Effectiveness of Sodium Zirconium Cyclosilicate in Hemodialysis Patients With Severe Hyperkalemia

Martin Ford[1,2], Steven Fishbane[3], Bruce Spinowitz[4], Anjay Rastogi[5], Nicolas Guzman[6] and Kieran McCafferty[7]

[1]Department of Renal Medicine, King's College Hospital NHS Trust, London, UK; [2]Faculty of Life Sciences and Medicine, King's College, London, UK; [3]Department of Medicine, Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York, USA; [4]Department of Medicine, New York-Presbyterian Queens, Queens, New York, USA; [5]UCLA CORE Kidney Program, University of California Los Angeles, Los Angeles, California, USA; [6]Global Medicines Development, AstraZeneca BioPharmaceuticals R&D, Gaithersburg, Maryland, USA; and [7]Department of Nephrology, Barts Health NHS Trust, London, UK

Correspondence: Martin Ford, Department of Renal Medicine, King's College Hospital NHS Trust, Denmark Hill, London SE5 9RS, UK. E-mail: martinford2@nhs.net

Received 30 April 2021; revised 31 August 2021; accepted 7 September 2021; published online 13 September 2021

Kidney Int Rep (2021) **6,** 3074–3078; https://doi.org/10.1016/j.ekir.2021.09.004
KEYWORDS: chronic kidney disease; hemodialysis; potassium; severe hyperkalemia; sodium zirconium cyclosilicate

Severe hyperkalemia is often defined as predialysis serum potassium (sK^+) concentration ≥6.0 mmol/l and is associated with a greater risk of hospitalization, major adverse cardiovascular events, and all-cause mortality versus referent predialysis sK^+ concentrations.[1,2]

Several approaches are available for managing potassium homeostasis in hemodialysis patients.[3] A challenge in selecting an appropriate dialysate potassium concentration is balancing removal of potassium to avoid hyperkalemia while minimizing the risk of adverse events associated with lowering potassium too rapidly. The use of nondialytic measures, such as potassium binders during the interdialytic period, to improve potassium homeostasis decreases the need to expose patients to a dialysate with low potassium concentrations.[3]

Sodium zirconium cyclosilicate (SZC) is a novel, highly selective potassium binder that preferentially captures potassium in the gastrointestinal lumen, increasing potassium fecal excretion and thereby reducing sK^+ concentration.[4,5] The phase IIIb DIALIZE study (NCT03303521) revealed that SZC is an effective and well-tolerated treatment for hyperkalemia in patients with end-stage kidney disease undergoing maintenance hemodialysis.[6] Here, we report the results of a *post hoc* analysis of DIALIZE that assessed the efficacy of SZC versus placebo in patients with severe hyperkalemia (predialysis sK^+ concentration ≥6.0 mmol/l) at baseline.

RESULTS

Patients

In DIALIZE, at baseline (visit 1, day −7), 88 patients (SZC $n = 46$, placebo $n = 42$) had predialysis sK^+ concentration ≥6.0 mmol/l and 106 patients (SZC $n = 49$, placebo $n = 57$) had predialysis sK^+ concentration <6.0 mmol/l (Supplementary Results and Supplementary Table S1).

Treatment Responders

Treatment responders were defined as patients who, during the 4-week evaluation period, maintained target predialysis sK^+ concentration for ≥3 of 4 hemodialysis treatments after the long interdialytic interval (LIDI) and did not require rescue therapy to lower sK^+ concentration. Among patients with baseline severe hyperkalemia, the proportions of treatment responders were significantly greater with SZC versus placebo using target predialysis sK^+ ranges of 4.0 to 5.0 mmol/l (34.8% vs. 0%, respectively; Figure 1a) and an extended range of 4.0 to 5.5 mmol/l (67.4% vs. 19.0%, respectively; Figure 1b) (both $P < 0.0001$ for SZC vs. placebo). For patients receiving SZC, there was no statistical difference between baseline predialysis sK^+ ≥6.0 mmol/l versus <6.0 mmol/l subgroups in responder rates using a target predialysis sK^+ range of 4.0 to 5.0 mmol/l (34.8% vs. 46.9%, respectively; $P = 0.2974$) and an extended range of 4.0 to 5.5 mmol/l (67.4% vs. 71.4%, respectively; $P = 0.8239$).

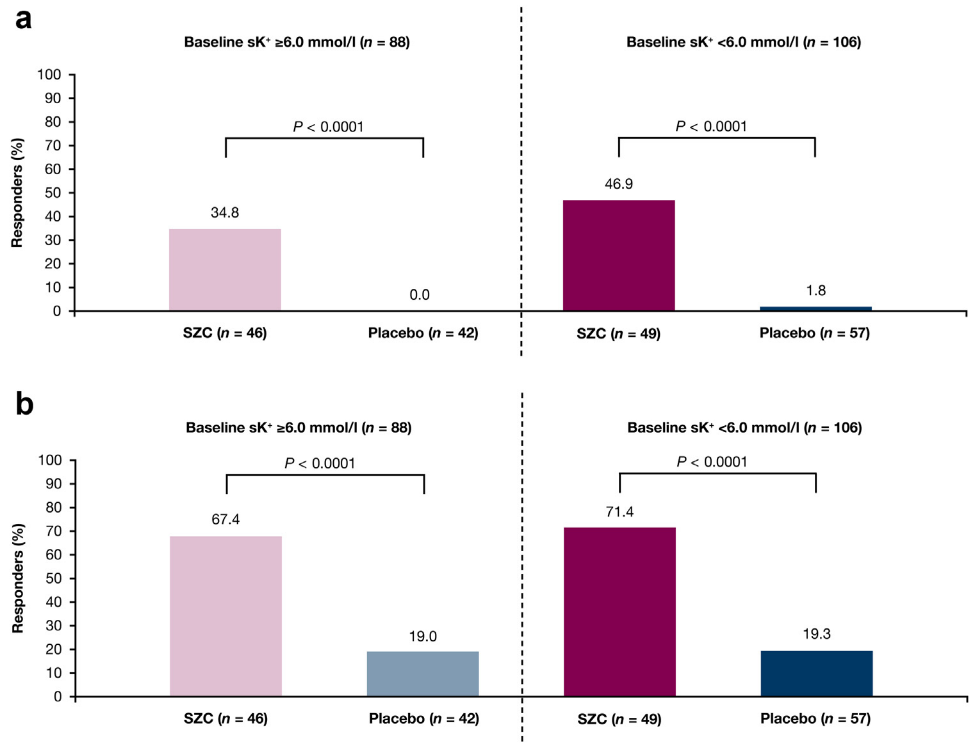

Figure 1. Proportions of responders with SZC and placebo, by baseline predialysis sK^+ subgroup (≥6.0 mmol/l and <6.0 mmol/l), using a target predialysis sK^+ concentration of (a) 4.0 to 5.0 mmol/l and (b) 4.0 to 5.5 mmol/l. Responders were defined as those who, during the 4-week evaluation period, achieved target predialysis sK^+ during ≥3 of 4 hemodialysis treatments after the long interdialytic interval and who did not require rescue therapy. All other patients were defined as nonresponders, that is, those who had >1 missing sK^+ measurement and/or if they received rescue therapy. Visit 1 (day −7) sK^+ measurement was used as the baseline sK^+ value. No imputation of missing data was conducted. sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

Patients Achieving Target sK^+ Concentrations

In the baseline severe hyperkalemia subgroup, the proportions of patients achieving target predialysis sK^+ ranges at ≥1, ≥2, ≥3, and 4 LIDI visits in the 4-week evaluation period were greater with SZC versus placebo at both target predialysis sK^+ ranges (Figure 2a and b). In the baseline severe hyperkalemia subgroup, 17.4% and 47.8% of patients receiving SZC achieved target predialysis sK^+ ranges of 4.0 to 5.0 mmol/l and 4.0 to 5.5 mmol/l at all 4 LIDI visits, respectively, versus 0% and 2.4% of patients receiving placebo, respectively (Figure 2a and b). Logistic regression analysis indicated that differences in the proportions of patients achieving target predialysis sK^+ ranges at ≥1, ≥2, ≥3, and 4 LIDI visits were significant for SZC versus placebo, based on 95% CIs not crossing 0% (Figure 2a and b).

Predialysis sK^+ Concentrations

With both SZC and placebo, mean predialysis sK^+ concentrations over the LIDI visits in the 4-week evaluation period were numerically greater for patients with baseline predialysis sK^+ ≥6.0 mmol/l than those with <6.0 mmol/l. Mean predialysis sK^+ concentrations were consistently and significantly lower with SZC versus placebo in both baseline predialysis sK^+ subgroups ($P < 0.0001$ for SZC versus placebo at each LIDI visit) (Supplementary Figure S1).

Hypokalemia

The frequency of predialysis hypokalemia (sK^+ <3.5 mmol/l) was low overall (Supplementary Table S3). The proportions of patients with hypokalemia were numerically higher with SZC in the baseline predialysis sK^+ <6.0 mmol/l subgroup than ≥6.0 mmol/l subgroup (Supplementary Table S3).

DISCUSSION

To the best of our knowledge, this is the first assessment of the efficacy of a potassium binder in maintenance hemodialysis patients with severe hyperkalemia (predialysis sK^+ concentration ≥6.0 mmol/l) based on data from a randomized controlled trial. Among the patients with severe hyperkalemia, the rates of treatment response were significantly greater with SZC versus placebo, regardless of target predialysis sK^+ range used (i.e., 4.0–5.0 mmol/l or 4.0–5.5 mmol/l). Among the patients receiving placebo with severe hyperkalemia, mean predialysis sK^+ concentrations over 4 weeks remained at approximately 6.0 mmol/l, indicating without additional strategies these patients

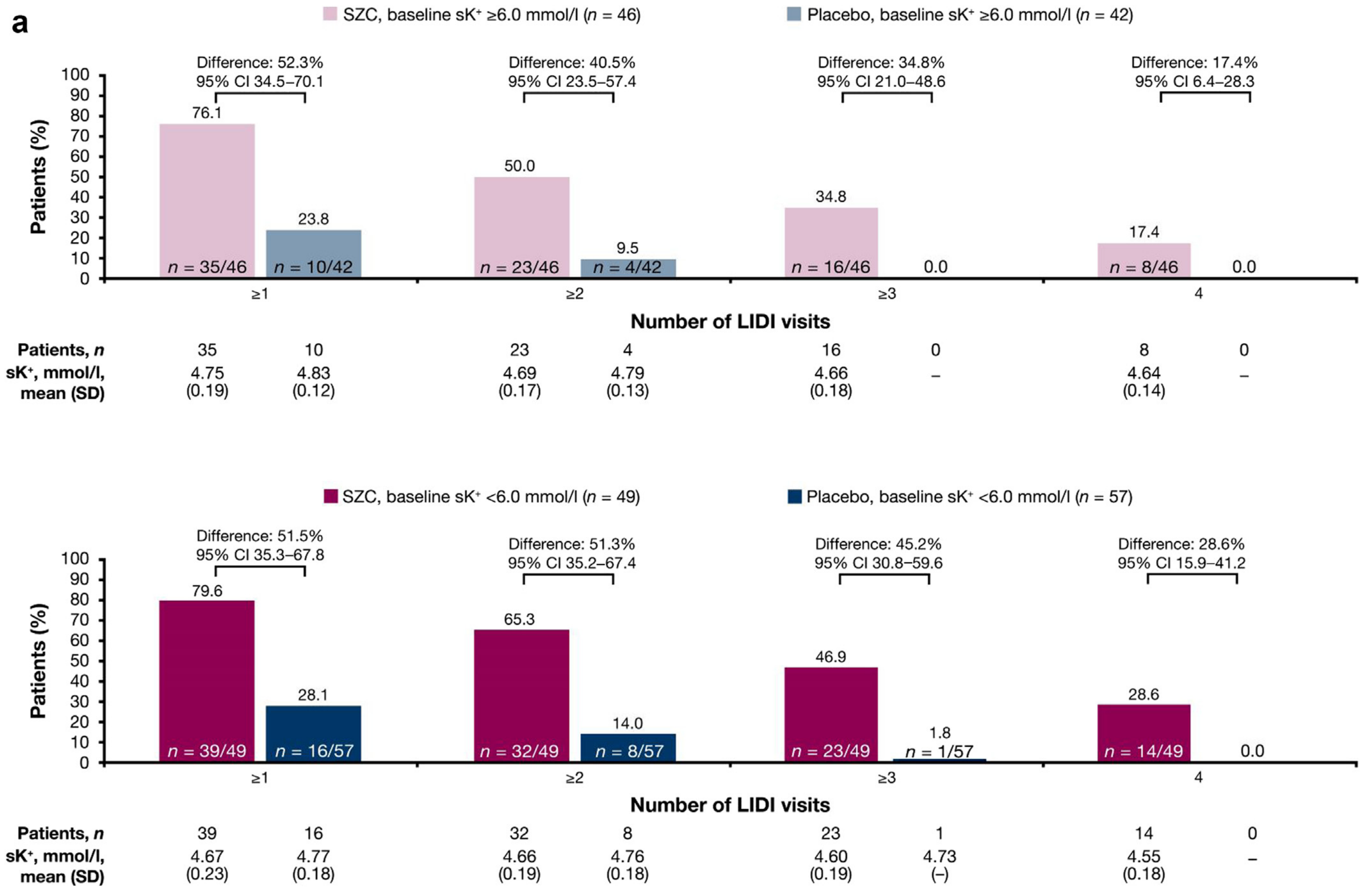

Figure 2. Proportions of patients with target predialysis sK^+ range of (a) 4.0 to 5.0 mmol/l and (b) 4.0 to 5.5 mmol/l at ≥1, ≥2, ≥3, and 4 LIDI visits and corresponding mean sK^+ concentrations, by baseline predialysis sK^+ subgroup. Visit 1 (day −7) predialysis sK^+ measurement was used as baseline. Only sK^+ data from LIDI visits during the evaluation period (days 36, 43, 50, and 57) were used. Patients who received rescue therapy were included. Percentages were calculated for each treatment arm using the number of patients in each predialysis sK^+ subgroup at baseline as the denominator; no imputation of missing data was conducted. sK^+ concentrations are overall mean (SD) for patients with target predialysis sK^+ range at ≥1, ≥2, ≥3, or 4 LIDI visits. LIDI, long interdialytic interval; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

continued to be at risk of persistent severe hyperkalemia and associated adverse events.[1,2]

Among SZC-treated patients, the extended predialysis sK^+ range of 4.0 to 5.5 mmol/l reduced the impact of severe hyperkalemia on the efficacy outcomes evaluated. Findings from the treatment responder analysis indicate that some SZC-treated patients had reductions from baseline in predialysis sK^+ concentration but were not deemed as responders using the target predialysis sK^+ range of 4.0 to 5.0 mmol/l because their sK^+ concentration was between 5.0 mmol/l and 5.5 mmol/l. Nevertheless, the extended predialysis sK^+ range of 4.0 to 5.5 mmol/l reflects one deemed to be acceptable in clinical practice, while avoiding concentrations >5.5 mmol/l associated with increased hospitalization and mortality.[2] These findings suggest that, among hemodialysis patients with severe hyperkalemia, SZC lowers and maintains predialysis sK^+ concentrations to a clinically acceptable range in most patients over 4 weeks.

The frequency of predialysis hypokalemia events was low overall and generally comparable for SZC and placebo. The events of postdialysis hypokalemia were numerically greater with SZC versus placebo, and among the baseline predialysis sK^+ <6.0 mmol/l versus ≥6.0 mmol/l subgroups, consistent with the potassium-lowering effects of SZC in addition to hemodialysis and the smaller reduction in sK^+ required to meet the hypokalemia threshold, respectively.

A challenging aspect of hyperkalemia management is the lack of a standardized definition for the grading of severity.[7,8] Collectively, there is consensus to immediately assess and treat patients with severe hyperkalemia.[7,8] The recent Renal Association Clinical Practice Guidelines on Hemodialysis recommend maintaining a predialysis sK^+ concentration range of 4.0 to 6.0 mmol/l,[9] as a sK^+ concentration ≥6.0 mmol/l is associated with a greater risk of hospitalization and all-cause mortality.[1] Nevertheless, the increased rates of hospitalization and mortality associated with predialysis sK^+ concentration >5.5 mmol/l[2] challenge the use of a target of 6.0 mmol/l. In our analysis, nearly two-thirds of hemodialysis patients with severe

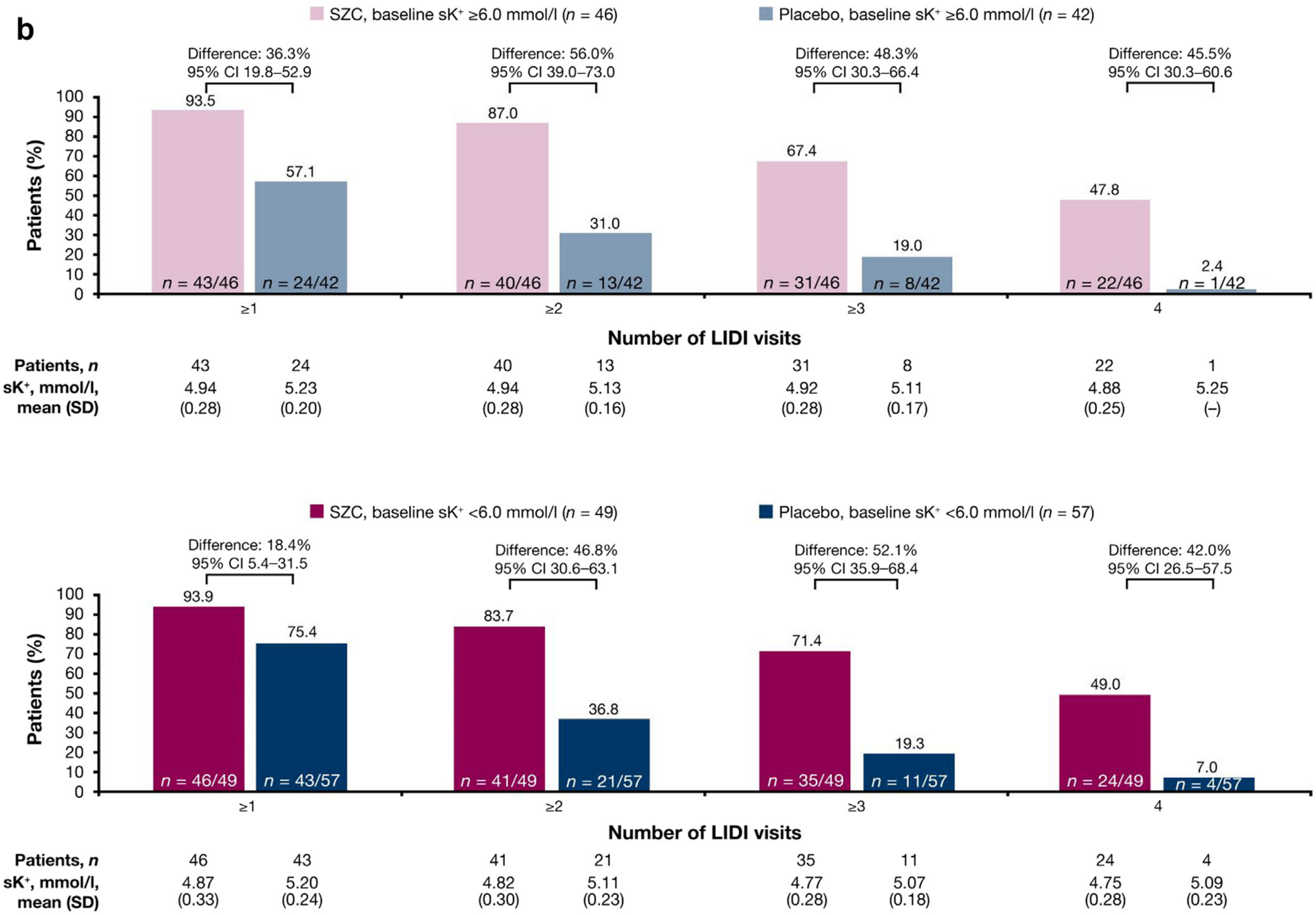

Figure 2. Continued

hyperkalemia receiving SZC achieved a target predialysis sK^+ concentration range of 4.0 to 5.5 mmol/l for ≥3 of 4 hemodialysis treatments after the LIDI and will be expected to be at lower risk of adverse events associated with higher predialysis sK^+ concentrations.

These analyses have limitations. The analyses are *post hoc* and were not prespecified; therefore, the results are exploratory. Patient numbers within each predialysis sK^+ subgroup were small and not powered to investigate treatment associations, which limits the interpretation of our findings. Finally, we did not evaluate the impact of severe hyperkalemia on safety outcomes, such as cardiovascular events. Regarding this point, the DIALIZE-Outcomes study (EudraCT 2020-005561-14) will evaluate the effect of SZC on arrhythmia-related cardiovascular outcomes among chronic hemodialysis patients with recurrent hyperkalemia (predialysis sK^+ concentration ≥5.5 mmol/l).

In conclusion, these *post hoc* findings suggest that SZC could be an effective addition to maintenance hemodialysis in reducing predialysis sK^+ concentration in patients with end-stage kidney disease and severe hyperkalemia who are at high risk of adverse events. The extended target predialysis sK^+ range of 4.0 to 5.5 mmol/l seemed to negate the impact of severe hyperkalemia. Evidence of the effectiveness of SZC in this subgroup of DIALIZE has clinical relevance and potential applicability beyond the tight confines of a clinical trial setting.

DISCLOSURE

MF reports receiving travel support from Amgen and AstraZeneca and serving as an advisory board member for AstraZeneca. SF reports receiving research support and consulting fees from AstraZeneca. BS reports receiving research grants, lecture fees, and/or consulting fees from AstraZeneca, Akebia, Reata Pharmaceuticals, and Fresenius Medical Care. AR reports receiving 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. NG reports being an employee of AstraZeneca. KM reports being an academic grant holder and an advisory board member for AstraZeneca.

ACKNOWLEDGMENTS

The primary DIALIZE study and this *post hoc* analysis were supported by AstraZeneca. The authors thank the patients, their families, and all investigators involved in the DIALIZE study, the dialysis services and research staff in each participating center, and the following members of the data monitoring committee: David Charytan, MD, Charles Herzog, MD, and David Wheeler, MD. Medical writing support was provided by Shaun W. Foley, BSc (Hons) CMPP, and editorial support was provided by Sinead Stewart, both of Core, London, UK, supported by AstraZeneca according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M15-0288). The sponsor was involved in the study design; collection, analysis, and interpretation of data; and data checking of information provided in the manuscript. Ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

DATA SHARING

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

AUTHOR CONTRIBUTIONS

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

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Results.

Supplementary References.

Table S1. Baseline patient characteristics by baseline predialysis sK^+ subgroup (<6.0 mmol/l and ≥6.0 mmol/l).

Table S2. Doses of SZC and placebo at the end of the dose titration period, by baseline predialysis sK^+ subgroup (<6.0 mmol/l and ≥6.0 mmol/l).

Table S3. Events of pre- and post-dialysis hypokalemia (sK^+ <3.5 mmol/l), by baseline predialysis sK^+ subgroup (<6.0 mmol/l and ≥6.0 mmol/l).

Figure S1. Mean predialysis sK^+ concentrations at LIDI visits during the 4-week evaluation period by treatment arm and baseline predialysis sK^+ subgroup (≥6.0 mmol/l and <6.0 mmol/l).

STROBE Statement (PDF).

REFERENCES

1. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med*. 2009;169:1156–1162. https://doi.org/10.1001/archinternmed.2009.132.
2. Karaboyas A, Zee J, Brunelli SM, et al. Dialysate potassium, serum potassium, mortality, and arrhythmia events in hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2017;69:266–277. https://doi.org/10.1053/j.ajkd.2016.09.015.
3. Pun PH, Middleton JP. Dialysate potassium, dialysate magnesium, and hemodialysis risk. *J Am Soc Nephrol*. 2017;28:3441–3451. https://doi.org/10.1681/ASN.2017060640.
4. Stavros F, Yang A, Leon A, Nuttall M, Rasmussen HS. Characterization of structure and function of ZS-9, a K+ selective ion trap. *PLoS One*. 2014;9:e114686. https://doi.org/10.1371/journal.pone.0114686.
5. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*. 2014;312:2223–2233.
6. Fishbane S, Ford M, Fukagawa M, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol*. 2019;30:1723–1733. https://doi.org/10.1681/ASN.2019050450.
7. Alfonzo A, Harrison A, Baines R, Chu A, Mann S, MacRury M. Clinical practice guidelines: treatment of acute hyperkalaemia in adults. The Renal Association. Published June 2020. Accessed October 15, 2021. https://ukkidney.org/sites/renal.org/files/RENAL%20ASSOCIATION%20HYPERKALAEMIA%20GUIDELINE%202020.pdf
8. Clase CM, Carrero JJ, Ellison DH, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int*. 2020;97:42–61. https://doi.org/10.1016/j.kint.2019.09.018.
9. Ashby D, Borman N, Burton J, et al. Renal Association clinical practice guideline on haemodialysis. *BMC Nephrol*. 2019;20:379. https://doi.org/10.1186/s12882-019-1527-3.