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Pro/Con Debate

PRO/CON DEBATE

Pharmacological strategies to manage hyperkalaemia: out with the old, in with the new? Not so fast…

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ABSTRACT

Since the 1950s, sodium polystyrene sulphonate (SPS) has been the dominant cation exchange agent prescribed for hyperkalaemia. Clinicians have had plenty of time to learn of SPS's advantages and limitations. The demands of drug regulatory agencies regarding the incorporation of medications into the market were not so stringent then as they are today, and the efficacy and safety of SPS have been questioned. In recent years, two novel cation exchangers, patiromer and sodium zirconium cyclosilicate, have received (or are in the process of receiving) regulatory approval in multiple jurisdictions globally, after scrutiny of carefully conducted trials regarding their short-term and mid-term efficacy. In this debate, we defend the view that all three agents are likely to have similar efficacy. Harms are much better understood for SPS than for newer agents, but currently there are no data to suggest that novel agents are safer than SPS. Drug choices need to consider costs, access and numbers-needed-to-treat to prevent clinically important events; for potassium exchangers, we need trials directly examining clinically important events.

Keywords: cardiovascular, elderly, epidemiology, hyperkalaemia, renin–angiotensin system

INTRODUCTION

When faced with a patient with hyperkalaemia, clinical management involves a reduction in dietary potassium intake, modification of contributing medications and the use of diuretics or cation exchangers [1, 2]. The first clinically available cation exchanger, sodium polystyrene sulphonate (SPS), was approved for use >70 years ago, an era with less stringent regulation, and remains the agent many clinicians are comfortable using. Two novel cation exchangers, patiromer and sodium zirconium cyclosilicate (SZC), have recently entered into the pharmacological armamentarium, with valuations of the global hyperkalaemia treatment market at $540 million in 2022, projected to quadruple by 2029 [3]. Perhaps because of successful marketing, or simply because clinicians are also humans who are attracted to new stuff, the efficacy and safety of SPS have been questioned.

'Out with the old, in with the new' is a phrase that people often say when getting a new leader, a new job or with the coming of a new year. We think we ought not to be so fast in relegating SPS to oblivion (Figure 1). In this controversy piece, we defend

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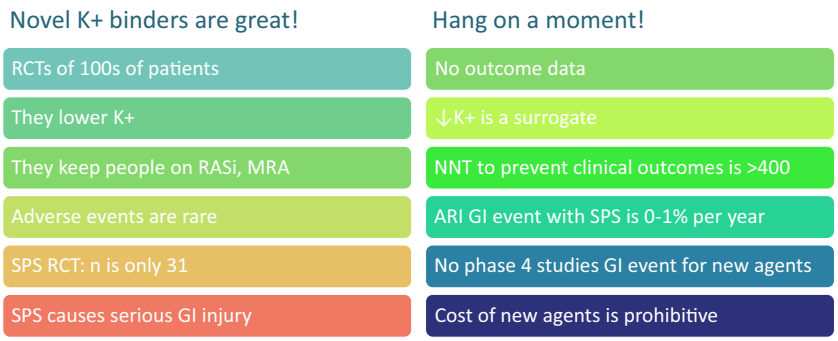

Figure 1: Contrasting perspectives on new and old potassium exchangers.
ARI: absolute risk increase.

the view that all three agents are likely to have similar efficacy and that at present there are no data to suggest that novel agents are safer than SPS.

FACT 1. ALL POTASSIUM EXCHANGERS ARE EFFECTIVE IN MANAGING HYPERKALAEMIA

With the exception of one trial [4], available randomized controlled trial (RCT) evidence compares a single agent against the non-pharmacological standard of care. This lack of effective comparisons essentially precludes the ability to conclude that one agent is more or less potent than another.

SPS is effective in reducing potassium

RCT evidence for SPS efficacy is limited; however, we argue that it is sufficient. In a placebo-controlled RCT of 33 haemodialysis patients treated for 1 week, potassium was lower by 1.0 mmol/L in patients who received SPS 30 g daily compared with those who did not [5]. Another crossover RCT compared SPS 15 g three times a day (tid) with patiromer 16.8 g daily, both given only on non-dialysis days: 48 patients were treated for 4 weeks. The mean weekly potassium was 4.6 mmol/L during SPS periods compared with 5.2 mmol/L during washout periods (difference of 0.6 mmol/L; $P < .01$) and compared with 5.0 mmol/L during patiromer periods (difference of 0.2; $P < .01$), suggesting higher efficacy for SPS than for patiromer [4].

Short-term efficacy data are absent for SPS and disappointing for new agents

For acute lowering of potassium, no data are available for SPS. However, the data for the new agents are not encouraging and give us no reason to expect that they will ultimately be demonstrated superior to SPS. In 753 outpatients with borderline hyperkalaemia randomized to SZC 10 g tid, 5 g tid or placebo, potassium at 24 hours was ≈5.1 mmol/L in patients taking placebo, ≈4.9 mmol/L in those taking 5 g tid and ≈4.7 mmol/L in those taking 10 g tid, the maximum approved dose: at most a 0.4 mmol difference from placebo at 24 hours [6]. In an uncontrolled experiment, potassium lowering 4 hours after 10 g SZC was 0.4 mmol/L [7], while in a controlled experiment the difference from placebo at 4 hours was ≈0.2 mmol/L [6]. In a controlled experiment of patients in emergency with hyperkalaemia, in which both groups received usual care with insulin and glucose, the decrease at 4 hours compared with placebo was a clinically and statistically non-significant 0.1 mmol/L [8].

The data for patiromer are similar for those for SZC. In an uncontrolled experiment, patiromer 8.4 g twice a day resulted in potassium lowering of 0.1 mmol/L at 4 hours, 0.2 mmol/L at 7 hours and 0.5 mmol/L at 24 hours [9]. In an observational study of administrative data, Di Palo *et al.* [10] identified >800 patients with hyperkalaemia treated with patiromer monotherapy, observing a 0.5 mmol/L decrease at 0–6 hours (mean 3). These data exaggerate the effect of patiromer, because any group selected on the basis of an extreme value (such as hyperkalaemia >5.0 mmol/L as in this work) will, on remeasurement, have a lower, less extreme average value, a phenomenon known as regression to the mean. Similarly, the uncontrolled OPAL study (NCT01810939) [11] observed a greater reduction in potassium in those with more extreme initial elevations. Furthermore, no dose–response effect was observed and potassium was lower than baseline in the first interval (0–6 hours) studied, with an average time to the second measurement of just 3 hours, and then did not decrease further in the subsequent 24 hours. In a controlled experiment of patients in emergency with hyperkalaemia, in which both groups received the standard of care, there was no difference between groups at 4 or 6 hours with patiromer 25.2 g as a single dose compared with the standard of care alone [12].

Medium-term efficacy is similar for all three agents

In medium-term use (weeks–months), meta-analysis of 741 patients in five RCTs of SZC compared with placebo found potassium lowering of a modest 0.4 mmol/L [13]. Between-group differences in potassium of 0.4–1.0 mmol/L were reported in the medium-term trials of patiromer [14]. For SPS, the difference was 0.6–1.0 mmol/L [4, 5]. These values suggest similar efficacy for all three agents.

Long-term efficacy is unknown for all agents

It is suggested that novel agents be used to maintain on mineralocorticoid receptor antagonists (MRAs) and renin–angiotensin system inhibitors (RASis) those patients who have evidence-based indications for them. Resistant hypertension, heart failure with reduced ejection fraction, cardiovascular risk and proteinuric kidney disease are all lifelong conditions. Studies of 3–5 years with patient-important outcomes are helpful in deter-

mining whether patients should be committed to therapy that may be lifelong, but no such studies exist for old or new agents.

Tolerability, adherence, side effects and patient preference

Tolerability for newer agents is generally acceptable [15, 16]. In a crossover trial comparing SPS with patiromer, no patient withdrew from either group because of intolerance. The percentage of missed doses was lower for patiromer at 2.4% compared with patients on SPS at 10.8% ($P < .001$), and the proportion of patients missing ≥10% of doses was lower for patiromer at 10% compared with patients on SPS at 29% ($P < .001$) [4]. Some of this difference in adherence might result from the three-times-daily schedule used for SPS. Gastrointestinal (GI) side effects were common in both groups ($P = .8$), reported in 25% of study weeks. GI symptoms are known to be highly prevalent in people undergoing haemodialysis [17]. The absence of placebo means that it is impossible to distinguish the proportion of these symptoms attributable to the medication; however, these data argue against the hypothesis that patiromer is associated with a lower risk for GI adverse effects. Although much discussed, we are not aware of any data on subjective unpleasantness or patient preference. All three, inconveniently, are powders that must be mixed with a liquid.

FACT 2: ALL POTASSIUM EXCHANGERS HAVE ADVERSE EFFECTS AND HARMS ARE MUCH BETTER UNDERSTOOD FOR SPS THAN FOR NEWER AGENTS

Large sample sizes and long follow-up periods are needed to identify rare harms, and data that at present are available only for SPS. For the newer agents, it is simply too early to know.

SPS and the fear of colonic necrosis or other serious GI events

SPS has been associated with colonic necrosis in multiple, convincing case reports. In 2009 the FDA issued a black box warning, noting that 'the majority of these cases involved the concomitant administration of sorbitol' [18]. Colonic necrosis is a severe adverse effect, but a rare occurrence even with sorbitol. In a case–control analysis of adult inpatients at a tertiary medical centre, 0.14% of individuals receiving SPS had colonic necrosis, compared with 0.07% of individuals who were not given SPS [19]. In another study of patients on haemodialysis, colonic surgery (taken here as a marker of colonic necrosis) was no more common in patients who received SPS (0.6%) than in those not given SPS (1.0%) [20].

In network meta-analysis, GI symptomatology (nausea, constipation and vomiting) were more common with patiromer than placebo, effects that were not seen for SPS or SZC [21]. Large-scale administrative data are required to observe harms that are more serious but rare; these are sometimes described as phase 4 or post-marketing studies. For SPS, three such studies examining serious GI events have been published, while at the time of writing, none have appeared for patiromer or SZC. The three studies report variable findings regarding the relative risks of SPS compared with no use, but all three report very low absolute risks. Noel *et al.* [22] compared 20 020 older adults (>65 years of age) from Canada who started SPS with 20 020 non-users. There was no information on glomerular filtration rate; 0.2% were undergoing dialysis. The study outcome was a composite of adverse GI events (hospitalization or emergency department visit with intestinal ischaemia/thrombosis, GI ulceration/perforation or resection/ostomy) within 30 days. The study found higher relative risks of adverse GI events among SPS users. However, absolute risks were very low: 37 events (0.14%) in the SPS users versus 18 events (0.10%) in non-users. Using the Swedish renal registry, Laureati *et al.* [23] studied 19 530 patients with chronic kidney disease (CKD) G4–5 referred to nephrologist care, of whom 3690 initiated SPS during follow-up. The study outcome was the same, but without time limits and could occur during the entire follow-up. In Sweden, SPS use is approved only for hyperkalaemia in CKD and is most often used at low dosages for hyperkalaemia prevention. Within this homogeneous patient population, the study observed higher relative risks of GI events for SPS initiators compared with non-users, but again these events were rare (16/1000 patient-years). Ferreira *et al.* [24] evaluated the safety of both SPS and calcium polystyrene sulphonate (CPS) in the French dialysis registry, exploring GI complications in >40 000 patients who were exposed to these agents during observation. With similar low incidence rates, this study found no differences in the risk of complications in periods with SPS/CPS use compared with periods without use (7.4 versus 9.5/1000 patient-years).

What can we conclude from the evidence thus far?

Despite a possible signal for increases in the relative risk of a serious GI adverse event, the absolute risk is exceedingly low, estimated at roughly 1 in 1000. However, all studies are affected by confounding-by-indication bias, and all three studies compare against no use. Hyperkalaemia is an indication for SPS; we hypothesize that SPS may not necessarily cause GI events, but rather may be spuriously associated because of the role GI events may play in the occurrence of hyperkalaemia. For example, patients with CKD are predisposed to non-occlusive mesenteric ischaemia by arteriosclerosis and angiotensin II–mediated vasoconstriction [25] and are often subjected to concomitant hypotension, ileus-induced colonic distension (resulting in reduced colonic blood flow) and decreased gut motility as a result of opioids, uraemia and constipation [26]. Constipation and reduced GI motility can increase potassium bioavailability in the intestine leading to hyperkalaemia [27].

Safety signals for new agents and comparisons across classes

Clinical trials are carefully conducted experiments with strict monitoring routines in highly selected patients that tend to observe fewer adverse events than in the heterogeneous clinical practice. The larger trials on patiromer or SPS lasted 52 weeks and included <400 patients [28]. In the original FDA fillings for SZC approval ($n = 746$), the adverse events reported were oedema (13.7%), hypertension (11%) and heart failure (4.6%) [29], with a higher incidence of oedema in high-risk individuals. In the original FDA fillings for patiromer approval ($n = 734$), hypokalaemia and hypomagnesemia were noted to occur in 3–10% and 5–17% based on dose, respectively [30]. Dong *et al.* [21] conducted a network meta-analysis of available trials to compare side effects between these agents among patients with CKD. Acknowledging that there are fewer trials of SPS, and within the lengths and doses provided in those trials, the authors concluded that the probability of nausea and constipation may be higher among patiromer users compared with users of SZC or SPS.

Clinical trials to date for newer agents report no major occurrence of serious GI adverse events. However, they are of too short a duration and of small size to detect these rare episodes. There are no data to confirm or refute that similar harms are absent for the newer agents. A 4-year post-marketing surveillance study for adverse effect reporting with patiromer described 'colonic necrosis and other serious GI AEs to be reported…in <0.05% per 100 person years', with no exact numbers provided [31].

Both SZC and SPS exchange molecules of sodium for potassium, but patiromer exchanges calcium. It has been hypothesized that increased sodium load may result in fluid retention, oedema and possibly a risk of heart failure. For SPS, other than our clinical experience that oedema may occasionally occur shortly after a new prescription, there are, to our knowledge, no direct data on these hypothesized risks. Meta-analyses of trials reported a 4-fold ($P = 0.03$) and 6-fold ($P = 0.05$) increased risk of oedema in patients treated with SZC compared with placebo [13]. In a US observational study, Zhuo *et al.* [32] used a new-user design in adults who were not on dialysis, 85% of whom had CKD G3–5. The study compared those who initiated SZC or patiromer and compared the risk of hospitalization for heart failure. A statistically non-significant tendency towards more events in people starting SZC was observed: SZC 36 versus patiromer 25 per 100 person-years {hazard ratio [HR] 1.22 [95% confidence interval (CI) 0.95–1.56]}. Information on dose and treatment duration were not available [32]. This is an example of potential risks that, if they exist, will only be unveiled as these medications are more widely used in clinical practice and large observational studies are conducted.

FACT 3. DRUG CHOICES NEED TO CONSIDER COSTS, ACCESS AND NUMBERS NEEDED TO TREAT

Novel agents are not available in all countries. Where available, they have not been competitively priced, with SPS often several-fold less costly than newer agents. This limits access to the new agents and probably many patients or prescribers take costs to the healthcare system or out-of-pocket costs into account. But perhaps the most compelling argument against their use as marketed—to maintain patients with modest hyperkalaemia on MRA or RASi—is the quantitative consideration of the number needed to treat (NNT) to prevent a clinically important event.

Packer [33] described this issue quantitatively in the editorial accompanying the DIAMOND trial (NCT03888066) [34]. In the 439 patients treated with patiromer for 6 months, 20 discontinued MRA (4.6%) compared with 31 (7.1%) in the group treated with placebo, a difference of 11 patients. He assumed this difference was sustained over the longer period of a trial with clinically important outcome events. A meta-analysis of trials on the effects of MRA on the outcome hospitalization for heart failure or cardiovascular death estimated the NNT over 3 years of follow-up resulted in NNTs of ≈11 [35]. Therefore, 439 patients would be treated with patiromer for 3 years to prevent 11 discontinuations; those 11 discontinuations avoided will prevent one outcome: the NNT for patiromer to prevent this clinically important outcome is 439. This is not in the same range as other NNTs in prevention of cardiovascular events. For example, the recommended Framingham risk threshold for consideration of lipid therapy is a 10% risk of a major adverse cardiovascular event at 10 years [36], and the effectiveness of lipid-lowering therapy is approximately a 20% relative risk reduction [37], translating into a 2% absolute risk reduction in this scenario, or an NNT of 50. In addition, when considering how this NNT compares with others, we should recall that the rare serious harms of RASi, MRA and lipid-lowering therapy have been directly ascertained from meta-analyses of RCTs, whereas the harms of novel agents have been assessed only in trials of a few hundred patients.

Two economic analyses identifying favourable cost-effectiveness ratios for the use of potassium exchangers were published before the publication of the DIAMOND results [38, 39]. In many jurisdictions, SPS is less expensive than novel agents, and in a network meta-analysis, had the highest point estimate for effectiveness of any binder, although CIs overlap [21]. The incremental costs per quality-adjusted life year would be lower if SPS rather than patiromer were included in the model.

FACT 4. THE PROBLEM IS NOT WHICH MEDICATION TO USE, BUT SIMPLY TO TREAT/PREVENT HYPERKALAEMIA

The use of SPS in patients with CKD is rooted in some countries, but sporadic in others. As shown by Jadoul *et al.* [20] in the DOPPS, SPS was used by an average of 40–45% of French dialysis patients, followed by Sweden with a 20–25% prevalence of SPS prescription. In Italy, Belgium and Canada, prevalence of use was 5–15%, and the UK, USA, Australia, New Zealand and Germany had a prevalence of <5%. Although these patterns have likely changed today, there is evidence of caution in the uptake of new potassium exchangers in clinical practice. In the German participants of the CKD DOPPS, only 140 patients prescribed patiromer have been identified to date [40]. In the Veterans Administration system, which provides care to millions of veterans in the USA, reports describe the prescription of patiromer to 458 patients treated with kidney replacement therapy [41]. In OPTUM, a large gathering of health systems in the USA providing care to >25 million users, ≈3000 persons prescribed either patiromer or SZC were identified by the end of 2020 [32]. Although these figures may reflect the delay it takes for scientific publications to appear in press (i.e. the proportion of users is much larger today), this surely also reflects caution in the nephrology community in the use of these treatments, or patient unaffordability.

How might clinically important outcomes be impacted by potassium exchangers?

In clinical practice, it is extremely unusual for outpatient mild–moderate hyperkalaemia to be followed by arrhythmic arrest. The NNT to prevent such an event would be large indeed. However, hyperkalaemia is a risk factor for discontinuation or reduction in medications that elevate potassium (RASis and MRAs), drugs which have been shown to reduce clinically important outcomes [42–45]. Performing a trial to answer which strategy is best (to stop or to continue with therapy) would be challenging, and well-designed observational studies within the target trial emulation network have tried to provide clarity here [46]. A cohort study of two separate populations in Canada [43] used a landmark design to compare the decision of continuing versus stopping RASi in persons with CKD G3–5 within 90 days of an episode of hyperkalaemia. Stopping RASi was associated with higher mortality [HR 1.32 (95% CI 1.22–1.41)] and higher cardiovascular mortality [HR 1.17 (95% CI 1.11–1.24)]. In addition, maximal doses of RASi were associated a higher survival benefit compared with submaximal doses. Limitations of that analysis

include immortal time bias (i.e. only patients surviving 90 days after the hyperkalaemia event can enter in the cohort).

Two studies from Sweden employed the novel method of cloning, censoring and weighting among new users of MRA [47] or RASi [48] who develop their first-detected hyperkalaemia event. Among adult patients initiating MRA and developing hyperkalaemia, [47] 30% stopped treatment within 6 months. Compared with continuing MRA, stopping therapy was associated with a lower 2-year risk of recurrent hyperkalaemia [HR 0.75 (95% CI 0.72–0.79)] but a higher risk of a composite of hospital admission with heart failure, stroke, myocardial infarction or death [HR 1.10 (95% CI 1.06–1.14)] [47]. Among adult patients with myocardial infarction who developed hyperkalaemia while on RASi, 25% stopped within 6 months. Compared with continuing RASi, stopping therapy was associated with a higher 3-year risk of death [HR 1.49 (95% CI 1.34–1.64)] and a major adverse cardiovascular event [HR 1.29 (95% CI 1.14–1.45)] but a lower risk of recurrent hyperkalaemia [HR 0.76 (95% CI 0.69–0.84)] [48]. Despite variations in study design and methodology applied, these studies collectively favour continuing with medications after hyperkalaemia, as it is associated with a reduced risk of mortality and cardiovascular events compared with stopping. This is consistent with guideline recommendations [49] and illustrates a gap in clinical practice [42, 43]. It has been hypothesized that the wider use of all three agents may allow continued use of therapy, but as shown above, absolute effects may be modest and, particularly for the novel agents, lack cost-effectiveness.

CONCLUSION

Until proven otherwise and upon examination of evidence to date, it is reasonable to assume that all three agents have similar efficacy, but the safety profile is best understood for the agent for which we have the most information, SPS.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to the writing of this manuscript.

CONFLICT OF INTEREST STATEMENT

J.J.C. has conducted studies for which Karolinska Institutet has received support from AstraZeneca (manufacturer of SZC), Vifor Pharma (manufacturer of patiromer), Novo Nordisk, Astellas and Amgen. He also reports receiving lecture fees from Baxter, Fresenius, AstraZeneca, Astellas and Abbott and participated in advisory boards for AstraZeneca, Nestle and Bayer. M.M.S. is involved in studies of SZC supported by AstraZeneca and reports lecture fees from Otsuka, GlaxoSmithKline and Bayer. C.M.C. has received consultation, advisory board membership, honoraria or research funding from the Ontario Ministry of Health, Sanofi, Pfizer, Leo Pharma, Astellas, Janssen, Amgen, Boehringer Ingelheim and Baxter and through the LiV Academy of AstraZeneca. In 2018 she co-chaired a Kidney Disease: Improving global Outcomes (KDIGO) potassium controversies conference sponsored at arm's length by Fresenius Medical Care, AstraZeneca, Vifor Fresenius Medical Care, Relypsa, Bayer HealthCare and Boehringer Ingelheim. She co-chairs the cloth mask knowledge exchange, a stakeholder group that includes cloth mask manufacturers and fabric distributors and is editor-in-chief of MaskEvidence.org. In 2019 she co-chaired the Canadian commentary on KDIGO metabolic bone disease guidelines, which was unfunded. She is a member of the Green Party of Ontario, American Society of Nephrology, Canadian Society of Nephrology (CSN), ASTM International and the American Association of Textile Chemists and Colorists. She is editor in chief of the *Canadian Journal of Kidney Health and Disease*, the official journal of the CSN. A.G.O. has no conflicts of interest to report.

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Opponents' comments

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1- If cost were not an issue -the new K lowering drugs would be the clear choice since there is no apparent advantage of SPS or CPS-and a potential disadvantage.

Of note, we did not quote in our review the short-term head-to-head comparison quoted by Carrero et al (Jacques et al, CKJ 2022) (1) of SPS TID vs. patiromer (both in non-dialysis days) for one month. Indeed, we felt that it may not be clinically relevant, since using SPS TID is neither sustainable on the long run (as demonstrated by the 4.5 times higher rates of missing doses after 4 weeks compared to patiromer) nor desirable owing to the unpracticability of maintaining a 3-hour separation with all other drugs to avoid drug-drug-interactions, as recommended by the updated (2017) FDA label (2), in our polymedicated CKD patients.

2- If costs are a major problem and the choice is SPS/CPS or nothing -then clearly SPS/CPS should be initiated to maintain RAASi therapy in HF and CKD-However if SPS/CPS is not tolerated then a newer K^+ lowering agent should be instituted. While they are more expensive than SPS/CPS in the long term if they enable RAASi and therefore avoid CV mortality and morbidity they will prove to be cost effective and cost saving for our health systems, as suggested by patient-level simulation models. (3)

3- Where cost is not a major problem most patients would prefer not to take a drug that might induce bowel necrosis -even though it is a rather infrequent event when there are alternatives that do not have this risk.

This risk initially emphasized by the Food and Drug Administration in the US also led to a recently (August 2021) updated marketing authorization by the European medicine Agency (4) The EMA indeed stated "Scientific conclusions Taking into account the Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report on the Periodic Safety Update Report (PSUR(s)) for polystyrene sulfonate, the scientific conclusions are as follows: **In view of available data on gastrointestinal serious reactions from the literature and spontaneous reports including cases where the gastrointestinal damage was accompanied by presence of polystyrene sulfonate crystals in biopsy samples, the PRAC considers a causal relationship between polystyrene sulfonate administered without sorbitol and gastrointestinal stenosis and ischaemia is at least a reasonable possibility.** The PRAC concluded that the product information of products containing polystyrene sulfonate should be amended accordingly. The Coordination Group for Mutual Recognition and Decentralised Procedures (human) (CMDh) agrees with the scientific conclusions made by the PRAC"

"**Grounds for the variation to the terms of the Marketing Authorisation(s)** On the basis of the scientific conclusions for polystyrene sulfonate the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing polystyrene sulfonate is unchanged subject to the proposed changes to the product information."

While bowel necrosis risk will we believe be a problem for many patients agreeing to institute this therapy a more important problem is the fact that SPS/CPS is poorly tolerable. Given busy practices there is a risk that patients might discontinue SPS/CPS and continue their RAASi thereby exposing them to the risk of hyperkalemia and sudden death, while others might discontinue both SPS/CPS and their RAASi thereby increasing their risk of heart failure (HF), progression of CKD to ESRD and death. Perhaps the greatest risk is in those who tolerate SPS- SPS exchanges K^+ for Na^+. There is clear evidence that the increase in Na^+ is associated with an increased risk of edema and blood pressure. While one might suggest that SPS if tolerated without evidence of edema and loss of BP control is cost effective and only if not tolerated should the newer K^+ lowering agents such as patiromer be instituted -it should be pointed out that most patients with hyperkalemia have CKD and or diabetes mellitus -an increase in Na^+ in these patients will result in an increase in blood volume and therefore an increase in wall stress and myocardial oxygen demands. An increase in Na^+ intake has also

been shown to increase mineralocorticoid receptor (MR) expression. Thus, while there may not be overt edema or loss of BP control the increase in blood volume and activation of the MR would place the patient at an increased risk for vascular stiffening, an increase in inflammatory cytokines and progression to HF, ESRD and death. In the long run a K^+ lowering agent such as patiromer that exchanges K^+ for Ca^+, is relatively well tolerated and effective, would be the clear choice for anyone who understands the pathophysiology of HF and CKD.

In conclusion, advocates of SPS have suggested the need for a randomized trial comparing SPS to one of the newer K^+ lowering agents, such as patiromer. We would welcome such a trial but wonder how many patients would accept to participate and potentially receive SPS given its risk of bowel necrosis, even if relatively infrequent, if a better tolerated and safer alternative was available, such as patiromer.

We strongly believe that except where cost is a major consideration and the choice is between SPS or not receiving a K^+ lowering drug that a newer K^+ lowering drug should be instituted and will be cost saving over the long run to our health systems -and more importantly reduce the risk of HF, ESRD and death in our patients. This is clearly a case of "Penny wise pound foolish".

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