemodialysis patients is sparse. **Objective.** These post hoc analyses of the placebo arm of the phase 3b DIALIZE study (NCT03303521) explored the course of hyperkalemia in hemodialysis patients receiving placebo. **Methods.** In DIALIZE, 196 patients receiving hemodialysis three times weekly were randomized to placebo or sodium zirconium cyclosilicate 5 g starting dose once daily on nondialysis days for 8 weeks. In these post hoc analyses of placebo patients overall ( $n = 86$ ) and by predialysis  $sK^+$  subgroups at randomization  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, we assessed mean predialysis  $sK^+$  concentration by visit and the proportions of patients with mean predialysis  $sK^+$  ranges of 4.0–5.0 and 4.0–5.5 mmol/L by visit. **Results.** In placebo patients, the mean predialysis  $sK^+$  concentration at randomization was 5.9 mmol/L, and 5.8 mmol/L at the end of the study (day 57). For placebo patients overall and across all predialysis  $sK^+$  subgroups, the mean predialysis  $sK^+$  concentration remained  $\geq 5.0$  mmol/L for all visits over 8 weeks. Overall, 7–21% and 27–62% of placebo patients had predialysis  $sK^+$  ranges of 4.0–5.0 and 4.0–5.5 mmol/L, respectively, at any visit. The proportions of placebo patients with either predialysis  $sK^+$  range were greatest for those who were least hyperkalemic ( $<5.5$  mmol/L) and generally decreased with increasing predialysis  $sK^+$  concentration. **Conclusions.** Patients receiving placebo and hemodialysis maintained high predialysis  $sK^+$  concentrations over 8 weeks following a hyperkalemic event. Most placebo patients remained hyperkalemic and may be at continued risk of adverse events.

## 1. Introduction

Patients with end-stage renal disease (ESRD) have reduced renal potassium excretion and require dialysis to remove accumulated potassium. Hyperkalemia in hemodialysis (HD) is common [1, 2], and predialysis serum potassium ( $sK^+$ ) concentration  $>5.5$  mmol/L is associated with increased mortality and hospitalization [3–6].

The extent of hyperkalemia and variation in  $sK^+$  concentration in HD patients depends on several

variables, including the frequency, duration, and prescription of HD [1]. Patients accumulate potassium between dialysis treatments and  $sK^+$  concentration rises toward predialysis concentrations [7]. In one analysis of 14 patients receiving standardized 4-hour HD three times weekly (TIW), the mean potassium concentration declined from 5.65 mmol/L predialysis to 3.62 mmol/L postdialysis, but it returned to 5.01 mmol/L at 6 hours postdialysis and 5.6 mmol/L at 38 hours postdialysis (i.e., the interval to the next HD) [8].

Evidence of longitudinal trajectory of  $sK^+$  concentration and risk of recurrent hyperkalemia following a hyperkalemic event is sparse [9–14], particularly among HD patients [1]. The frequency of potassium monitoring in clinical practice is typically performed based on the clinician's judgement and varies across regions [10]. Nephrologists typically monitor predialysis  $sK^+$  concentration monthly in HD patients [7, 15]. Evaluation of the longitudinal trajectory of  $sK^+$  concentration and risk of recurrent hyperkalemia following a hyperkalemic event is needed to inform physicians of the likely course and burden of hyperkalemia in HD patients, and to provide more information regarding the need for impact management strategies.

The phase 3b DIALIZE study (NCT03303521) [16] evaluated sodium zirconium cyclosilicate (SZC) compared with placebo in the management of hyperkalemia in HD patients. The placebo arm of this clinical trial provides the opportunity to evaluate the trajectory of  $sK^+$  concentration in hyperkalemic HD patients who received placebo in addition to maintenance HD. Here, we report the results of post hoc analyses of the placebo arm from the phase 3b DIALIZE study to examine the course of hyperkalemia in patients who received placebo.

## 2. Materials and Methods

**2.1. Study Design and Patients.** DIALIZE was an international, randomized, double-blind, placebo-controlled phase 3b study; the full details have been reported previously [16]. The study consisted of a 1-week screening period, an 8-week treatment period comprising 4 weeks for dose titration and 4 weeks for evaluation on stable dose, and a 2-week follow-up period. Patients were randomized 1:1 in a blinded manner to orally receive a starting dose of 5 g of SZC or placebo once daily on nondialysis days (4 days/week). All patients received HD TIW and routine dietary counselling as per local guidelines, including dietary potassium restriction. Management of dialysis prescription was implemented according to local clinical practices. Rescue therapy in accordance with local practice patterns to reduce  $sK^+$  in the setting of severe hyperkalemia ( $>6.0$  mmol/L) included potassium binders, acute potassium-lowering agents, additional dialysis sessions, and a reduction in dialysate potassium ( $dK^+$ ) concentration.

Eligible patients were adults aged  $\geq 18$  years with ESRD who were managed for  $\geq 3$  months before randomization by HD TIW and had a prescribed  $dK^+$  concentration of  $\leq 3.0$  mmol/L at screening. During screening, patients were required to have hyperkalemia despite maintenance HD, defined as predialysis  $sK^+ > 5.4$  mmol/L after the long interdialytic interval (LIDI) on day  $-7$  and predialysis  $sK^+ > 5.0$  mmol/L after at least one short interdialytic interval (SIDI) on days  $-5$  and  $-3$ . Patients were required to have sustained blood flow ( $Q_b$ )  $\geq 200$  mL/min and single-pool Kt/V ( $spKt/V$ )  $\geq 1.2$  (or urea reduction ratio [URR]  $\geq 63\%$ ) on stable HD during screening, with prescription expected to remain unchanged during the study.

**2.2. Data Collection.** Central laboratory  $sK^+$  samples were obtained throughout the study (both predialysis and postdialysis at visits after the LIDI and only predialysis for visits after the SIDI). Parameters of dialysis adequacy (target  $spKt/V$  and/or URR) and prescription (dialysate flow [ $Q_d$ ],  $dK^+$  concentration, prescribed ultrafiltration, and  $Q_b$ ) were recorded longitudinally. Study sites consistently used either  $spKt/V$  or URR in determining dialysis adequacy.

**2.3. Post Hoc Analyses.** In these post hoc analyses, we assessed biochemical outcomes in placebo patients. Analyses included predialysis and postdialysis  $sK^+$  concentrations and shift in  $sK^+$  concentration from predialysis to postdialysis at each study visit during the dose-titration and 4-week evaluation periods. Predialysis  $sK^+$  concentrations were available at all LIDI visits (days 1, 8, 15, 22, 29, 36, 43, 50, and 57) and SIDI visits (days 3, 5, 10, 12, 17, 24, 31, 38, 45, and 52); postdialysis  $sK^+$  concentrations and shift in  $sK^+$  concentration from predialysis to postdialysis were available at all LIDI visits and some SIDI visits during the dose-titration period (days 3, 5, and 12). Furthermore, we assessed the proportions of patients at each LIDI and SIDI visit who had a prespecified predialysis  $sK^+$  range of 4.0–5.0 mmol/L and an extended range of 4.0–5.5 mmol/L, and the number of LIDI visits ( $\geq 1$ ,  $\geq 2$ ,  $\geq 3$ , and 4) during the 4-week evaluation period (days 36, 43, 50, and 57), in which patients had  $sK^+$  concentrations that fell within these ranges. The extended predialysis  $sK^+$  range of 4.0–5.5 mmol/L reflected one that was deemed to be acceptable in clinical practice, as predialysis  $sK^+$  concentrations  $> 5.5$  mmol/L are associated with increased hospitalization and mortality [3, 5, 6]. To assess the risk of recurrent hyperkalemia, we assessed the incidence of predialysis  $sK^+$  concentrations  $> 5.5$  or  $> 6.0$  mmol/L at LIDI visits during the 4-week evaluation period. Parameters of dialysis prescription and adequacy are reported. Concentrations of  $dK^+$  were available at days  $-7$ ,  $-5$ ,  $-3$ , 1, 3, 5, 8, 12, 15, 22, 29, 36, 43, 50, and 57; dialysis adequacy parameters were available at days  $-7$ , 29, and 57; and dialysis prescription parameters were available at days  $-7$ , 1, 29, and 57. Shift from baseline (visit 1, day  $-7$ ) to the end of treatment (visit 15, day 57) in the proportions of patients with  $dK^+$  concentration categories of 1, 2, and 3 mmol/L is reported.

**2.4. Statistical Analysis.** Analyses were stratified by predialysis  $sK^+$  concentration at randomization (visit 4, day 1):  $< 5.5$  mmol/L, 5.5 to  $< 6.0$  mmol/L, 6.0 to  $< 6.5$  mmol/L, and  $\geq 6.5$  mmol/L. Baseline for subgroup stratification was defined as the last visit before study drug initiation (i.e., randomization visit) to account for variation from screening in predialysis  $sK^+$  concentration and to assess patients with a predialysis  $sK^+$  concentration of  $< 5.5$  mmol/L. No imputation of missing data was conducted. Concentration of  $sK^+$  and shift in  $sK^+$  concentration from predialysis to postdialysis at study visits are reported as mean (standard deviation [SD]) and range. The proportions of patients with the two ranges of predialysis  $sK^+$  at study visits are reported descriptively; patients receiving rescue therapy were included in the analyses. For each predialysis  $sK^+$  subgroup,

the incidence of predialysis  $sK^+$   $>5.5$  or  $>6.0$  mmol/L at subsequent LIDI visits during the 4-week evaluation period was calculated as follows:

[Number of hyperkalemic events/total number of possible hyperkalemic events based on patients with evaluable data]  $\times 100$

Parameters of dialysis prescription and adequacy are reported as mean (SD).

### 3. Results

**3.1. Patients.** Overall, 99 patients were randomized to receive placebo. Of these, 86 had predialysis  $sK^+$  measurements at randomization (visit 4, day 1); data were missing for 13 patients. Among these 86 placebo patients, the baseline (visit 1, day -7) mean (SD) age was 60.3 (13.2) years, with 45.3% of patients aged 65–84 years, mean (SD) body mass index was 26.7 (5.5) kg/m<sup>2</sup>, 41.9% of patients were female, and the mean (SD) predialysis  $sK^+$  concentration was 6.0 (0.4) mmol/L (Table 1). At baseline, most patients had hypertension (80.2%) and 25.6% had type 2 diabetes; 14.0% and 26.7% of patients were receiving concomitant angiotensin-converting enzyme inhibitors and angiotensin II antagonists, respectively, during study treatment (Table 1). Mean (SD) dialysis parameters at baseline were  $dK^+$  concentration 2.2 (0.5) mmol/L,  $spKt/V$  1.7 (0.4), and  $Qd$  548.0 (131.1) mL/min, and most patients (73.3%) had a  $dK^+$  concentration of 2 mmol/L (Table 1). Overall, 14, 37, 21, and 14 patients had predialysis  $sK^+$  concentrations at randomization of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, respectively, measured after the LIDI.

**3.2. Predialysis  $sK^+$ .** In placebo patients overall ( $n = 86$ ) and across all randomization predialysis  $sK^+$  subgroups, the mean predialysis  $sK^+$  concentration remained  $\geq 5.0$  mmol/L for all study visits (Figure 1). In placebo patients overall, the mean (SD) predialysis  $sK^+$  concentration at the end of the study (visit 15 [LIDI], day 57) was 5.8 (0.7) mmol/L. Among the randomization predialysis  $sK^+$  subgroups of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, a mean (SD) predialysis  $sK^+$  concentration at end of study was 5.4 (0.5) mmol/L, 5.9 (0.5) mmol/L, 5.6 (0.5) mmol/L, and 5.9 (1.2) mmol/L, respectively.

The proportions of placebo patients who exhibited a predialysis  $sK^+$  range of 4.0–5.0 mmol/L and an extended range of 4.0–5.5 mmol/L at study visits were also assessed. The proportions of placebo patients with a predialysis  $sK^+$  range of 4.0–5.0 mmol/L and extended range of 4.0–5.5 mmol/L were greatest for those who were least hyperkalemic (i.e.,  $<5.5$  mmol/L) at randomization, and generally decreased with increasing randomization predialysis  $sK^+$  concentration (Figures 2(a) and 2(b)).

Overall, 27% of all placebo patients ( $n = 86$ ) had a predialysis  $sK^+$  concentration of 4.0–5.0 mmol/L at  $\geq 1$  of the four LIDI visits during the 4-week evaluation period

(Figure 3). Meanwhile, 57%, 16%, 29%, and 21% of patients in the randomization predialysis  $sK^+$  subgroups of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, respectively, had a predialysis  $sK^+$  concentration of 4.0–5.0 mmol/L at  $\geq 1$  of the four LIDI visits during the 4-week evaluation period (Figure 3). No placebo patient overall ( $n = 86$ ) had a predialysis  $sK^+$  concentration of 4.0–5.0 mmol/L at all four LIDI visits (Figure 3).

Overall, 67% of all placebo patients ( $n = 86$ ) had a predialysis  $sK^+$  concentration within the extended range of 4.0–5.5 mmol/L at  $\geq 1$  of the four LIDI visits during the 4-week evaluation period; corresponding proportions were 93%, 70%, 62%, and 43% in the randomization predialysis  $sK^+$  subgroups of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, respectively (Figure 3). Meanwhile, 6% of all placebo patients ( $n = 86$ ) had a predialysis  $sK^+$  concentration of 4.0–5.5 mmol/L at all four LIDI visits; the proportions in the randomization predialysis  $sK^+$  subgroups of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L were 14%, 3%, 10%, and 0%, respectively (Figure 3).

**3.3. Postdialysis  $sK^+$ .** At randomization, mean (SD) postdialysis  $sK^+$  concentration was 3.6 (0.5) mmol/L, 3.7 (0.6) mmol/L, 3.9 (0.4) mmol/L, and 4.2 (0.4) mmol/L in the randomization predialysis  $sK^+$  subgroups of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, respectively. Mean (SD) postdialysis  $sK^+$  concentrations at day 57 were similar to randomization values: 4.0 (1.1) mmol/L, 3.8 (0.5) mmol/L, 3.7 (0.5) mmol/L, and 4.0 (0.5) mmol/L, respectively (Figure 4). Minor fluctuations from randomization at the end of the study in mean postdialysis  $sK^+$  concentration corresponded with fluctuations in predialysis  $sK^+$  concentration.

**3.4. Shift in  $sK^+$  From Pre- to Postdialysis.** At randomization, mean (SD) shift in  $sK^+$  concentration was 1.5 (0.7) mmol/L, 2.0 (0.6) mmol/L, 2.3 (0.4) mmol/L, and 2.7 (0.5) mmol/L in the randomization predialysis  $sK^+$  subgroups of  $<5.5$  mmol/L, 5.5 to  $<6.0$  mmol/L, 6.0 to  $<6.5$  mmol/L, and  $\geq 6.5$  mmol/L, respectively (Figure 5). Mean (SD) shift in  $sK^+$  at day 57 was similar to randomization values, with the biggest change from randomization in the most hyperkalemic patients: 1.4 (1.3) mmol/L, 2.1 (0.6) mmol/L, 2.0 (0.6) mmol/L, and 2.1 (0.9) mmol/L, respectively (Figure 5).

**3.5. Probability of Recurrent Hyperkalemia.** The risk of placebo patients having predialysis  $sK^+$  concentrations  $>5.5$  or  $>6.0$  mmol/L at LIDI visits during the 4-week evaluation period, determined as the proportion of hyperkalemic events divided by the total number of possible events, was 64.3% ( $n = 202/314$ ) and 27.7% ( $n = 87/314$ ), respectively. This risk increased among patients who were most hyperkalemic at randomization (Table 2). Patients with the lowest ( $<5.5$  mmol/L) and highest ( $\geq 6.5$  mmol/L) predialysis  $sK^+$  concentrations at randomization

TABLE 1: Baseline (visit 1, day -7) characteristics of placebo patients.

Summary statistic	Overall, N = 86	Predialysis sK <sup>+</sup> at randomization (visit 4, day 1) (mmol/L)			
		<5.5, n = 14	5.5 to <6.0, n = 37	6.0 to <6.5, n = 21	≥6.5, n = 14
<i>Demographics</i>					
Age, years, mean (SD)	60.3 (13.2)	53.4 (12.3)	64.1 (11.1)	58.2 (14.7)	60.1 (14.7)
Age, years, n (%)					
18–50	18 (20.9)	6 (42.9)	5 (13.5)	4 (19.0)	3 (21.4)
51–64	28 (32.6)	4 (28.6)	11 (29.7)	8 (38.1)	5 (35.7)
65–84	39 (45.3)	4 (28.6)	21 (56.8)	8 (38.1)	6 (42.9)
≥85	1 (1.2)	0 (0)	0 (0)	1 (4.8)	0 (0)
Female sex, n (%)	36 (41.9)	3 (21.4)	15 (40.5)	11 (52.4)	7 (50.0)
Race, n (%)					
White	43 (50.0)	5 (35.7)	18 (48.6)	11 (52.4)	9 (64.3)
Black or African American	6 (7.0)	3 (21.4)	2 (5.4)	1 (4.8)	0 (0)
Asian	31 (36.0)	3 (21.4)	17 (45.9)	8 (38.1)	3 (21.4)
American Indian or Alaska Native	2 (2.3)	2 (14.3)	0 (0)	0 (0)	0 (0)
Other	4 (4.7)	1 (7.1)	0 (0)	1 (4.8)	2 (14.3)
<i>Clinical characteristics</i>					
Height, cm, mean (SD)	165.0 (9.2)	169.1 (10.1)	164.3 (7.9)	164.9 (11.8)	162.7 (5.9)
Weight, kg, mean (SD)	72.7 (16.4)	75.2 (15.0)	70.2 (15.3)	78.7 (20.1)	68.1 (12.0)
Body mass index, kg/m <sup>2</sup> , mean (SD)	26.7 (5.5)	26.2 (4.6)	25.9 (5.3)	28.9 (6.7)	25.7 (4.4)
Predialysis sK <sup>+</sup> , mmol/L, mean (SD)	6.0 (0.4)	5.9 (0.3)	5.9 (0.4)	6.0 (0.3)	6.3 (0.7)
Serum bicarbonate, mmol/L, mean (SD)	20.1 (2.4)	19.3 (1.9)	20.0 (2.2)	20.9 (3.3)	19.8 (1.9)
<i>Dialysis parameters</i>					
Vintage, years, mean (SD)	7.9 (7.8)	5.2 (3.9)	9.7 (8.8)	7.3 (8.9)	6.9 (4.8)
Duration of dialysis session, minutes, mean (SD)	241.7 (31.9)	236.1 (41.5)	245.7 (34.4)	242.8 (17.8)	235.1 (31.9)
Dialysate potassium, mmol/L, mean (SD)	2.2 (0.5)	2.1 (0.5)	2.2 (0.4)	2.3 (0.5)	2.4 (0.5)
Dialysate potassium, mmol/L, n (%)					
1	1 (1.2)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
2	63 (73.3)	11 (78.6)	30 (81.1)	14 (66.7)	8 (57.1)
3	22 (25.6)	2 (14.3)	7 (18.9)	7 (33.3)	6 (42.9)
spKt/V, mean (SD)	1.7 (0.4)	1.5 (0.2)	1.7 (0.4)	1.8 (0.4)	1.9 (0.3)
Dialysate flow, mL/min, mean (SD)	548.0 (131.1)	583.6 (220.8)	563.4 (113.1)	521.9 (98.9)	511.1 (92.8)
Prescribed ultrafiltration rate, mL, mean (SD)	2785.8 (1228.1)	2426.6 (1665.1)	2929.8 (1250.4)	2871.4 (998.1)	2635.7 (996.6)
Urea removal rate, %, mean (SD)	74.3 (5.8)	71.8 (6.4)	74.1 (5.2)	74.1 (6.1)	75.9 (6.7)
<i>Key medical history, n (%)</i>					
Hypertension	69 (80.2)	11 (78.6)	31 (83.8)	16 (76.2)	11 (78.6)
Dyslipidemia	14 (16.3)	2 (14.3)	5 (13.5)	5 (23.8)	2 (14.3)
Cardiac failure	4 (4.7)	0 (0.0)	3 (8.1)	0 (0.0)	1 (7.1)
Diabetes mellitus	10 (11.6)	1 (7.1)	5 (13.5)	2 (9.5)	2 (14.3)
Type 1 diabetes mellitus	2 (2.3)	0 (0.0)	1 (2.7)	0 (0.0)	1 (7.1)
Type 2 diabetes mellitus	22 (25.6)	4 (28.6)	11 (29.7)	4 (19.0)	3 (21.4)
<i>Key allowed concomitant medications, n (%)</i>					
ACE inhibitors	12 (14.0)	3 (21.4)	4 (10.8)	3 (14.3)	2 (14.3)
Angiotensin II antagonists	23 (26.7)	2 (14.3)	16 (43.2)	3 (14.3)	2 (14.3)
Angiotensin II antagonists + calcium channel blockers	2 (2.3)	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)
Aldosterone antagonists	3 (3.5)	0 (0.0)	2 (5.4)	1 (4.8)	0 (0.0)

ACE, angiotensin-converting enzyme; SD, standard deviation; spKt/V, target single pool Kt/V.

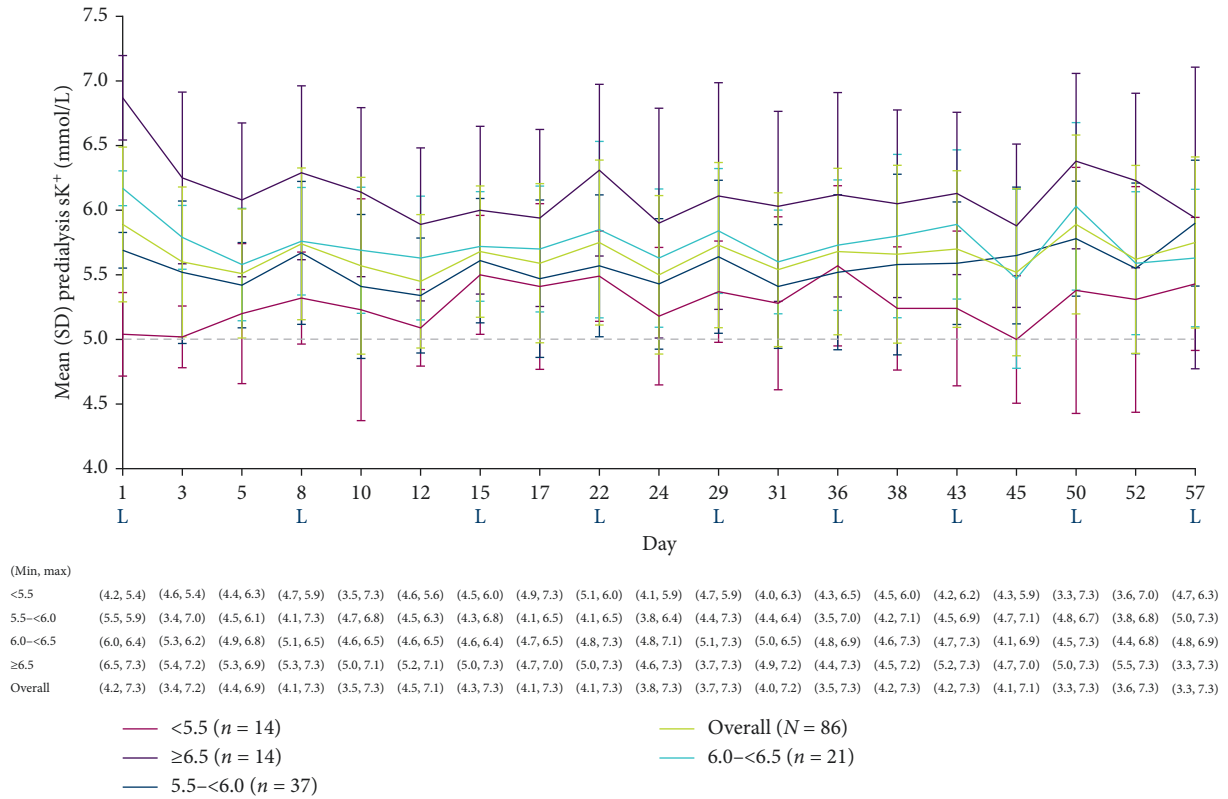
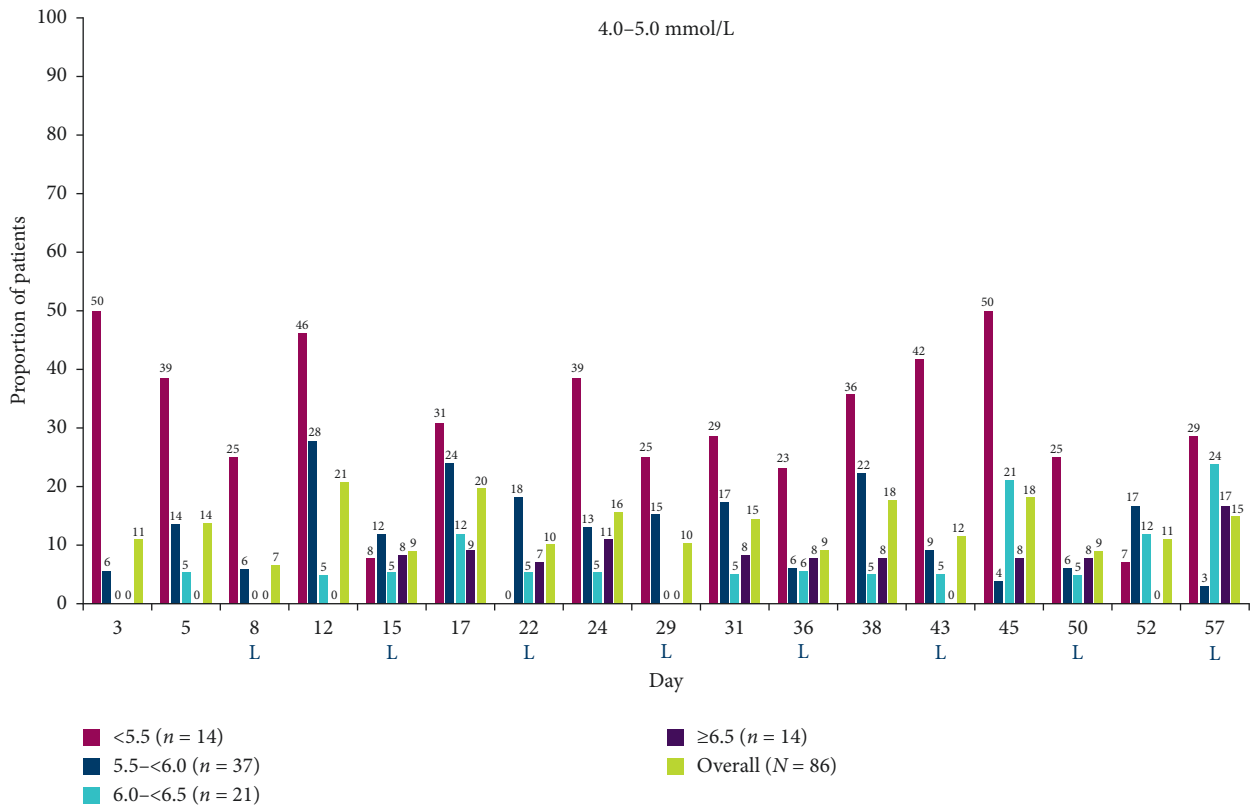
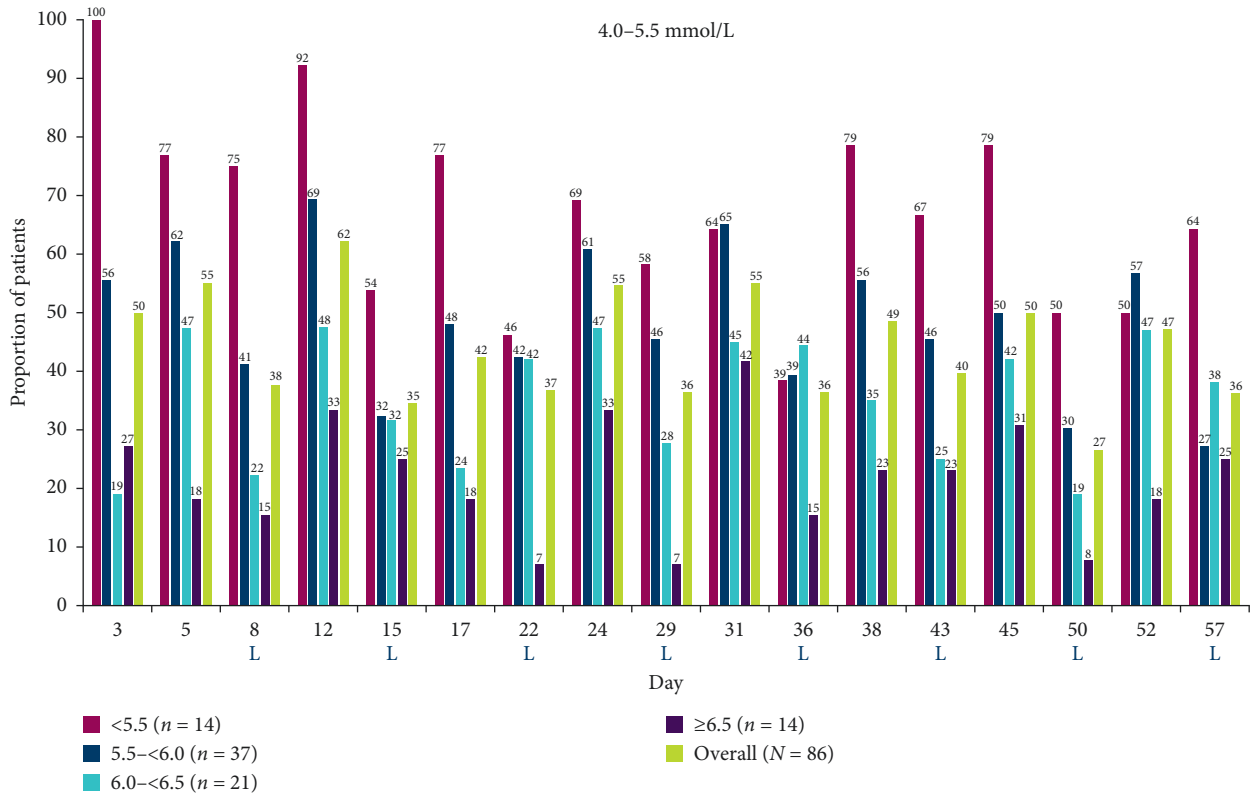


FIGURE 1: Predialysis sK<sup>+</sup> concentration at each study visit in placebo patients overall and by predialysis sK<sup>+</sup> concentration at randomization. Predialysis sK<sup>+</sup> measurement at randomization (visit 4, day 1) was used for subgroup stratification. No imputation of missing data was conducted. The dashed line represents the upper limit of normokalemia (i.e., sK<sup>+</sup> 5.0 mmol/L). L represents the LIDI visits. LIDI, long interdialytic interval; SD, standard deviation; sK<sup>+</sup>, serum potassium.



(a)  
FIGURE 2: Continued.



(b)

FIGURE 2: Proportions of placebo patients with predialysis sK<sup>+</sup> ranges of (a) 4.0–5.0 mmol/L and (b) 4.0–5.5 mmol/L at each study visit, by predialysis sK<sup>+</sup> concentration at randomization. Predialysis sK<sup>+</sup> measurement at randomization (visit 4, day 1) was used for subgroup stratification. Patients receiving rescue therapy were included in the analysis. No imputation of missing data was conducted. L represents the LIDI visits. LIDI, long interdialytic interval; sK<sup>+</sup>, serum potassium.

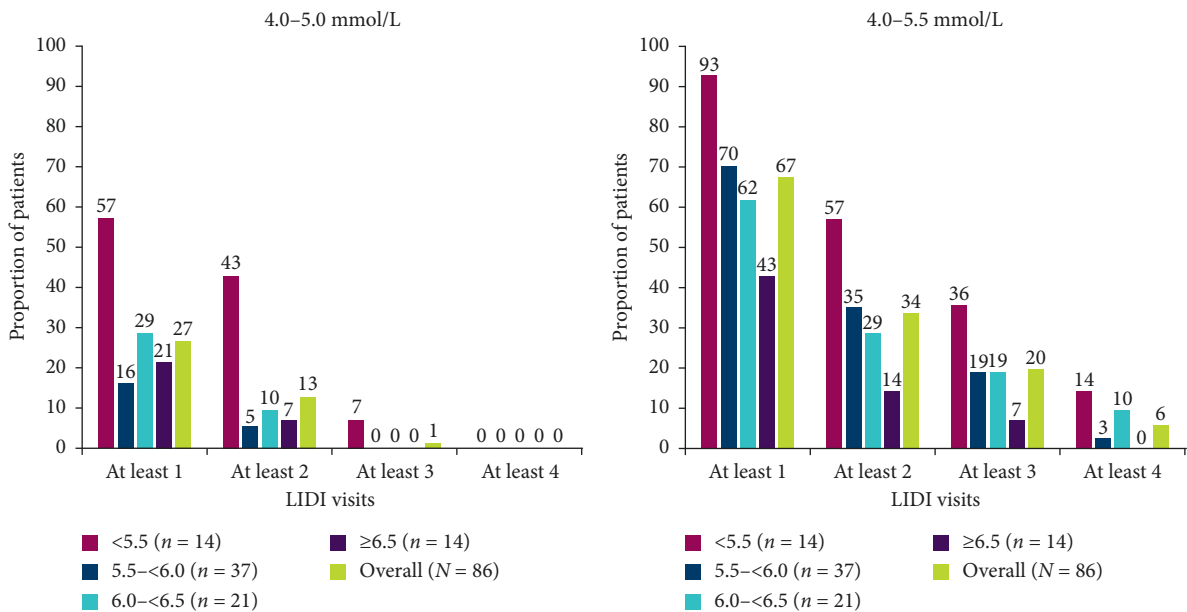


FIGURE 3: Proportion of placebo patients with predialysis sK<sup>+</sup> ranges of 4.0–5.0 and 4.0–5.5 mmol/L for ≥1, ≥2, ≥3, and 4 LIDI visits during the 4-week evaluation period, by predialysis sK<sup>+</sup> concentration at randomization. Predialysis sK<sup>+</sup> measurement at randomization (visit 4, day 1) was used for subgroup stratification. Predialysis sK<sup>+</sup> values obtained at the LIDI visits in the 4-week evaluation period. No imputation of missing data was conducted. Patients receiving rescue therapy were included in the analysis. LIDI, long interdialytic interval; sK<sup>+</sup>, serum potassium.

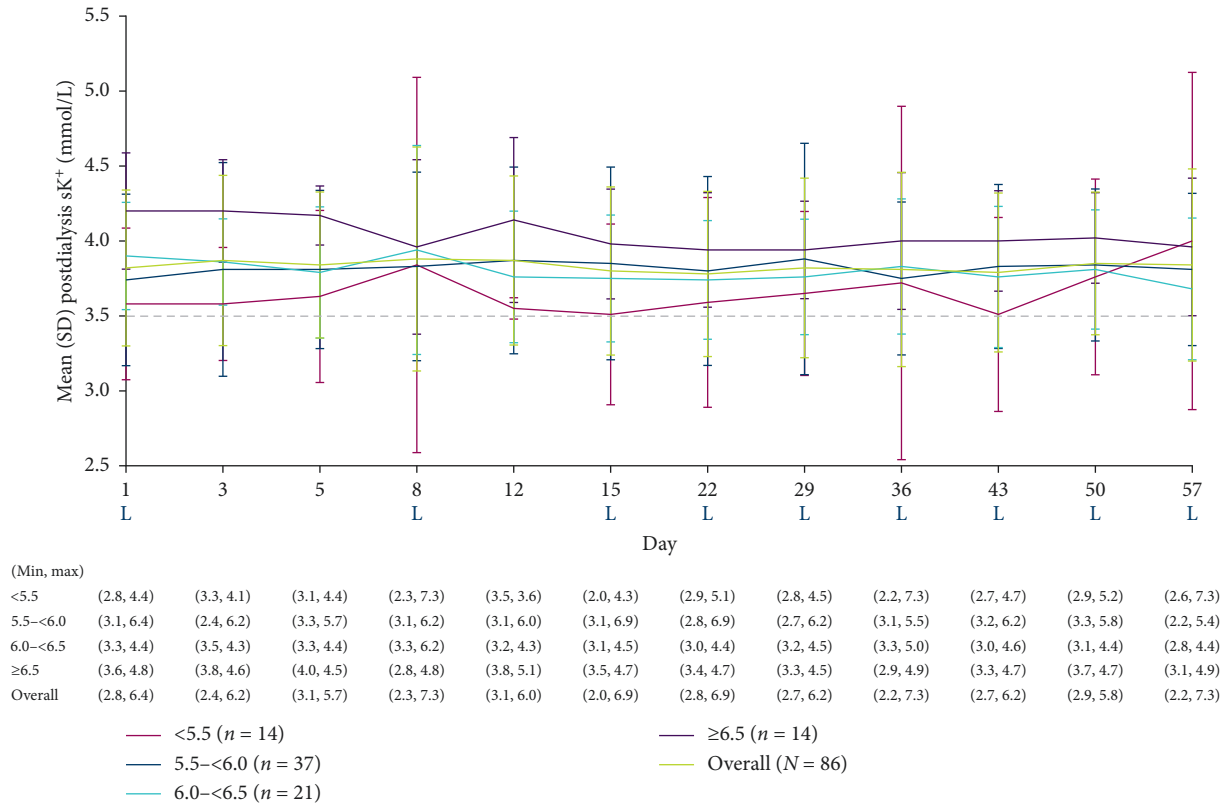


FIGURE 4: Postdialysis sK<sup>+</sup> concentration at each study visit in placebo patients overall and by predialysis sK<sup>+</sup> concentration at randomization. Predialysis sK<sup>+</sup> measurement at randomization (visit 4, day 1) was used for subgroup stratification. No imputation of missing data was conducted. The dashed line represents the threshold for hypokalemia (i.e., sK<sup>+</sup> 3.5 mmol/L). L represents the LIDI visits. LIDI, long interdialytic interval; SD, standard deviation; sK<sup>+</sup>, serum potassium.

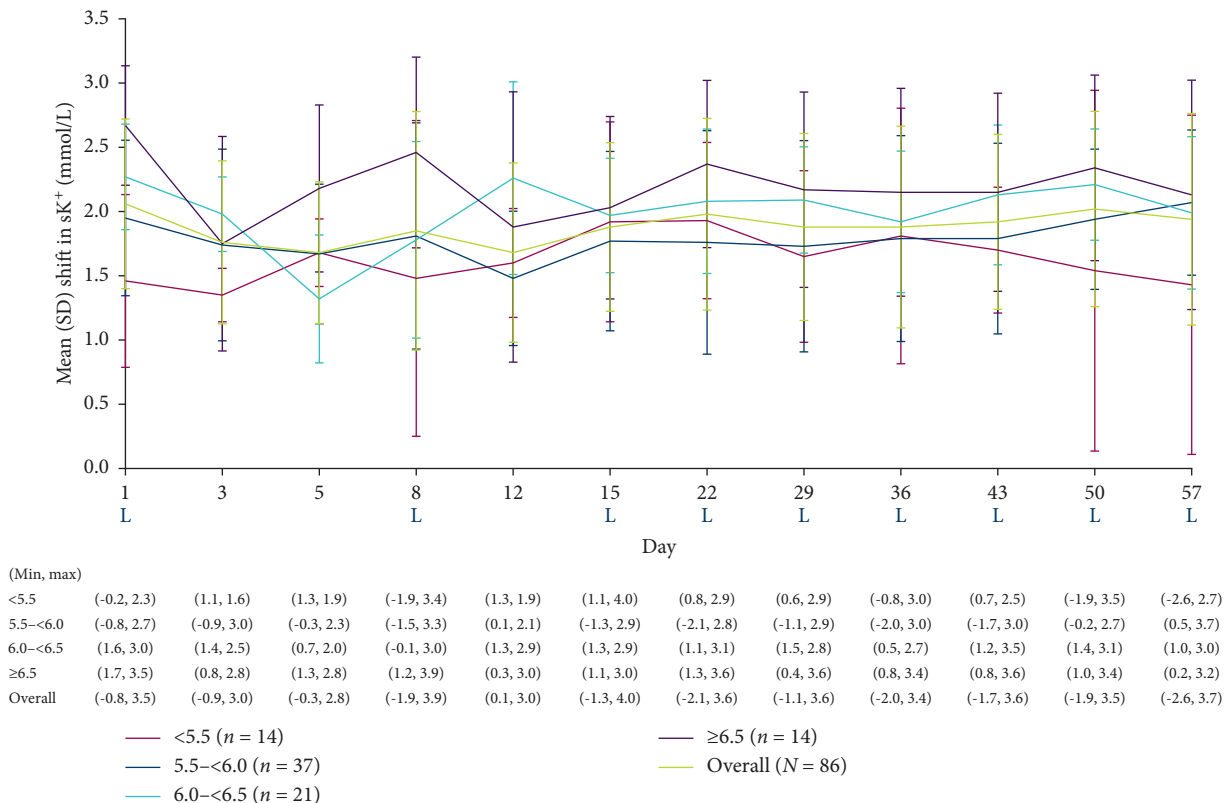


FIGURE 5: Shift in sK<sup>+</sup> concentration from predialysis to postdialysis at each study visit in placebo patients overall and by sK<sup>+</sup> concentration at randomization. Predialysis sK<sup>+</sup> measurement at randomization (visit 4, day 1) was used for subgroup stratification. sK<sup>+</sup> shift = predialysis sK<sup>+</sup> - postdialysis sK<sup>+</sup> for each visit. No imputation of missing data was conducted. L represents the LIDI visits. LIDI, long interdialytic interval; SD, standard deviation; sK<sup>+</sup>, serum potassium.

TABLE 2: Risk of predialysis  $sK^+$  concentration  $>5.5$  or  $>6.0$  mmol/L at LIDI visits during the 4-week evaluation period following the initial hyperkalemic event.

LIDI visit	Predialysis $sK^+$ at randomization (visit 4, day 1) (mmol/L)			
	$<5.5$ , $n = 14$	$5.5$ to $<6.0$ , $n = 37$	$6.0$ to $<6.5$ , $n = 21$	$\geq 6.5$ , $n = 14$
<i>Incidence of predialysis <math>sK^+ &gt;5.5</math> mmol/L</i>				
Visit 12 (day 36)	8/13 (61.5)	19/33 (57.6)	10/18 (55.6)	11/13 (84.6)
Visit 13 (day 43)	4/12 (33.3)	18/33 (54.5)	15/20 (75.0)	10/13 (76.9)
Visit 14 (day 50)	5/12 (41.7)	23/33 (69.7)	17/21 (81.0)	12/13 (92.3)
Visit 15 (day 57)	5/14 (35.7)	24/33 (72.7)	13/21 (61.9)	8/12 (66.7)
<b>Overall</b>	<b>22/51 (43.1)</b>	<b>84/132 (63.6)</b>	<b>55/80 (68.8)</b>	<b>41/51 (80.4)</b>
<i>Incidence of predialysis <math>sK^+ &gt;6.0</math> mmol/L</i>				
Visit 12 (day 36)	2/13 (15.4)	3/33 (9.1)	4/18 (22.2)	8/13 (61.5)
Visit 13 (day 43)	1/12 (8.3)	4/33 (12.1)	6/20 (30.0)	6/13 (46.2)
Visit 14 (day 50)	3/12 (25.0)	10/33 (30.3)	9/21 (42.9)	10/13 (76.9)
Visit 15 (day 57)	2/14 (14.3)	10/33 (30.3)	2/21 (9.5)	7/12 (58.3)
<b>Overall</b>	<b>8/51 (15.7)</b>	<b>27/132 (20.5)</b>	<b>21/80 (26.3)</b>	<b>31/51 (60.8)</b>

Data are shown as the number (%) of hyperkalemic events. Hyperkalemia was defined as  $sK^+ >5.5$  or  $>6.0$  mmol/L after the LIDI. No imputation of missing data was conducted. For each randomization predialysis  $sK^+$  subgroup, the probability of whether patients with hyperkalemia will be hyperkalemic ( $sK^+ >5.5$  or  $>6.0$  mmol/L) at subsequent visits was calculated as follows: [Number of hyperkalemic events/total number of possible hyperkalemic events based on patients with evaluable data]  $\times 100$ . LIDI, long interdialytic interval;  $sK^+$ , serum potassium.

TABLE 3: Dialysis adequacy and prescription parameters in placebo patients ( $n = 86$ ).

Day	spKt/V	Urea removal rate (%)	Dialysate flow (mL/min)	Dialysate potassium concentration (mmol/L)	Prescribed ultrafiltration rate (mL)	Blood flow (mL/min)
-7	1.71 (0.38)	74.3 (5.8)	548.0 (131.1)	2.24 (0.46)	2785.8 (1228.1)	321.0 (95.8)
1	1.99 (0.85)	73.3 (6.4)	545.3 (133.7)	2.23 (0.48)	2753.0 (1197.1)	316.0 (95.8)
3	—	—	—	2.24 (0.48)	—	—
5	—	—	—	2.23 (0.48)	—	—
8	—	—	—	2.22 (0.47)	—	—
12	—	—	—	2.22 (0.47)	—	—
15	—	—	—	2.24 (0.48)	—	—
22	—	—	—	2.26 (0.57)	—	—
29	1.67 (0.35)	72.3 (7.1)	545.9 (143.3)	2.21 (0.47)	2807.6 (1176.5)	317.3 (95.0)
36	—	—	—	2.22 (0.47)	—	—
43	—	—	—	2.22 (0.48)	—	—
50	—	—	—	2.22 (0.48)	—	—
57	1.70 (0.43)	73.6 (5.4)	548.7 (130.4)	2.24 (0.46)	2843.0 (1098.3)	320.7 (98.8)

Data are mean (standard deviation). Data are shown for the 86 placebo patients with predialysis  $sK^+$  measurements at randomization (visit 4, day 1).  $sK^+$ , serum potassium; spKt/V, target single pool Kt/V.

had a 43% and 80% chance, respectively, of having predialysis  $sK^+ >5.5$  mmol/L, and a 16% and 61% chance, respectively, of having predialysis  $sK^+ >6.0$  mmol/L at a LIDI visit during the 4-week evaluation period (Table 2).

**3.6. Dialysis Parameters.** Dialysis adequacy and prescription parameters at day 57 were generally comparable with baseline

levels among placebo patients ( $n = 86$ ) (Table 3). In particular, the mean (SD)  $dK^+$  concentration at day -7 (2.24 [0.46] mmol/L) was similar to day 57 (2.24 [0.46] mmol/L) (Table 3). When analyzed using  $dK^+$  concentration categories of 1, 2, and 3 mmol/L, from day -7 to day 57,  $dK^+$  concentration remained the same in the majority of placebo patients, increased in one patient, and decreased in four patients (Figure 6).





FIGURE 6: Shift in  $dK^+$  concentration category of 1, 2, and 3 mmol/L from baseline (visit 1, day -7) to the end of treatment (visit 15, day 57) in placebo patients. No imputation of missing data was conducted. Only subjects with visit 4 predialysis  $sK^+$  measurement were included.  $dK^+$ , dialysate potassium; EOT, end of treatment;  $sK^+$ , serum potassium.

#### 4. Discussion and Conclusions

These novel analyses utilized the placebo group of a randomized, double-blind phase 3b study to generate the first longitudinal trajectory of  $sK^+$  concentration among hyperkalemic HD patients. The mean predialysis  $sK^+$  concentration did not return to normokalemic levels (i.e., 4.0–5.0 mmol/L) in the placebo group overall and across all baseline predialysis  $sK^+$  subgroups over 8 weeks, with no change in  $dK^+$  concentration.

Evidence of longitudinal trajectory of  $sK^+$  concentration and risk of recurrent hyperkalemia following a hyperkalemic event is sparse [9–14], particularly among HD patients [1]. Among maintenance HD patients, a prospective French 2-year survey by Rossignol et al. reported that 26.4%, 13.8%, and 4.9% of patients had predialysis  $sK^+$  concentrations of >5.1 mmol/L, >5.5 mmol/L, and >6.0 mmol/L, respectively, and 73.8%, 57.9%, and 34.5% of patients had predialysis  $sK^+$  concentrations of >5.1 mmol/L, >5.5 mmol/L, and >6.0 mmol/L, respectively, during follow-up [1]. Furthermore, only 6.3% of patients became normokalemic within 3 months following a hyperkalemic event ( $sK^+$  >5.5 mmol/L) [1]. Adelborg et al. followed  $sK^+$  trajectories before and after a first hyperkalemic event among a broad population, which included patients with chronic kidney disease, although findings in dialysis patients alone were not presented separately [13]. In patients with a single hyperkalemic event,  $sK^+$  returned to prehyperkalemia concentrations in 2–4 weeks, while the reduction in  $sK^+$  concentrations in patients with repeated hyperkalemia occurred more slowly and did not reach the prehyperkalemia concentration [13]. Our findings in maintenance HD patients build on previous data to provide information on the likely trajectory of predialysis

$sK^+$  concentration following a hyperkalemic event and support the persistence of hyperkalemia reported previously. Importantly, as an  $sK^+$  concentration of >5.5 mmol/L is associated with increased mortality and hospitalization in HD patients [3–6], the patients in our analysis would be left at continued risk of adverse events.

In our analyses, more severe baseline hyperkalemia was associated with lower proportions of patients achieving  $sK^+$  ranges of 4.0–5.0 mmol/L and 4.0–5.5 mmol/L over 8 weeks. Furthermore, the risk of a subsequent hyperkalemic event (predialysis  $sK^+$  concentration >5.5 or >6.0 mmol/L) at LIDI visits during the 4-week evaluation period increased, with increasing baseline hyperkalemia. Similarly, Rossignol et al. determined the evolution of  $sK^+$  concentration among HD patients after an initial hyperkalemic event ( $sK^+$  >5.5 mmol/L) and reported that 80.2% and 59.7% of patients experienced a recurrent event of  $sK^+$  >5.1 mmol/L or of the same magnitude, respectively, within 3 months [1]. Furthermore, 35.6% of HD patients with an initial event of  $sK^+$  >6.0 mmol/L had a recurrent event of the same magnitude within 3 months [1]. Our findings among HD patients may inform physicians of the likely course of hyperkalemia based on a patient's baseline predialysis  $sK^+$  concentration. This is particularly important given the relationship between the greater severity of hyperkalemia and increased rates of mortality and hospitalization [9, 11, 14, 17].

Inadequate dialysis is associated with an increased predialysis  $sK^+$  concentration [18]. A recent position paper endorsed by the Italian Society of Nephrology stated that it is essential to evaluate dialysis adequacy in hyperkalemic patients [7]. Practice guidelines by the

Kidney Disease Outcomes Quality Initiative (KDOQI) recommend a spKt/V of 1.4 per HD session for patients treated TIW, with a minimum delivered spKt/V of 1.2 [19]. In our analysis, the spKt/V exceeded the target level of 1.4 for patients receiving HD TIW as recommended by KDOQI [19], and parameters of dialysis adequacy and prescription were generally stable over time. Therefore, the impact of this variable on longitudinal changes in  $sK^+$  was minimized.

The significance of postdialysis  $sK^+$  concentration is less well-defined than for predialysis  $sK^+$  concentration, partly because postdialysis values are not routinely measured in clinical practice [15]. Our observed trends in longitudinal postdialysis  $sK^+$  concentration were not as clear as with predialysis  $sK^+$  concentration. Mean postdialysis  $sK^+$  concentration over 8 weeks remained above the threshold for hypokalemia (i.e., 3.5 mmol/L) in all baseline predialysis  $sK^+$  subgroups. However, normal postdialysis  $sK^+$  concentration may not prevent certain patients with marked hyperkalemia from a rebound of  $sK^+$  to potentially dangerous levels. A previous study noted a close correlation between predialysis and an increase in 6-hours postdialysis  $sK^+$  concentration ( $r=0.78$ ,  $P<0.01$ ) [8]. Furthermore, Rossignol et al. reported that ~5% of HD patients who had an initial predialysis  $sK^+$  concentration  $>5.5$  mmol/L were then hypokalemic ( $<3.5$  mmol/L) within 3 months [1]. Together, these findings suggest a degree of potassium variability that deserves further attention.

The persistence of hyperkalemia observed in our analyses, despite maintenance HD, indicates that additional therapies and closer monitoring of HD patients following a hyperkalemic event may have a role in minimizing the risks of future hyperkalemia. The persistence of hyperkalemia reported by Rossignol et al. [1], despite widespread use of sodium polystyrene sulfonate, suggests that additional potassium binders are warranted. In the phase 3b DIALIZE study, SZC was shown to be an effective and well-tolerated treatment for predialysis hyperkalemia in patients with ESRD undergoing maintenance HD [16]. Data from real-world evaluations suggest that the potassium binder patiomer may also be effective at reducing  $sK^+$  concentration in HD patients [20, 21].

Our analyses have several limitations. The analyses are post hoc in nature and were not prespecified; therefore, the results are exploratory and hypothesis-generating. The patient numbers within the predialysis  $sK^+$  subgroups were small, which limits the interpretation of these findings. The impact of rescue therapy on mean  $sK^+$  concentration in placebo patients was not determined; however, in DIALIZE, a low proportion of placebo patients (5.1% [ $n=5/99$ ]) needed rescue therapy to reduce the  $sK^+$  concentration [16]. For the calculation of the risk of recurrent hyperkalemia, the definition of hyperkalemia differed from the stricter version used for study entry. Furthermore, the impact of a placebo effect resulting from clinical trial participation is unknown. Finally, rebound hyperkalemia is likely to be more severe in patients with shorter and less adequate HD, although this could not be assessed as patients received adequate HD.

In conclusion, mean predialysis  $sK^+$  concentration remains high over 8 weeks following a hyperkalemic event in patients receiving maintenance HD and routine dietary counselling. Most placebo patients remained hyperkalemic during this period, and so they may be at continued risk of adverse events. These findings may inform physicians of the likely course of hyperkalemia. Nephrologists may need to monitor predialysis  $sK^+$  concentration in hyperkalemic HD patients more closely and consider therapies, such as potassium binders, to minimize the risks of future hyperkalemia.

## Data Availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagroup-dt.pharmam.com/DT/Home>.

## Ethical Approval

The study was performed in accordance with the Declaration of Helsinki, the International Council for Harmonisation, and Good Clinical Practice.

## Consent

All participants provided written informed consent.

## Disclosure

The results presented in this paper have not been published previously in whole or part, except in abstract format.

## Conflicts of Interest

BS received research grants, lecture fees, and/or consulting fees from AstraZeneca, Akebia, Reata Pharmaceuticals, and Fresenius Medical Care. SF received research support and consulting fees from AstraZeneca. MFu received consulting fees and lecture fees from AstraZeneca Japan. MFo received travel support from Amgen and AstraZeneca and is an advisory board member for AstraZeneca. NG is an employee of AstraZeneca. AR received research or travel support from, and/or is a speaker, consultant, or advisory board member for AstraZeneca, Vifor Pharma, Fresenius Medical Care, Sanofi, Kadmon, Amag, Otsuka, Genzyme, GlaxoSmithKline, Omeros, Janssen, Reata Pharmaceuticals, Ironwood, and Amgen.

## Authors' Contributions

All authors contributed to the data interpretation, critically reviewed the manuscript, approved the final version, and accepted accountability for the overall work.

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## References

- [1] P. Rossignol, Z. Lamiral, L. Frimat et al., “Hyperkalaemia prevalence, recurrence and management in chronic haemodialysis: a prospective multicentre French regional registry 2-year survey,” *Nephrology Dialysis Transplantation*, vol. 32, no. 12, pp. 2112–2118, 2017.
- [2] A. A. Yusuf, Y. Hu, B. Singh, J. A. Menoyo, and J. B. Wetmore, “Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study,” *American Journal of Nephrology*, vol. 44, no. 3, pp. 179–186, 2016.
- [3] C. P. Kovesdy, D. L. Regidor, R. Mehrotra et al., “Serum and dialysate potassium concentrations and survival in hemodialysis patients,” *Clinical Journal of the American Society of Nephrology*, vol. 2, no. 5, pp. 999–1007, 2007.
- [4] S. Genovesi, M. G. Valsecchi, E. Rossi et al., “Sudden death and associated factors in a historical cohort of chronic haemodialysis patients,” *Nephrology Dialysis Transplantation*, vol. 24, no. 8, pp. 2529–2536, 2009.
- [5] S. M. Brunelli, C. Du Mond, N. Oestreicher, V. Rakov, and D. M. Spiegel, “Serum potassium and short-term clinical outcomes among hemodialysis patients: impact of the long interdialytic interval,” *American Journal of Kidney Diseases*, vol. 70, no. 1, pp. 21–29, 2017.
- [6] A. Karaboyas, J. Zee, S. M. Brunelli et al., “Dialysate potassium, serum potassium, mortality, and arrhythmia events in hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS),” *American Journal of Kidney Diseases*, vol. 69, no. 2, pp. 266–277, 2017.
- [7] S. Bianchi, F. Aucella, L. De Nicola, S. Genovesi, E. Paoletti, and G. Regolisti, “Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology,” *Journal of Nephrology*, vol. 32, no. 4, pp. 499–516, 2019.
- [8] A. Blumberg, H. W. Roser, C. Zehnder, and J. Muller-Brand, “Plasma potassium in patients with terminal renal failure during and after haemodialysis; relationship with dialytic potassium removal and total body potassium,” *Nephrology Dialysis Transplantation*, vol. 12, no. 8, pp. 1629–1634, 1997.
- [9] L. M. Einhorn, M. Zhan, V. D. Hsu et al., “The frequency of hyperkalemia and its significance in chronic kidney disease,” *Archives of Internal Medicine*, vol. 169, no. 12, pp. 1156–1162, 2009.
- [10] E. Nilsson, A. Gasparini, J. Ärnlöv et al., “Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system,” *International Journal of Cardiology*, vol. 245, pp. 277–284, 2017.
- [11] L. Horne, A. Ashfaq, S. MacLachlan et al., “Epidemiology and health outcomes associated with hyperkalemia in a primary care setting in England,” *BMC Nephrology*, vol. 20, no. 1, p. 85, 2019.
- [12] R. W. Thomsen, S. K. Nicolaisen, P. Hasvold et al., “Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes—a Danish population-based cohort study,” *Nephrology Dialysis Transplantation*, vol. 33, no. 9, pp. 1610–1620, 2017.
- [13] K. Adelborg, S. K. Nicolaisen, P. Hasvold, E. Palaka, L. Pedersen, and R. W. Thomsen, “Predictors for repeated hyperkalemia and potassium trajectories in high-risk patients—a population-based cohort study,” *PLoS One*, vol. 14, no. 6, Article ID e0218739, 2019.
- [14] N. Kashihara, S. Kohsaka, E. Kanda, S. Okami, and T. Yajima, “Hyperkalemia in real-world patients under continuous medical care in Japan,” *Kidney International Reports*, vol. 4, no. 9, pp. 1248–1260, 2019.
- [15] P. H. Pun and J. P. Middleton, “Dialysate potassium, dialysate magnesium, and hemodialysis risk,” *Journal of the American Society of Nephrology*, vol. 28, no. 12, pp. 3441–3451, 2017.
- [16] S. Fishbane, M. Ford, M. Fukagawa et al., “A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia,” *Journal of the American Society of Nephrology*, vol. 30, no. 9, pp. 1723–1733, 2019.
- [17] P. H. Pun, R. W. Leich, E. F. Honeycutt, C. A. Herzog, and J. P. Middleton, “Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics,” *Kidney International*, vol. 79, no. 2, pp. 218–227, 2011.
- [18] R. Stolic, G. Trajkovic, D. Stolic, V. Peric, and G. Subaric-Gorgieva, “Nutrition parameters as hemodialysis adequacy markers,” *Hippokratia*, vol. 14, pp. 193–197, 2010.
- [19] National Kidney Foundation, “KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update,” *American Journal of Kidney Diseases*, vol. 66, pp. 884–930, 2015.
- [20] C. P. Kovesdy, C. G. Rowan, A. Conrad et al., “Real-world evaluation of patiromer for the treatment of hyperkalemia in hemodialysis patients,” *Kidney International Reports*, vol. 4, no. 2, pp. 301–309, 2019.
- [21] D. A. Bushinsky, P. Rossignol, D. M. Spiegel et al., “Patiromer decreases serum potassium and phosphate levels in patients on hemodialysis,” *American Journal of Nephrology*, vol. 44, no. 5, pp. 404–410, 2016.