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Sodium Zirconium Cyclosilicate for the Treatment of Hyperkalemia in End-Stage Renal Disease Patients: A Meta Analysis

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Abstract

Hyperkalemia, characterized by elevated serum potassium levels, is a common and serious condition in patients with Chronic Kidney Disease (CKD). Sodium zirconium cyclosilicate (SZC) is an oral medication that enhances potassium excretion in the feces by selectively capturing potassium ions in exchange for sodium and hydrogen ions. This meta-analysis aims to evaluate the efficacy of SZC in managing hyperkalemia in CKD patients. A comprehensive literature search was conducted up to December 28, 2024, across databases including PubMed, ScienceDirect, and the Cochrane Library, using specific keywords related to sodium zirconium cyclosilicate and hyperkalemia in CKD. Inclusion criteria focused on studies assessing the effect of SZC on serum potassium levels in CKD patients with hyperkalemia. A total of 4 studies were included for quantitative synthesis, and the risk of bias was assessed using the RoB-2 tool. The meta-analysis revealed a significant mean difference in serum potassium levels between the SZC and placebo groups, with a reduction of -0.53 (95% CI -0.65 to -0.41; $p < 0.00001$). The analysis indicated moderate heterogeneity ($I^2 = 51\%$). SZC demonstrated rapid efficacy in lowering serum potassium levels, achieving significant reductions within 48 hours of treatment. Sodium zirconium cyclosilicate is effective in rapidly reducing serum potassium levels in patients with hyperkalemia associated with Chronic Kidney Disease. Its ability to maintain normokalemia for up to four weeks highlights its potential as a preferred treatment option for acute hyperkalemia. Further research with larger sample sizes is warranted to confirm these findings and explore long-term outcomes.

Keywords: chronic kidney disease, hyperkalemia, serum potassium levels.

INTRODUCTION

Hyperkalemia, or increased blood potassium [sK+], and metabolic acidosis often co-occur in individuals with Chronic Kidney Disease (CKD). These conditions are related by a complicated interaction in which hyperkalemia can both cause and be caused by metabolic acidosis (Cook et al., 2021). Furthermore, each of the three factors-hyperkalemia, decreased eGFR, and decreased renal ammonium excretion-more than doubles the likelihood of developing metabolic acidosis (Raphael et al., 2017), (Raphael et al., 2014). Hyperkalemia can encourage the development of metabolic acidosis by reducing renal ammoniagenesis, according to evidence of a tight feedback/regulatory mechanism between potassium homeostasis and renal ammonia production (Harris et al., 2018).

A frequent electrolyte imbalance linked to severe cardiac dysrhythmias and higher mortality is hyperkalemia (Khanagavi et al., 2014); (An et al., 2012); (Jain et al., 2012). Hyperkalemia is more likely to occur in patients with diabetes and renal impairment (Jain

et al., 2012). Although there is compelling evidence that RAAS-inhibiting therapies are beneficial for proteinuric Chronic Kidney Disease, diabetic nephropathy, systolic heart failure, and diabetic nephropathy, they are also linked to hyperkalemia in patients with kidney disease or heart failure (McCullough et al., 2014); (Vardeny et al., 2014). The efficacy of using currently available polymer resins, such as sodium polystyrene sulfonate, is questionable and their side-effect profile is low. Therefore, more medications that may safely treat hyperkalemia in individuals with acute and chronic conditions are required.

Adults with hyperkalemia can be treated with sodium zirconium cyclosilicate (SZC), an oral non absorbed medication that increases potassium excretion in the feces by preferentially capturing potassium ions in the gastrointestinal lumen in exchange for sodium and hydrogen ions (Stavros et al., 2014). SZC clinical studies demonstrated a dose-dependent rise in sHCO3− with SZC, and post hoc analysis of phase 3 randomized trials also revealed a substantial reduction in sK+ levels and maintenance of normokalemia for up to 1 year with ongoing treatment (Packham et al., 2015); (Ash et al., 2015); (Spinowitz et al., 2019); (Roger et al., 2021). Clinical data further supports the pleiotropic benefits of SZC, such as improved acid-base balance that protects the kidneys (Ash et al., 2015); (Mori et al., 2022).

Although the exact mechanism or mechanisms are unknown, they most likely entail either binding and removing ammonium by SZC in the gastrointestinal tract or increasing renal ammoniagenesis by correcting hyperkalemia (Stavros et al., 2014); (Pourafshar et al., 2018). SZC binds both cations in vitro in aqueous solution and has a comparable ionic binding site diameter for potassium and ammonium (Stavros et al., 2014); (Roger et al., 2021). SZC can sequester both potassium and ammonium in feces, indicating that these cations bind in the gastrointestinal system, according to recent in vivo experimental experiments conducted in a mouse model of Chronic Kidney Disease (Marmol et al., 2023).

In the intestinal tract, potassium is trapped by sodium zirconium cyclosilicate, a highly selective cation exchanger that exchanges sodium and hydrogen for potassium (Packham et al., 2015). In a phase 2 research, patients with stage 3 Chronic Kidney Disease (estimated glomerular filtration rate [eGFR], 30 to 60 ml per minute per 1.73 m2 of body-surface area) and serum potassium levels of 5 to 6 mmol per liter experienced significant decreases in serum potassium levels within the first 48 hours of treatment when ZS-9 was compared to a placebo (Ash et al., 2015).

Based on the above background, the aim of this research is to evaluate the effectiveness of sodium zirconium cyclosilicate (SZC) in reducing serum potassium (sK+) levels and improving acid-base balance in patients with Chronic Kidney Disease (CKD) who experience hyperkalemia and metabolic acidosis. Thus, the benefit of this research is to provide stronger clinical evidence regarding the therapeutic potential of SZC in managing hyperkalemia and metabolic acidosis in patients with CKD. This research may serve as a basis for the development of more effective and safe therapies for patients with hyperkalemia associated with Chronic Kidney Disease, as well as provide further insight into the role of this therapy in improving electrolyte and acid-base balance, which in turn may improve the quality of life of patients with CKD.

METHOD

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards were followed in the conduct and reporting of this meta-analysis. Up to December 28th, 2024, a thorough search of the literature was carried out using PubMed, ScienceDirect, and the Cochrane Library. The specified keywords for the literature search were "Sodium Zirconium Cyclosilicate and (CKD or Chronic Kidney Disease or End Stage Renal Disease) and (Hyperkalemia or Potassium)". This procedure would include articles with pertinent titles and abstracts so they could be thoroughly assessed and put through further qualitative and quantitative examination.

Inclusion and exclusion criteria

Studies were screened according to the inclusion criteria as follows: 1) studies of the effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease patients with hyperkalemia with extractable outcomes, and 2) the primary outcome of the research is serum potassium level. Afterwards, exclusion criteria were also set, which include: 1) irretrievable full-text articles, and 2) inappropriate research design, intervention, or outcome. Details of research search strategy are shown in Figure 1.

Data extraction and risk of bias assessment

We then took information out of the articles we had chosen. CONSORT (Consolidated Standards of Reporting Trials) was also used to evaluate the quality of the articles. All reviewers worked together to analyze the quality until they came to an agreement. The RoB-2 techniques from Cochrane were used to assess the risk of bias.

Statistical Analysis

Review Manager version 5.4 (Copenhagen: The Nordic Cochrane Center. The Cochrane Collaboration) was used to conduct the meta-analysis. The standard metric for assessing the impact of the intervention on the main outcome was the Mean Difference (MD) and its 95% confidence interval (CI). Random-effects models were used to pool effect estimates since clinical heterogeneity was expected. If the p-value is less than 0.005, the analytical result is deemed significant. The Higgins I-squared (I2) statistical model was used to examine heterogeneity. The results of the heterogeneity test were categorized as low (25%–50%), moderate (50–75%), high (<75%), and insignificant (0–25%).

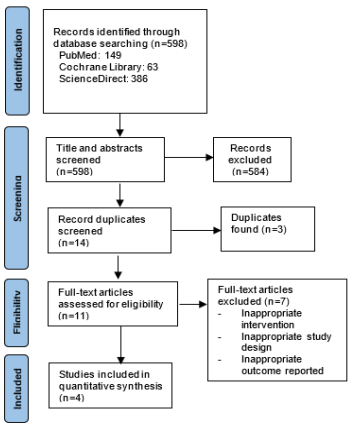

Figure 1. Diagram flow of literature search strategy for this meta-analysis

Table 1. Result and characteristics of included studies

Author	Year of publication	Population	Intervention	Control	Intervention (n)	Control (n)	Outcome	Serum potassium level			
								Intervention	SD	Control	SD
Ash	2015	CKD patients with mild hyperkalemia	Sodium Zirconium Cyclosilicate	Placebo	24	30	pre-dialysis serum potassium level	4.13 (-0.92)	0.52	4.88 (-0.26)	0.4
Ni, et al.	2023	CKD patients with mild hyperkalemia	Sodium Zirconium Cyclosilicate	Placebo	67	67	pre-dialysis serum potassium level	5.3	0.15	5.75	0.1
Ash, et al.	2024	CKD patients with mild hyperkalemia	Sodium Zirconium Cyclosilicate	Placebo	17	20	pre-dialysis serum potassium level	4.6 (-0.8)	0.5	5.2 (-0.3)	0.5
Fishbane, et al.	2019	CKD patients with mild hyperkalemia	Sodium Zirconium Cyclosilicate	Placebo	97	99	pre-dialysis serum potassium level	5.2	0.5	5.7	0.7

Table 2. RoB-2 results on risk of bias assessment

Research ID	Experimental	Comparator	Weight	D1	D2	D3	D4	D5	Overall		
Ash, et al.	Sodium Zirconium Cyclosilicate	Placebo	1	+	+	!	+	+	+	+	Low risk
Ni, et al.	Sodium Zirconium Cyclosilicate	Placebo	1	+	+	+	+	+	+	!	Some concerns
Ash, et al.	Sodium Zirconium Cyclosilicate	Placebo	1	+	+	+	+	+	+	-	High risk
Fishbane, et al.	Sodium Zirconium Cyclosilicate	Placebo	1	+	+	+	+	!	+		
										D1	Randomisation process
										D2	Deviations from the intended interventions
										D3	Missing outcome data
										D4	Measurement of the outcome
										D5	Selection of the reported result

RESULT AND DISCUSSION

Included studies

The initial search yielded 598 studies from all databases. Among them, 584 of them were excluded after screening the titles and abstracts. In addition, 3 of them were duplicates hence being excluded. After that, 7 more studies were being excluded because the outcome of those studies were not relevant to this review. At the end, 25 studies were included for quantitative synthesis. Table 1 presented the result of qualitative synthesis of all of the included studies.

Research characteristics and outcomes

The main characteristics of included studies in this systematic review are shown in Table 1. In terms of risk assessment, out of all included studies, the lowest calculated CONSORT score was 20.00/25.00. This means that in all studies, more than two-thirds of the criteria were fulfilled which indicates that all the included studies were of lower risk of bias and relatively good qualities.

Quantitative synthesis

Serum potassium level.

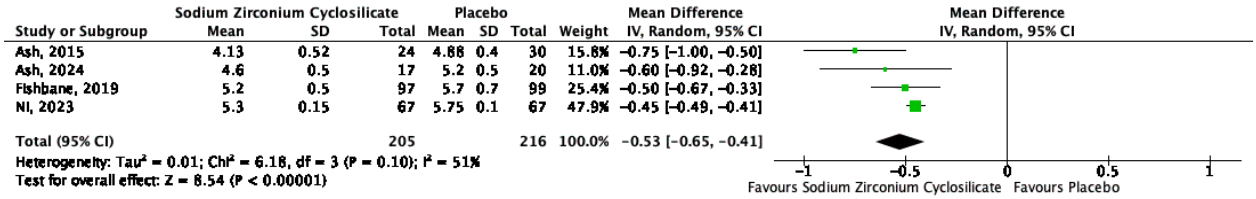

Figure 2. Forrest plot of serum potassium level.

Figure 2 presented the mean difference of the serum potassium level between the Sodium Zirconium Cyclosilicate group and placebo group. We found that the MD serum potassium level between both groups was -0,53 (95%CI -0,65 - -0,41; p<0,00001) with moderate heterogeneity showed by an I2 of 51%.

When hyperkalemia occurs, SZC helps lower potassium levels quickly—within 48 hours. In a prior meta-analysis, Meaney et al. found that SZC reduced potassium by –0.17 mEq/L when compared to a placebo, whereas Kosiborod et al. found a mean potassium decrease of –0.4 mEq/L (Meaney et al., 2017); (Kosiborod et al., 2015). Edema was the most common adverse effect associated with SZC, and it was probably caused by the medication's high salt concentration. An increase in blood volume is suggested by an increase in edema brought on by an increase in salt absorption.

Any additional increase in blood volume brought on by an increase in sodium absorption would be accompanied by an activation of the renin-angiotensin-aldosterone system, which would include an increase in aldosterone, in patients with Chronic Kidney Disease and/or heart failure who already have an increase in blood volume. Myocardial and vascular fibrosis would suffer from a long-term rise in aldosterone. Meaney et al discovered that patients using SZC had a decreased risk of GI side effects and hypomagnesemia than those receiving a placebo (Meaney et al., 2017). Although these results were documented in our included trials, there were no differences in GI side effects, headaches, or urinary tract infections between individuals receiving SZC and those getting a placebo (Packham et al., 2015).

The results of three SZC clinical studies have been interpreted to show a dose-dependent, predictable potassium-lowering response with an impact that starts one hour later. Although none

of the SZC clinical trials examined patients with acute hyperkalemia, data from patients with mild-to-moderate hyperkalemia show a predictable decrease in potassium concentration of -0.11 to -0.2 mEq/L by hour 1 and -0.73 to -1.1 mEq/L by 48 hours. Therefore, more research in this population is required (Ash et al., 2015); (Packham et al., 2015); (Kosiborod et al., 2015). Despite having a 7-hour delayed start of action and a mean potassium decrease of 0.21 mEq/L (Bushinsky et al., 2015). According to the findings, SZC seems to be the better option for treating hyperkalemia by rapidly lowering potassium.

The information that was provided supported our conclusions by demonstrating that SZC had advantages for the long-term regulation of sK+ and was linked to a considerable drop in sK+ within 48 hours. The effects of SZC and patiromer on hyperkalemia were assessed in a 2017 comprehensive review and meta-analyses, which revealed that SZC decreased sK+ 0.67 mEq/L after 48 hours (Meaney et al., 2017). According to Kosiborod et al., after receiving SZC therapy, 84 and 98% of patients, respectively, had normal sK+ concentrations within 24 and 48 hours (Kosiborod et al., 2015).

Numerous published research assessed potassium control's long-term consequences. According to Bruce et al., the majority of subjects (82%) attained normokalemia following the injection of 30 g of SZC (three 10-g doses) over the course of 24 hours (Spinowitz et al., 2019). The potassium level decreased from ≥5.1 mmol/L at baseline to 4.7 mmol/L within 3–12 months as a result of the SZC treatment. For ≤11 months while receiving continuous SZC therapy, 88.3% of participants in the harmonize trial with an 11-month open-label extension kept their mean sK+ within the normokalemic range (Roger et al., 2019). SZC was linked in our research to a reduction in sK+ levels and a greater percentage of patients who had normokalemia after 48 hours and who continued to have it for two to four weeks. The current research offered more proof in favor of the theory that SZC helped sustain long-term normokalemia and successfully lower sK+ concentration.

However, our investigation demonstrated no impact on reducing sK+ of SZC at 1, 2, and 4 hours when compared to a placebo. Following a 10-g dose, the mean sK+ level decreased by 0.4 mmol per liter (95% CI, 0.2 to 0.5) at 1 hour, by 0.6 mmol per liter (95% CI, 0.4 to 0.8) at 2 hours, and by 0.7 mmol per liter (95% CI, 0.6–0.9) at 4 hours ($p < 0.001$ for the comparison of each time point with baseline), according to a research by Mikhail. According to a research in The New England Journal of Medicine, the SZC dramatically reduced sK+ from baseline by 0.11 mEq/l one hour after the initial 10-g dosage, while the placebo group experienced an increase of 0.01 mmol per liter ($p = 0.009$). This discrepancy might be caused by the fact that the SZC dose in the aforementioned research was 10 g, but the SZC dose in our research was 0.3 g, 3 g, etc., which would have lessened the impact of SZC in lowering sK+. Due to inadequate data, we did not do a subgroup analysis of the potassium-lowering impact of various SZC dosages within 4 hours. According to Naoki's research, the median time to normalize sK+ concentration was shorter with SZC 10 g compared to placebo (1.8 vs. 3.9 h), and it was comparable for the SZC 5 g and placebo groups (3.9 and 3.9 h, respectively) (Kashihara et al., 2020). This suggests that a higher dose of SZC was associated with a shorter time to normalize sK+ concentration.

Therefore, our meta-analysis's lack of good impacts at 1, 2, and 4 hours shouldn't be seen as contradicting the body of research. We think that the benefits of SZC in quickly lowering the sK+ of patients with hyperkalemia, particularly those with severe hyperkalemia, will become increasingly apparent when more and more large-scale trials are added in the future.

The function of new potassium binders, such as SZC, in the management of hyperkalemia is examined in our research. When a patient has acute hyperkalemia, SZC is the recommended medication. Our research's validity and strength are increased by combining the findings of these

analyses, given the majority of the included studies were Phase II or Phase III randomized clinical trials. In the analysis, the majority of the results showed little variation. The small number of included studies and the variation in research designs and demographics were among the limitations of our meta-analysis. Patients with diabetes mellitus, congestive heart failure, and Chronic Kidney Disease were included in the majority of the included trials; however, dialysis or renal transplant recipients who are at high risk of hyperkalemia were not included. Age groups, the causes of hyperkalemia, and the coadministration of diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, which can affect the decrease of blood potassium, were all varied among the patient populations in the studies that made up our analysis. The limited sample size, open-label design, brief follow-up period, and exclusion of hospitalized patients were among the drawbacks of the included studies.

CONCLUSION

. The conclusion of this study shows that sodium zirconium cyclosilicate (SZC) is effective in reducing serum potassium levels (sK+) in patients with Chronic Kidney Disease (CKD) who have hyperkalemia. A meta-analysis showed that SZC significantly reduced serum potassium levels within 48 hours of treatment, with the ability to maintain normokalemia for up to four weeks. In addition, SZC was also shown to have pleiotropic effects that support acid-base balance, which may provide additional benefits in renal protection for CKD patients. The future contribution of this study is to serve as a basis for the development of safer and more effective therapies to manage hyperkalemia in CKD patients. Further studies with larger samples and longer treatment durations are needed to confirm these findings as well as explore the long-term impact of SZC therapy in patients with acute and chronic hyperkalemia, especially in more diverse populations, including those receiving dialysis or kidney transplantation.

REFERENCES

An, J. N., Lee, J. P., Jeon, H. J., Kim, D. H., Oh, Y. K., Kim, Y. S., & Lim, C. S. (2012). Severe hyperkalemia requiring hospitalization: predictors of mortality. *Critical Care*, *16*, 1–14.

Ash, S. R., Singh, B., Lavin, P. T., Stavros, F., & Rasmussen, H. S. (2015). A phase 2 study on the treatment of hyperkalemia in patients with Chronic Kidney Disease suggests that the selective potassium trap, ZS-9, is safe and efficient. *Kidney International*, *88*(2), 404–411.

Bushinsky, D. A., Williams, G. H., Pitt, B., Weir, M. R., Freeman, M. W., Garza, D., Stasiv, Y., Li, E., Berman, L., & Bakris, G. L. (2015). Patiromer induces rapid and sustained potassium lowering in patients with Chronic Kidney Disease and hyperkalemia. *Kidney International*, *88*(6), 1427–1433.

Cook, E. E., Davis, J., Israni, R., Mu, F., Betts, K. A., Anzalone, D., Yin, L., Szerlip, H., Uwaifo, G. I., & Fonseca, V. (2021). Prevalence of metabolic acidosis among patients with Chronic Kidney Disease and hyperkalemia. *Advances in Therapy*, *38*(10), 5238–5252.

Harris, A. N., Grimm, P. R., Lee, H.-W., Delpire, E., Fang, L., Verlander, J. W., Welling, P. A., & Weiner, I. D. (2018). Mechanism of hyperkalemia-induced metabolic acidosis. *Journal of the American Society of Nephrology*, *29*(5), 1411–1425.

Jain, N., Kotla, S., Little, B. B., Weideman, R. A., Brilakis, E. S., Reilly, R. F., & Banerjee, S. (2012). Predictors of hyperkalemia and death in patients with cardiac and renal disease. *The American Journal of Cardiology*, *109*(10), 1510–1513.

Kashihara, N., Nishio, T., Osonoi, T., Saka, Y., Imasawa, T., Ohtake, T., Mizuno, H., Shibagaki, Y., Kim, H., & Yajima, T. (2020). Correction of serum potassium with sodium zirconium cyclosilicate in Japanese patients with hyperkalemia: a randomized, dose–response, phase 2/3 study. *Clinical and Experimental Nephrology*, *24*, 1144–1153.

Khanagavi, J., Gupta, T., Aronow, W., Shah, T., Garg, J., Ahn, C., Sule, S., & Peterson, S. (2014). Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. *Archives of Medical Science*, *10*(2), 251–257.

Kosiborod, M., Peacock, W. F., & Packham, D. K. (2015). Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. *New England Journal of Medicine*, *372*(16), 1577–1578.

Marmol, F., Badaruddin, M., Baig, A., Ye, M., Wysocki, J., Tahaei, E., Welling, P., Bamberg, K., & Batlle, D. (2023). Fecal ammonium in mice with CKD: Gastrointestinal sequestration by sodium zirconium cyclosilicate. *American Journal of Physiology-Renal Physiology*, *324*(5), F464–F471.

McCullough, P. A., Beaver, T. M., Bennett-Guerrero, E., Emmett, M., Fonarow, G. C., Goyal, A., Herzog, C. A., Kosiborod, M., & Palmer, B. F. (2014). Acute and chronic cardiovascular effects of hyperkalemia: new insights into prevention and clinical management. *Reviews in Cardiovascular Medicine*, *15*(1), 11–23.

Meaney, C. J., Beccari, M. V, Yang, Y., & Zhao, J. (2017). Systematic review and meta-analysis of patiromer and sodium zirconium cyclosilicate: a new armamentarium for the treatment of hyperkalemia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *37*(4), 401–411.

Mori, D., Namiki, Y., Sugimachi, A., Kado, M., Tamai, S., Nomi, H., Haga, R., Nagatoya, K., & Yamauchi, A. (2022). The effect of sodium zirconium cyclosilicate on acid-base balance in Chronic Kidney Disease. *Clinical Nephrology*, *97*(5), 255.

Packham, D. K., Rasmussen, H. S., Lavin, P. T., El-Shahawy, M. A., Roger, S. D., Block, G., Qunibi, W., Pergola, P., & Singh, B. (2015). Sodium zirconium cyclosilicate in hyperkalemia. *New England Journal of Medicine*, *372*(3), 222–231.

Pourafshar, N., Pourafshar, S., & Soleimani, M. (2018). Urine ammonium, metabolic acidosis and progression of Chronic Kidney Disease. *Nephron*, *138*(3), 222–228.

Raphael, K. L., Carroll, D. J., Murray, J., Greene, T., & Beddhu, S. (2017). Urine ammonium predicts clinical outcomes in hypertensive kidney disease. *Journal of the American Society of Nephrology*, *28*(8), 2483–2490.

Raphael, K. L., Zhang, Y., Ying, J., & Greene, T. (2014). Prevalence of and risk factors for reduced serum bicarbonate in Chronic Kidney Disease. *Nephrology*, *19*(10), 648–654.

Roger, S. D., Spinowitz, B. S., Lerma, E. V, Fishbane, S., Ash, S. R., Martins, J. G., Quinn, C. M., & Packham, D. K. (2021). Sodium zirconium cyclosilicate increases serum bicarbonate concentrations among patients with hyperkalaemia: exploratory analyses from three randomized, multi-dose, placebo-controlled trials. *Nephrology Dialysis Transplantation*, *36*(5), 871–883.

Roger, S. D., Spinowitz, B. S., Lerma, E. V, Singh, B., Packham, D. K., Al-Shurbaji, A., & Kosiborod, M. (2019). Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalemia: an 11-month open-label extension of HARMONIZE. *American Journal of Nephrology*, *50*(6), 473–480.

Spinowitz, B. S., Fishbane, S., Pergola, P. E., Roger, S. D., Lerma, E. V, Butler, J., von Haehling, S., Adler, S. H., Zhao, J., & Singh, B. (2019). Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clinical Journal of the American Society of Nephrology*, *14*(6), 798–809.

Stavros, F., Yang, A., Leon, A., Nuttall, M., & Rasmussen, H. S. (2014). Characterization of structure and function of ZS-9, a K+ selective ion trap. *PloS One*, *9*(12), e114686.

Vardeny, O., Claggett, B., Anand, I., Rossignol, P., Desai, A. S., Zannad, F., Pitt, B., & Solomon, S. D. (2014). Incidence, predictors, and outcomes related to hypo-and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circulation: Heart Failure*, *7*(4), 573–579.