



**HAL**  
open science

## **Sodium polystyrene is unsafe and should not be prescribed for the treatment of hyperkalaemia: primum non nocere !**

Patrick Rossignol, Bertram Pitt

### ► To cite this version:

Patrick Rossignol, Bertram Pitt. Sodium polystyrene is unsafe and should not be prescribed for the treatment of hyperkalaemia: primum non nocere!. *Clinical Kidney Journal*, 2023, 16 (8), pp.1221-1225. <10.1093/ckj/sfad090>. <hal-04176544>

**HAL Id: hal-04176544**

**<https://hal.univ-lorraine.fr/hal-04176544v1>**

Submitted on 3 Aug 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

PRO/CON DEBATE

# Sodium polystyrene is unsafe and should not be prescribed for the treatment of hyperkalaemia: *primum non nocere!*

Patrick Rossignol <sup>1,2</sup> and Bertram Pitt<sup>3</sup>

<sup>1</sup>Université de Lorraine, Centre d'Investigations Cliniques-Plurithématique 14-33, Inserm U1116, CHRU Nancy, and F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France, <sup>2</sup>Medicine and Nephrology-Dialysis Departments, Princess Grace Hospital, and Monaco Private Hemodialysis Centre, Monaco, Monaco and <sup>3</sup>University of Michigan School of Medicine, Ann Arbor, MI, USA

Correspondence to: Patrick Rossignol; E-mail: [p.rossignol@chru-nancy.fr](mailto:p.rossignol@chru-nancy.fr)

## ABSTRACT

'Old-generation' potassium (K) binders [i.e. sodium (SPS) and calcium polystyrene sulfonate] are widely used, but with substantial heterogeneity across countries to treat hyperkalaemia (HK). However, there are no randomized data to support their chronic use to manage HK, nor have they been shown to have a renin-angiotensin-aldosterone system inhibitor (RAASi)-enabling effect. These compounds have poor tolerability and an unpredictable onset of action and magnitude of K lowering. Furthermore, SPS may induce fluid overload, owing to the fact that it exchanges K for sodium. Its use has also been associated with colonic necrosis, as emphasized by a black box warning from the US Food and Drug Administration. In contrast, two new K binders, patiromer and sodium zirconium cyclosilicate, have been shown to be safe and well tolerated for chronic management of HK, thereby enabling RAASi optimization, as acknowledged by the latest international cardiorenal guidelines. In view of the lack of reliable evidence regarding the efficacy and safety of the old-generation K binders compared with the placebo-controlled randomized and real-world evidence demonstrating the safety, efficacy and RAASi-enabling effect of the new K binders, clinicians should now use these new K binders to treat HK (*primum non nocere!*).

**Keywords:** chronic kidney disease, heart failure, hyperkalaemia, mineralocorticoid receptor antagonist, potassium binder

'Old-generation' potassium (K) binders, i.e. sodium (SPS) and calcium (CPS) polystyrene sulfonate, are used widely to treat hyperkalaemia (HK), with substantial heterogeneity across countries [1–3]. SPS is the most frequently used old-generation K binder in several countries, while CPS is more commonly used in Spain [4]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) 2002–2011 data showed that France is the country where K-binding agents are most frequently prescribed. Indeed, in Belgium, Canada, Italy and Sweden, ≥5% of patients undergoing

renal dialysis were prescribed a sodium-based K-binding agent. In contrast, in the UK, Spain and Japan it was <1%, and in the USA, Australia/New Zealand and Germany it was 1–3%. In France, 40–50% of patients undergoing renal dialysis were prescribed a K-binding agent, in contrast to 20% overall [1]. A more recent prospective French survey from the Lorraine region (2 January 2014–31 December 2015) of 14 chronic haemodialysis centres reported that 61% of patients were prescribed a K-binding agent, mainly SPS [3]. Such heterogeneity is observed not only

Received: 28.2.2023; Editorial decision: 12.4.2023

© The Author(s) 2023. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

in haemodialysis centres, but throughout the cardiorenal continuum, as shown by a European survey [2].

As yet, there are no randomized data to support the chronic use of the old-generation K binders to manage HK, nor has there been evidence of a renin–angiotensin–aldosterone system inhibitor (RAASi)-enabling effect. These compounds have poor tolerability and their long-term adherence is negatively impacted by poor palatability, a high incidence of constipation [4], an unstable onset of action and an unpredictable degree of K lowering [5]. Furthermore, SPS may induce fluid overload [6], owing to the fact that it exchanges K for sodium [5].

These old-generation K binders were approved decades ago, at a time when adequately designed randomized controlled trials were not required to determine efficacy and safety. So far, there are only three recently published short-term trials: a 3-day randomized study of SPS or CPS in 97 CKD patients with HK, which found an increase in diastolic blood pressure in SPS-assigned patients, associated with its K<sup>+</sup>–sodium (Na<sup>+</sup>) exchange mechanism versus K–calcium [7]; a one day-single dose study in 6 patients with chronic renal failure [8] and a 7-day randomized trial in 33 patients [9]. In the latter, a single-centre trial in 33 mildly HK (K<sup>+</sup> 5–5.9 mmol/L) CKD outpatients randomized to 30 g SPS or placebo, SPS was found to be superior to placebo in reducing serum K levels [mean difference between groups –1.04 mEq/L (95% confidence interval –1.37 to –0.71)]. A higher proportion of patients in the SPS group attained normokalaemia at the end of their treatment compared with those on placebo, but the difference did not reach statistical significance (73% versus 38%; *P* = 0.07). Furthermore, there was a trend toward a higher rate of electrolytic disturbances and an increase in gastrointestinal (GI) side effects in the group receiving SPS [9].

Real-world observational data provide conflicting results regarding the old-generation K binders, with some suggesting that SPS may induce colonic necrosis [10, 11], while others do not [12, 13]. The DOPPS from 2002–2011 showed that K agent prescription was associated with an additional 250 g of interdialytic weight gain, which in previous studies has been associated with worse outcomes in an adjusted model, likely as a result of the Na content of the Na-based agent SPS increasing thirst and fluid consumption. Despite this, fully adjusted models after multivariate adjustment did not suggest either a benefit or a concern, as survival was similar with or without K agent use [1]. In a nationwide French observational survey, SPS and CPS users did not experience more adverse GI events in the year, and even 5 years, after initiation. Surprisingly, SPS and CPS use was found to be associated with a lower rate of non-GI hospitalizations and deaths [12]. The authors acknowledged, however, that ‘patients who took SPS were younger and had a lower comorbid burden than patients who never took SPS’ and that ‘all these data are observational and are prone to many sources of bias, including attribution bias, unmeasured confounding, reverse causation and therefore causality cannot be inferred’ [12]. The authors also point out that it has also been suggested that the SPS-associated GI risk may be linked to sorbitol, a cathartic agent often given with SPS to prevent constipation. Kayexalate, the commercial SPS used in France, does not contain sorbitol, and the absence of GI risk found in France could be due to the SPS formulation [12].

While randomized evidence is lacking to determine the efficacy and safety of SPS and real-world evidence is conflicting, there is a black box warning from the US Food and Drug Administration (FDA) related to the safety of SPS [6]. The FDA warning states that SPS may cause ‘Intestinal Necrosis: Cases of intestinal necrosis which may be fatal. Other serious gastrointestinal

adverse events (bleeding, ischemic colitis and perforation) have also been reported in association with Kayexalate use. The majority of these cases however reported the concomitant use of sorbitol. Risk factors for gastrointestinal adverse events were present in many of the cases including prematurity, history of intestinal disease or surgery, hypovolemia, renal insufficiency and failure. Concomitant administration of sorbitol is not recommended (see PRECAUTIONS, Drug Interactions).

- Use only in patients who have normal bowel function. Avoid use in patients who have not had a bowel movement post-surgery (including those with history of impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, or bowel obstruction).
- Discontinue use in patients who develop constipation’.

Furthermore, the FDA emphasizes that ‘Caution is advised when Kayexalate is administered to patients who cannot tolerate even a small increase in sodium load (i.e. severe congestive heart failure, severe hypertension, or marked edema). In such instances compensatory restriction of sodium intake from other sources may be indicated. In the event of clinically significant constipation, treatment with Kayexalate should be discontinued until normal bowel motion is resumed’. An increase in serum Na as a result of SPS administration to patients with CKD is of concern, even in the absence of overt oedema. Even an inapparent increase in blood volume in patients with CKD, who tend to be volume overloaded, could lead to an increase in the RAAS, resulting in an increase in vascular stiffness and cardiac and renal fibrosis and thus an increase in adverse cardiorenal outcomes.

These recommendations from the FDA, as well as our understanding of the consequences of increasing Na in patients with CKD, should prevent clinicians from using SPS chronically in cardiorenal patients with or at risk of HK.

In contrast, the recently available new K binders patiromer and sodium zirconium cyclosilicate (SZC) are safe and well tolerated. These new K binders are a major advance in the chronic management of HK, potentially enabling RAASi optimization [5], as demonstrated in the randomized clinical trials of patiromer [14–17], especially regarding the use of mineralocorticoid receptor antagonists. Both patiromer and SZC are well tolerated and have a sustainable effect, ascertained by uncontrolled 52-week open-label studies [18–20] in initially HK patients. Importantly, a consistent rebound increase in serum K has been observed following their discontinuation. This underlines the need for chronic administration and patient education in patients prone to recurrent HK [21]. The safety and tolerability of patiromer was recently confirmed by a global pharmacovigilance database collected over 4 years, in that no new safety issues were reported compared with data from the clinical trial program [22].

Preventing or managing HK with the new K binders reduces the need for down-titration or cessation of RAASi, as acknowledged by the latest guidelines [23–26]. Furthermore, Kidney Disease: Improving Global Outcomes guidelines endorse the new potassium binders for the treatment of HK in patients with CKD [24, 25]. The latest European Society of Cardiology heart failure guidelines state that administration of the K-lowering agents patiromer or sodium zirconium cyclosilicate may allow renin–angiotensin–aldosterone system (RAAS) inhibitor initiation or up-titration in a larger proportion of patients [26]. While RAASi maintenance is associated with better cardiovascular outcomes in observational studies, evidence of cardiovascular and renal protection via RAASi enablement through the use of the new K binders from adequately powered, long-term randomized

trials is currently lacking. Accordingly, the latest American College of Cardiology/American Heart Association heart failure guidelines state that in patients with heart failure who experience hyperkalaemia (serum K level  $\geq 5.5$  mEq/L) while taking a renin-angiotensin-aldosterone system inhibitor (RAASI), the effectiveness of K binders (patiromer, sodium zirconium cyclosilicate) to improve outcomes by facilitating continuation of RAASI therapy is uncertain [27] and this is presented as an area of evidence gaps and a future research direction. It should be noted that a patient-level simulation model designed to characterize the natural history of patients with CKD supports the notion that maintaining normokalaemia enables optimal RAASI therapy and improves long-term health and economic outcomes in CKD patients [28].

Finally, a multidisciplinary academic panel including nephrologists and cardiologists was recently convened to develop a consensus therapeutic algorithm aimed at optimizing the use of the two novel K binders (patiromer and SZC) in stable adults who require treatment with RAASI and experience HK. The panel proposed using pragmatic diagnostic and therapeutic algorithms to optimize new K binder use in cardiorenal disease. However, algorithms for the old-generation K binders were not considered, in view of the lack of randomized data and related reliable evidence necessary to generate a diagnostic (including monitoring regimen) and therapeutic algorithm as well as the warnings related to colonic necrosis associated with their long term-use [21].

In conclusion, in view of the lack of reliable evidence from adequately powered randomized trials and real-world evidence regarding the efficacy and safety of the old-generation K binders, along with the FDA black box warning for colonic necrosis associated with the use of SPS, compared with the randomized trials and real-world evidence supporting the use of the new K binders to treat HK over the long term and the RAASI-enabling effect, there is compelling evidence for clinicians to prescribe the new K binders for the treatment of HK (*Primum non nocere!*). While some clinicians in countries where both old-generation and new K binders are available/reimbursed may be tempted to prescribe the old-generation K binders since they are generic in most parts of the world and thus relatively inexpensive, their poor tolerability and side-effect profile will in the long run result in increased costs to our patients and healthcare systems (penny wise and pound foolish!).

## FUNDING

None declared.

## AUTHORS' CONTRIBUTIONS

P.R. drafted the first version of the manuscript and approved the final version. B.P. corrected the first version of the manuscript and approved the final version.

## CONFLICT OF INTEREST STATEMENT

P.R. reports consulting for Idorsia and G3 Pharmaceuticals; honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Cincor, CVRx, Fresenius, KBP Biosciences, Novartis, Novo Nordisk, Relypsa, Servier and Vifor Fresenius Medical Care Renal Pharma; and travel grants from AstraZeneca, Bayer, CVRx, Novartis and Vifor Fresenius Medical Care Renal Pharma. P.R. is cofounder of CardioRenal. B.P. reports consulting for Bayer, AstraZeneca, Boehringer Ingelheim, Merck, Lexicon, KBP Biosciences, Vifor, Sarfez, scPharmaceuticals, SQ Innovations, G3 Pharmaceuticals,

Proton Intelligence, Cereno Scientific and Brainstorm Medical. P.R. holds stock options in KBP Biosciences, Vifor, Sarfez, scPharmaceuticals, SQ Innovations, G3 Pharmaceuticals, Proton Intelligence, Cereno Scientific and Brainstorm Medical. P.R. holds US patent 9931422, Site specific delivery of eplerenone to the myocardium, and pending patent 63/045783, Histone acetylation modulating agents for the protection and treatment of organ damage.

## REFERENCES

- Jadoul M, Karaboyas A, Goodkin DA et al. Potassium-binding resins: associations with serum chemistries and interdialytic weight gain in hemodialysis patients. *Am J Nephrol* 2014;**39**:252–9. <https://doi.org/10.1159/000360094>
- Rossignol P, Rulope LM, Cupisti A et al. Recurrent hyperkalaemia management and use of renin-angiotensin-aldosterone system inhibitors: a European multi-national targeted chart review. *Clin Kidney J* 2020;**13**:714–9. <https://doi.org/10.1093/ckj/sfz129>
- Rossignol P, Lamiral Z, Frimat L et al. Hyperkalaemia prevalence, recurrence and management in chronic haemodialysis: a prospective multicentre French regional registry 2-year survey. *Nephrol Dial Transplant* 2017;**32**:2112–8. <https://doi.org/10.1093/ndt/gfx053>
- Valdivielso JM, Balafa O, Ekart R et al. Hyperkalemia in chronic kidney disease in the new era of kidney protection therapies. *Drugs* 2021;**81**:1467–89. <https://doi.org/10.1007/s40265-021-01555-5>
- Ferreira JP, Butler J, Rossignol P et al. Abnormalities of potassium in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:2836–50. <https://doi.org/10.1016/j.jacc.2020.04.021>
- Sanofi-Aventis. Kayexalate® Sodium Polystyrene Sulfonate, USP. Cation-Exchange Resin. Reference ID: 2879674. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/011287s023lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/011287s023lbl.pdf)
- Nasir K, Ahmad A. Treatment of hyperkalemia in patients with chronic kidney disease: a comparison of calcium polystyrene sulfonate and sodium polystyrene sulfonate. *J Ayub Med Coll Abbottabad* 2014;**26**:455–8.
- Gruy-Kapral C, Emmett M, Santa Ana CA et al. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol* 1998;**9**:1924–30. <https://doi.org/10.1681/ASN.V9101924>
- Lepage L, Dufour AC, Doiron J et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol* 2015;**10**:2136–42. <https://doi.org/10.2215/CJN.03640415>
- Noel JA, Bota SE, Petrcich W et al. Risk of hospitalization for serious adverse gastrointestinal events associated with sodium polystyrene sulfonate use in patients of advanced age. *JAMA Intern Med* 2019;**179**:1025–33. <https://doi.org/10.1001/jamainternmed.2019.0631>
- Laureati P, Xu Y, Trevisan M et al. Initiation of sodium polystyrene sulfonate and the risk of gastrointestinal adverse events in advanced chronic kidney disease: a nationwide study. *Nephrol Dial Transplant* 2020;**35**:1518–26. <https://doi.org/10.1093/ndt/gfz150>
- Ferreira JP, Couchoud C, Edet S et al. Adverse gastrointestinal events with sodium polystyrene sulfonate and calcium polystyrene sulfonate use in dialysis patients: a nationwide registry study. *Nephrol Dial Transplant* 2021;**36**:339–45. <https://doi.org/10.1093/ndt/gfaa229>

13. Labriola L, Jadoul M. Sodium polystyrene sulfonate: still news after 60 years on the market. *Nephrol Dial Transplant* 2020;**35**:1455–8. <https://doi.org/10.1093/ndt/gfaa004>
14. Agarwal R, Rossignol P, Romero A et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019;**394**:1540–50. [https://doi.org/10.1016/S0140-6736\(19\)32135-X](https://doi.org/10.1016/S0140-6736(19)32135-X)
15. Pitt B, Anker SD, Bushinsky DA et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;**32**:820–8. <https://doi.org/10.1093/eurheartj/ehq502>
16. Weir MR, Bakris GL, Bushinsky DA et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;**372**:211–21. <https://doi.org/10.1056/NEJMoa1410853>
17. Butler J, Anker SD, Lund LH et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J* 2022;**43**:4362–73. <https://doi.org/10.1093/eurheartj/ehac401>
18. Roger SD, Spinowitz BS, Lerma EV et al. Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalemia: an 11-month open-label extension of HARMONIZE. *Am J Nephrol* 2019;**50**:473–80. <https://doi.org/10.1159/000504078>
19. Spinowitz BS, Fishbane S, Pergola PE et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol* 2019;**14**:798–809. <https://doi.org/10.2215/CJN.12651018>
20. Bakris GL, Pitt B, Weir MR et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA* 2015;**314**:151–61. <https://doi.org/10.1001/jama.2015.7446>
21. Rossignol P, Silva-Cardoso J, Kosiborod MN et al. Pragmatic diagnostic and therapeutic algorithms to optimize new potassium binder use in cardiorenal disease. *Pharmacol Res* 2022;**182**:106277. <https://doi.org/10.1016/j.phrs.2022.106277>
22. Rossignol P, David L, Chan C et al. Safety and tolerability of the potassium binder patiromer from a global pharmacovigilance database collected over 4 years compared with data from the clinical trial program. *Drugs Real World Outcomes* 2021;**8**:315–23. <https://doi.org/10.1007/s40801-021-00254-7>
23. Visseren FLJ, Mach F, Smulders YM et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337. <https://doi.org/10.1093/eurheartj/ehab484>
24. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;**98**:S1–115. <https://doi.org/10.1016/j.kint.2020.06.019>
25. Kidney Disease: Improving Global Outcomes Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021;**99**:S1–87. <https://doi.org/10.1016/j.kint.2020.11.003>
26. McDonagh TA, Metra M, Adamo M et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–726. <https://doi.org/10.1093/eurheartj/ehab368>
27. Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:e263–421. <https://doi.org/10.1016/j.jacc.2021.12.012>
28. Evans M, Palaka E, Furuland H et al. The value of maintaining normokalaemia and enabling RAASi therapy in chronic kidney disease. *BMC Nephrol* 2019;**20**:31. <https://doi.org/10.1186/s12882-019-1228-y>

## Opponents' comments

Juan Jesus Carrero<sup>1,2</sup>, Manish M. Sood<sup>3,4</sup>, Ailema Gonzalez-Ortiz<sup>1,5</sup> and Catherine M. Clase<sup>6,7</sup>

<sup>1</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, <sup>2</sup>Division of Nephrology, Danderyd Hospital, Department of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden, <sup>3</sup>Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, <sup>4</sup>Department of Medicine, Ottawa Hospital, Ottawa, Ontario, Canada, <sup>5</sup>Translational Research Center, Instituto Nacional de Pediatría, Mexico City, Mexico, <sup>6</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada and <sup>7</sup>Department of Health Research Methodology, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Correspondence to: Juan Jesus Carrero; E-mail: [juan.jesus.carrero@ki.se](mailto:juan.jesus.carrero@ki.se)

We read with interest the viewpoint of Rossignol and Pitt suggesting that clinicians should avoid prescribing SPS because of harms.<sup>1</sup> An absolute injunction against harm, “*primum non nocere*”, would disqualify almost all current therapeutic and preventative interventions. A more useful framework is the concept of risks and benefits, numbers-needed-to-harm and numbers-needed-to-treat.

Our debating partners emphasize the lack of trial evidence regarding efficacy of SPS. We agree there are fewer trials for SPS, but existing randomized evidence is sufficient to demonstrate efficacy for all agents.<sup>2</sup>

They also emphasize adverse effects associated with SPS use, particularly colonic necrosis when administered with sorbitol, identified by spontaneous safety reporting over decades of SPS use.<sup>3</sup> To our knowledge, this contrasts with one pharmacovigilance study of 4 years' duration for one novel binder (patiromer).<sup>4</sup> As discussed in our viewpoint,<sup>5</sup> there are currently four large observational studies of gastrointestinal complications associated with SPS use without sorbitol compared with non-use. No colonic necrosis events were detected in those studies; Two reported a risk increase that is low in absolute magnitude (numbers-needed-to-harm of 1000 new users<sup>6</sup> or 1000 patient-years of use<sup>7</sup>). Two further studies reported no risk increase.<sup>8,9</sup> *No parallel data are available for novel binders.* At present, there is no evidence than one agent is safer than another, but risks are better quantified for SPS because of our long experience.

SPS is associated with constipation: however, a network meta-analysis of the small comparative randomized trials available found that patiromer was associated with a higher risk of constipation compared to all other potassium resins.<sup>2</sup> A similar pattern was seen for nausea and for vomiting.<sup>2</sup>

We agree with the authors' concerns about the exchange of potassium for sodium by SPS, a property it however shares with sodium zirconium cyclosilicate.<sup>10</sup>

Finally, evidence in support of the statement "...[SPS's] poor tolerability and side-effect profile will, in the long run, result in increased costs to our patients and healthcare systems" is lacking. For all the binders, we would reiterate that cost-effectiveness has not been demonstrated and that based on the results DIAMOND, the number-needed-to-treat for patiromer to prevent one cardiovascular event attributed to discontinuing spironolactone is 439 people for 3 years.<sup>11</sup>

We acknowledge that in this type of academic debate opponents and proponents are forced to polarize their views and defend extremes. Maybe the newer binders will prove safer. At present, however, the evidence-based verdict is 'not proven'.

## REFERENCES

- Rossignol, P. & Pitt, B. Sodium polystyrene is unsafe and should not be prescribed for the treatment of hyperkalaemia: primum non nocere! *Clin Kidney J*, doi:10.1093/ckj/sfad090 (2023).
- Dong, L., Xu, W., Deng, Y., Tan, J. & Qin, W. Efficacy and safety of potassium binders in the treatment of patients with chronic kidney disease and hyperkalemia. *European journal of pharmacology* **931**, 175174, doi:10.1016/j.ejphar.2022.175174 (2022).
- Federal Drug Administration. *Kayexalate. Sodium Polystyrene Sulphonate USP. Cation Exchange Resin*, ([https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/011287s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011287s022lbl.pdf)) (2009).
- Rossignol, P., David, L., Chan, C., Conrad, A. & Weir, M. R. Safety and Tolerability of the Potassium Binder Patiromer From a Global Pharmacovigilance Database Collected Over 4 Years Compared with Data from the Clinical Trial Program. *Drugs - Real World Outcomes* **8**, 315-323, doi:10.1007/s40801-021-00254-7 (2021).
- Carrero, J. J., Sood, M. M., Gonzalez-Ortiz, A. & Clase, C. M. Pharmacological strategies to manage hyperkalaemia: out with the old, in with the new? Not so fast.... *Clin Kidney J*, doi:10.1093/ckj/sfad089 (2023).
- Noel, J. A. et al. Risk of Hospitalization for Serious Adverse Gastrointestinal Events Associated With Sodium Polystyrene Sulfonate Use in Patients of Advanced Age. *JAMA internal medicine* **179**, 1025-1033, doi:10.1001/jamainternmed.2019.0631 (2019).
- Laureati, P. et al. Initiation of sodium polystyrene sulphonate and the risk of gastrointestinal adverse events in advanced chronic kidney disease: a nationwide study. *Nephrol Dial Transplant* **35**, 1518-1526, doi:10.1093/ndt/gfz150 (2020).
- Ferreira, J. P., Couchoud, C., Edet, S., Brunet, P. & Frimat, L. Adverse gastrointestinal events with sodium polystyrene sulphonate and calcium polystyrene sulphonate use in dialysis patients: a nationwide registry study. *Nephrol Dial Transplant* **36**, 339-345, doi:10.1093/ndt/gfaa229 (2021).
- Farfan Ruiz, A. R., E.;Clark,E.;Hundemer, G.;Karaboyas, A.;Robinson, F.;Pecoits Filho, R.;Sood,M. Adverse gastrointestinal events with sodium polystyrene sulfonate use in patients on maintenance hemodialysis: an international cohort study. *Can J Kidney Health Dis*, in press (2023).
- Zhuo, M., Kim, S. C., Patorno, E. & Paik, J. M. Risk of Hospitalization for Heart Failure in Patients With Hyperkalemia Treated With Sodium Zirconium Cyclosilicate Versus Patiromer. *J Card Fail* **28**, 1414-1423, doi:10.1016/j.cardfail.2022.04.003 (2022).
- Packer, M. Potassium binders for patients with heart failure? The real enlightenment of the DIAMOND trial *European Heart Journal* **43**, 4374-4377, doi:10.1093/eurheartj/ehac399 (2022).