Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Clinical Research Quantitative

Canadian Journal of Kidney Health and Disease
Volume 7: 1–19

DOI: 10.1177/2054358120965838
journals.sagepub.com/home/cjk
SAGE

Polysulfonate Resins in Hyperkalemia: A Systematic Review

Sheung Wing Sherwin Wong[1], Grace Zhang[1], Patrick Norman[2], Hasitha Welihinda[3,4], and Don Thiwanka Wijeratne[3,4]

Abstract

Background: Hyperkalemia is a potentially life-threatening electrolyte abnormality defined as a serum potassium above the lab reference range (usually >5.0-5.5 mEq/L). Polystyrene resins, including sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS), have long been used to treat hyperkalemia. Sodium polystyrene sulfonate/calcium polystyrene sulfonate act by exchanging a cation for potassium within the intestinal lumen. While SPS and CPS have been available since the 1960s, there are rising concerns about the validity of the data supporting its use and about serious adverse gastrointestinal effects.

Objective: The objective of this systematic review was to quantify the efficacy and safety of polystyrene sulfonate resins (SPS/CPS) in the treatment of adults with hyperkalemia. This review focuses on the randomized control trial (RCT), interventional non-RCT, and observational data available on SPS/CPS use.

Design: Systematic review.

Setting: Any country of origin. Both inpatient and outpatient settings.

Patients: Adults with hyperkalemia treated with polystyrene sulfonate resins.

Measurements: The primary outcome was change in serum potassium. The secondary outcomes included adverse effects of SPS/CPS and prevention of recurrent hyperkalemia.

Methods: We conducted a systematic review using Cochrane Library, EMBASE (1947-2019), and Medline (1946-2019) databases. Literature reviews, systematic reviews, case studies, case series, and editorial pieces were excluded. Included studies were assessed for risk of bias.

Results: Four RCTs, 21 observational studies, and 5 quasi-experimental trials were included. A total of 212351 patients were included. Two thousand and fifty-eight patients were studied for the primary outcome and 210293 patients were studied for the secondary outcomes. Study designs were heterogeneous and not amenable to meta-analysis. Most studies included nonhemodialysis outpatients older than 65 years. Of the included studies, 22/25 (88%) demonstrated a reduction of serum potassium >0.5 mEq/L over the study period. The magnitude of reduction in serum potassium of potassium resin compared with placebo or matched controls in the 3 low-risk studies identified was 0.14 to 1.04 mEq/L. However, each study used different dosing regimens. Ten of 22 studies reported the effects of polystyrene resins on serum potassium within 24 hours. A few high-quality observational studies suggest an increased risk of serious adverse gastrointestinal events with a relative risk of 2.10 and a hazard ratio of 1.25 to 1.94; however, the absolute risk remains low. The incidence of adverse gastrointestinal events is 16 to 23 events per 1000 person-years.

Limitations: We acknowledge several limitations in this study. Case studies and case series were excluded from the search results. Large case series may have been excluded despite having comparable sample sizes to studies included due to lack of a comparator and calculated estimates. Due to the heterogeneity of the studies, the data were unable to be meta-analyzed and as such the potassium-lowering effect of polystyrene sulfonate resins remains founded on small studies with potential confounders.

Conclusions: This systematic review demonstrates a continued lack of high-quality evidence for the use of SPS/CPS in hyperkalemia. Studies investigated highly variable timelines and the most robust evidence for SPS/CPS use is in chronic hyperkalemia. While the absence of high-quality evidence does not exclude the possibility of benefit, prescribers must understand that the use of SPS/CPS in acute hyperkalemia is not supported by high-quality evidence.

Trial registration: The protocol for this systematic review was not registered.

Abrégé

Contexte: L'hyperkaliémie est un déséquilibre électrolytique potentiellement mortel qui se définit par une concentration sérique en potassium supérieure aux valeurs de référence (généralement supérieure à 5,0-5,5 mEq/L). Les résines polystyréniques, le sulfonate de polystyrène sodique (SPS) et le sulfonate de polystyrène calcique (SPC), sont depuis longtemps utilisées pour traiter l'hyperkaliémie. Le SPS et le SPC agissent dans la lumière intestinale en échangeant un cation contre du potassium. Bien que ces résines soient disponibles depuis les années 1960, la validité des données justifiant leur utilisation et le risque d'effets indésirables graves qu'elles posent pour le système gastro-intestinal suscitent de plus en plus d'inquiétudes.

Objectif: Cette revue systématique visait à quantifier l'efficacité et l'innocuité des résines SPS/SPC dans le traitement de l'hyperkaliémie chez les adultes. Cette revue se concentre sur les données issues d'essais contrôlés randomisés, d'études interventionnelles non randomisées et d'études observationnelles portant sur cette utilisation.

Type d'étude: Revue systématique

Cadre: Les études étaient incluses peu importe le pays d'origine. Patients traités en ambulatoire ou en milieu hospitalier.

Sujets: Des adultes atteints d'hyperkaliémie traités avec les résines de sulfonate de polystyrène.

Mesures: Le principal résultat était une modification de la kaliémie. Les résultats secondaires incluaient les effets indésirables des SPS/SPC et la prévention de l'hyperkaliémie récurrente.

Méthodologie: Nous avons procédé à une revue systématique des bases de données Cochrane Library, EMBASE (1947 à 2019) et Medline (1946 à 2019). Les revues de littérature, revues systématiques, études de cas, séries de cas et éditoriaux ont été exclus. Les études incluses ont fait l'objet d'une évaluation du risque de biais.

Résultats: Quatre essais contrôlés randomisés, vingt-et-une études observationnelles et cinq essais quasi expérimentaux ont été inclus, pour un total de 212 351 patients étudiés. Plus précisément, 2 058 patients ont été examinés pour le résultat principal et 210 293 patients pour les résultats secondaires. L'hétérogénéité des plans d'étude n'a pas permis de procéder à une méta-analyse. La plupart des études comprenaient des patients non hémodialysés de plus de 65 ans et traités en ambulatoire. Parmi les études incluses, 88 % (22/25) ont démontré une réduction de la kaliémie supérieure à 0,5 mEq/L au cours de la période étudiée. Dans les trois études jugées à faible risque, l'ampleur de la réduction de la kaliémie observée avec les résines par rapport au placebo ou aux témoins appariés s'établissait entre 0,14 et 1,04 mEq/L. Chaque étude avait cependant utilisé des schémas posologiques différents. Dix études sur vingt-deux rapportaient un effet des résines de polystyrène sur la kaliémie en moins de 24 heures. Quelques études observationnelles de grande qualité suggéraient un risque accru d'événements gastro-intestinaux graves (risque relatif de 2,10 et rapport de risque entre 1,25 et 1,94), mais le risque absolu demeure faible. L'incidence des événements indésirables gastro-intestinaux s'établissait entre 16 et 23 événements par 1 000 années-personnes.

Limites: Nous reconnaissons que cette étude comporte plusieurs limites. Les études de cas et les séries de cas ont été exclues de nos résultats de recherche. De vastes séries de cas ont été exclues faute de comparateur et d'estimations calculées, bien que leurs échantillons étaient comparables à ceux d'études incluses. L'hétérogénéité des études n'a pas permis de procéder à une méta-analyse. Par conséquent, l'effet de réduction du potassium par les résines de sulfonate de polystyrène demeure fondé sur les résultats de petites études comportant de possibles variables confusionnelles.

Conclusion: Cette revue systématique démontre l'insuffisance constante de données probantes de grande qualité appuyant l'utilisation des résines SPS et SPC pour le traitement de l'hyperkaliémie. Les études portaient sur des périodes de temps très variables et les preuves les plus robustes en faveur de l'utilisation des résines SPS et SPC concernent l'hyperkaliémie chronique. Si l'absence de données probantes de qualité n'exclut pas la possibilité de bienfaits, les médecins doivent comprendre que l'utilisation des résines SPS/SPC pour traiter l'hyperkaliémie aiguë n'est pas étayée par des preuves robustes.

Enregistrement de l'essai: Le protocole de cette revue systématique n'a pas été enregistré.

Keywords

polystyrene exchange resin, sodium polystyrene sulfonate, hyperkalemia, adverse events

Received April 30, 2020. Accepted for publication August 24, 2020.

[1]Department of Internal Medicine, Queen's University, Kingston, ON, Canada
[2]Kingston General Health Research Institute, ON, Canada
[3]School of Medicine, Queen's University, Kingston, ON, Canada
[4]Kingston Health Sciences Centre, ON, Canada

Corresponding Author:
Sheung Wing Sherwin Wong, Department of Internal Medicine, Queen's University, 76 Stuart St, Kingston, ON, Canada K7L 2V7.
Email: sherwin.wong@queensu.ca

Introduction

Hyperkalemia is a common and potentially life-threatening electrolyte abnormality defined as a serum potassium concentration above the upper limit of normal (5.0-5.5 mEq/L). The estimated prevalence of hyperkalemia in patients with chronic kidney disease (CKD) without renal replacement therapy is 9.6%.[1] Those requiring renal replacement therapy in the form of hemodialysis and continuous ambulatory peritoneal dialysis have a prevalence of 16.5% and 10.6%, respectively.[1] An increase in extracellular potassium lowers the cardiac membrane potential and predisposes the heart to fatal arrhythmias.[2] Observational data have demonstrated a U-shaped association between serum potassium and mortality.[3-6] A variety of management options are available including pharmacological (intracellular shifting and increasing excretion) and nonpharmacological (dietary restriction and renal replacement therapy).[7-9] One such pharmacological therapy for hyperkalemia is the use of potassium binding resins: sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS). These resins are administered orally or rectally and exchange their respective cation for the potassium ion within the large intestine. While these agents have been considered one of the few pharmacological methods of potassium elimination, the literature supporting their use is inconsistent. In the United States, the approval of SPS was based largely on a study by Scherr et al published in 1961 conducted on 32 patients with hyperkalemia.[10] With a mean dose of 40 g of SPS in water per day, the study demonstrated a reduction of serum potassium of 1.8 mEq/L over the mean duration of 3 days and 1.0 mEq/L in the first 24 hours in the oral SPS group. However, the efficacy of SPS has recently been questioned.[11-13] The lack of placebo-controlled studies as well as the concomitant use of a low-potassium diet and dextrose in the Scherr study created a challenge in establishing the true effect of SPS. The lack of placebo-controlled trials may be in part due to the ethical implications of withholding a potentially efficacious treatment for which few alternatives exist.

In addition, there have been concerns for severe adverse events, primarily colonic necrosis.[14] Following the Scherr et al 1961 study, Flinn et al added the cathartic sorbitol to the preparation to improve delivery of the medication to the colon.[15] This study prompted the widespread use of sorbitol with SPS due to apparent increased efficacy. In the subsequent decades, case studies on intestinal ischemia were reported with SPS use. Initial case reports showed that postoperative patients, patients with uremia, and those exposed to SPS with sorbitol were the patients most at risk.[16,17] In 2009, the U.S. Food and Drug Administration (FDA) subsequently published a black box warning highlighting the association with colonic necrosis and recommended against coadministration with sorbitol.[8] The role of sorbitol in generating intestinal injury remains unclear. Two studies using rat models, Ayoub et al and Lillemoe et al, provide conflicting conclusions on the culpability of SPS in the observed mortality and colonic necrosis.[18,19] Despite a lack of a demonstrated causal relationship, there has been a shift to administering polystyrene sulfonate resins with water since the 2009 FDA recommendation. Previous systematic reviews studying the serious gastrointestinal (GI) adverse events associated with SPS use have assessed case report and case series data and therefore have been unable to provide data on incidence and prevalence of adverse GI events associated with polystyrene resin use.[14]

Treatment of hyperkalemia can be divided into therapies for acute and chronic hyperkalemia.[20,21] These terms are not well-defined in the literature. However, there is evidence that supports that the rate of hyperkalemia development is clinically relevant.[2] Treatment modalities can also be classified into acute and chronic treatments based on their time of onset and duration of effect.[21]

Previously published reviews have predominantly examined the data from randomized control trials (RCTs).[7,8] Both Batterink et al and Mahoney et al only identified one RCT by Gruy-Kapral et al from 1998 which demonstrated no difference 4 hours after resin administration.[22] In 2017, a systematic review published by Palaka et al was the first to include observational studies in the review.[23] Palaka et al identified 3 RCTs on SPS/CPS which included a total of 136 participants. While observational studies were included, they were not discussed or analyzed beyond a count of the number of available articles. The review primarily focused on a variety of management strategies for hyperkalemia beyond SPS/CPS.

Objective

The objective of this systematic review was to identify the literature investigating the efficacy and safety of polystyrene sulfonate resins (SPS/CPS) in the treatment adults with hyperkalemia. The questions we aimed to address were as follows: (1) What is the direction and magnitude of effect of polystyrene resins on serum potassium in adults with hyperkalemia? (2) What adverse events are associated with polystyrene resin use? This review focuses on the RCT, interventional non-RCT and observational data available on SPS/CPS use. Data from studies without controls, placebo controls, and active comparators were included in this review.

Methods/Search Strategy

A systematic review was conducted using the EMBASE (1947-2019), MEDLINE (1946-2019), and Cochrane Database of Systematic Reviews databases. The search was initially performed on July 13, 2018 and updated on October 6, 2019. Citations of previous reviews were also searched. Terms for hyperkalemia were combined with terms for cation exchange resins, SPS, CPS, and their brand names. The full search strategy can be found in the Supplemental

Table 1. Study Characteristics of Randomized Control Trials on Polystyrene Exchange Resins.

			Study population characteristics			
Study ID and design	Intervention group	Sample size	Mean age (years)	Renal function (serum creatinine in μmol/L/eGFR/ creatinine clearance in mL/min)	Setting	Nondialysis or dialysis
Lepage et al[32]	SPS 30 g PO daily × 7 d	16	72.7 ± 11.6	eGFR: 20.0 ± 7.2	Outpatient	No
Randomized Control Trial	Placebo	17	71.9 ± 9.6	eGFR: 17.7 ± 6.6		
Nakayama et al[37]	SPS 5 g PO TID × 4 wk	10	70.2 ± 11.7	eGFR: 18.7 ± 5.7	Outpatient	No
Prospective open labeled randomized crossover trial	CPS 5 g PO TID × 4 wk	10	69.1 ± 12.0	eGFR: 13.0 ± 4.7		
Nasir and Ahmad[38]	SPS 5 g PO TID × 3 d	47	53.08 ± 12.86 y	CKD stages 1-4	Emergency Department	No
Randomized Control Trial	CPS 5 g PO TID × 3 d	50				
Wang et al[46]	CPS 5 g PO TID × 3 wk	29	60.55 ± 10.43	Mean SCr: 877.66 ± 326.47	Outpatient	Yes, all on maintenance hemodialysis
Randomized controlled trial of crossover design	Placebo	29	57.34 ± 11.23	Mean SCr: 978.10 ± 273.77		

Note. eGFR = estimated glomerular filtration rate; SPS = sodium polystyrene sulfonate; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; SCr = serum creatinine.

Table 2. Study Characteristics of Observational Studies on Polystyrene Exchange Resins.

Study ID and design	Intervention group	Sample size	Study population characteristics			
			Mean age, y	Renal function (serum creatinine in μmol/L, eGFR/CrCl in mL/min, or reported CKD stage)	Setting	Nondialysis or dialysis
Arroyo et al[51] Prospective single-arm study	Withdrawal of CPS	7	66	Mean eGFR: 41.3 ± 10.8	Outpatient	Nondialysis
Batterink et al[49] Retrospective cohort study	Varying doses of SPS with sorbitol Control	66 72	69 ± 16 69 ± 17	Mean eGFR: 56 ± 32 Mean eGFR: 59 ± 27	Inpatient Inpatient	Nondialysis
Chernin et al[52] Retrospective cohort single-arm study	15 g SPS once daily	14	75.9 ± 9.2 Outpatients on ACE-inhibitor therapy	CKD stage breakdown: Stage 3 (21.4%) Stage 4 (64.3%) Stage 5 (14.3%)	Outpatient	Nondialysis
Fordjour et al[53] Prospective chart review	SPS 10-20 g (mostly single dose) SPS 30-40 g (mostly single dose) SPS 45-120 g (mostly single dose)	26 66 SPS 45-120 g 18 154 total (including co-intervention)	52 (range 18-95)	Mean SCr 282.9 70% of patients had eGFR < 30 or were on HD	Inpatient	Both Hemodialysis (13%)
Georgianos et al[54] Retrospective single-arm cohort study	Low-dose SPS (15 g daily mixed in a glass of water)	26	71 ± 9.2	Mean eGFR: 33.3 ± 11.4	Outpatient	Nondialysis
Hagan et al[48] Retrospective single-arm cohort study (chart review)	Single-dose SPS (mean 32.4 g)	501	67.5 (95% CI = 66.4-68.8) y	Mean SCr: 309.4 (95% CI = 285.5-327.9)	Inpatient	No
Hunt et al[28] Retrospective single-center cohort	SPS 15 g SPS 30 g	53 61	66 (IQR: 56-77)	CKD staging: Stage 4 (30%) Stage 5 (14%) ESRD on RRT (56%)	Inpatient	Both (56% n RRT)
Jadoul et al[29] Database prospective cohort study (DOPPS)	SPS (most common were 15 g daily, 15 g weekly and 15 g 4 times per week) Control	2296 9113	63.4 ± 14.6 65.6 ± 14.6	Residual kidney function: 37% (urine output >200 mL/day) Residual kidney function: 50% (urine output >200mL/day)	Outpatient	Yes Hemodialysis
Kessler et al[50] Retrospective cohort single arm	Single dose of SPS of varying doses (15, 30, 45, 60 g)	122	69.0 ± 11.4	Mean SCr: 227.2 ± 212.2	Inpatient	No
Laureati et al[31] Retrospective cohort study (SRR) Swedish Renal Registry	SPS exposure (single dispensation or chronic usage)	19530	73 (IQR: 64-80)	CKD staging: Stage 4 (69%) Stage 5 (17%) ESRD on HD (10%) ESRD on PD (4%)	Outpatient	Both
McGowan et al[33] Retrospective single-arm chart review of pathology database	Intestinal ischemia with SPS-sorbitol exposure Mean dose: SPS 92 g oral	11	70.8	No data on renal function	Inpatient	Yes
Mikrut and Brockmiller-Sell[34] Retrospective and prospective single-arm cohort study	Retrospective 30 g Retrospective 60 g Prospective 30 g Prospective 30 g	30 7 24 4	21/30 patients were 65 y of age or older	12/24 patients had a CrCl <30 mL/min (incomplete data)	Inpatient	No
Mistry et al[35] Retrospective single-arm cohort study (chart review)	Oral SPS 15 g Oral SPS 30 g Oral SPS 60 g Rectal SPS 30 g	50 50 13 5	70.6 ± 13.0 66.7 ± 15.0 66.9 ± 14.4 60 ± 16.4	Mean CrCl: 35.1 ± 22.6 Mean CrCl: 43.0 ± 47.3 Mean CrCl: 54.7 ± 44.3 Mean CrCl: 19.8 ± 3.1	Inpatient	No
Nakamura et al[36] Retrospective cohort study	Change group (Ca-resin to Na-resin) New Start (Na-resin)	11 29	68.9 ± 12.0 66.3 ± 10.6	All on maintenance hemodialysis	Outpatient	Yes—all on maintenance hemodialysis
Noel et al[40] Population-based retrospective matched cohort study	SPS exposure	27704 matched to 27704 nonusers	74 (IQR: 69-81)	eGFR < 60 (77.1%)	Outpatient	Both (Chronic dialysis = 0.2%)
Rossignol et al[41] Prospective Multicenter Registry Study	SPS (72%) CPS (4%)	527	60.3 ± 16.1	All on maintenance hemodialysis	Outpatient	Yes
Sandal et al[42] Retrospective cohort study	SPS 15 g in 20 g sorbitol	135	No data	Mean SCr: 206 ± 172	Inpatient	No
Sevitt and Wrong[43] Retrospective single-arm cohort study	CPS (15-45 g daily)	10	30.8 ± 9.78	No data on renal function	No data	No
Watson et al[47] Retrospective cohort study	SPS exposed	2194 compared to 121 197 unexposed	Mean age: Colonic necrosis + SPS: 78.2 ± 7.0 Colonic necrosis without SPS: 57.7 ± 2.2 No colonic necrosis + SPS: 64.5 ± 0.4 No colonic necrosis—SPS: 43.3 ± 0.06	eGFR < 30 Colonic necrosis + SPS: 100% Colonic necrosis without SPS: 46% No colonic necrosis + SPS: 90% No colonic necrosis—SPS: 8%	Inpatients and outpatients	Not stated
Yousaf and Spinowitz[55] Retrospective single-arm cohort study	SPS (15-30 g)	92	76.0 ± 13.3	No data on renal function	Emergency department	No
Yu et al[45] Retrospective single-arm cohort study	CPS 2.5 g-15 g/d (mean dose 8 g/d)	247	64 ± 14 outpatient	Mean eGFR: 30 ± 15	Outpatient	No

Note. eGFR = estimated glomerular filtration rate; CrCl = creatinine clearance; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; SPS = sodium polystyrene sulfonate; SCr = serum creatinine; CI = confidence interval; HD = hemodialysis; ESRD = End-stage renal disease.

Table 3. Study Characteristics of Quasi-Experimental Studies on Polystyrene Exchange Resins.

			Study population characteristics			
Study ID and design	Intervention group	Sample size	Mean age, y	Renal function (serum creatinine in μmol/L, eGFR/creatinine clearance in mL/min, or reported CKD stage)	Setting	Nondialysis or dialysis
Flinn et al[15] Quasi-experimental design	Oral SPS + sorbitol Sorbitol Rectal SPS + sorbitol	5 3 2	No data	Severe oliguria—urine volumes <400 mL/day	No data	Nondialysis
Johnson et al[30] Quasi-experimental study	SPS candy 5 g PO TID Control	Treatment 6 6	No data	Mean SCr = >1105	Outpatient	Yes Hemodialysis
Ng et al[39] Quasi-experimental study design	SPS 10 g PO TID × 3 d	7	60.5 ± 5.12 y	Mean SCr: 13.0 ± 1.63 (units not provided)	No data	No
Scherr et al[10] Quasi-experimental study design	Oral SPS Rectal SPS Long-term oral SPS	22 8 2	No data	No data	No data	No
Tomino et al[44] Quasi-experimental study design	CPS jelly preparation 5 g PO daily, increased by 5 g per month up to 15 g/d	23	61.2	Mean eGFR: 3.1 ± 0.4	Inpatient	No

Note. eGFR = estimated glomerular filtration rate; SPS = sodium polystyrene sulfonate; SCr = serum creatinine; CPS = calcium polystyrene sulfonate.

Table 4. Primary Outcome Data on Polystyrene Exchange Resins.

Study ID and design	Intervention group	Control/comparator	Co-intervention allowed	Duration of follow-up	Study outcomes (primary/secondary)	Primary outcome		
						Starting [K], mmol/L	Postresin [K], mmol/L	Change in [K], mmol/L
Lepage et al[32] Randomized control trial	SPS 30 g PO daily	Placebo	No	6.9 d	Primary Mean difference in serum potassium at day 7	Treatment 5.26 ± 0.22 Control 5.23 ± 0.22	Treatment 3.99 ± 0.56 Control 5.03 ± 0.34	Treatment −1.25 ± 0.57 Control −0.21 ± 0.29
Nakayama et al[37] Prospective open labeled randomized crossover trial	SPS 5 g PO TID	CPS 5 g PO TID	No	4 wk + crossover of 4 wk	Pre-resin potassium, postresin potassium	SPS 5.6 ± 0.54 CPS 5.39 ± 0.49	SPS 4.12 ± 0.64 CPS 4.14 ± 0.91	SPS −1.48 (95% CI = −1.88 to −1.08) CPS −1.25 (95% CI −1.90 to −0.60)
Nasir and Ahmad[38] Randomized Control Trial	SPS 5 g PO TID	CPS 5 g PO TID	No	3 d	Pre-resin potassium, postresin potassium	SPS 5.8 ± 0.6 CPS 5.8 ± 0.26	SPS 4.3 ± 0.53 CPS 4.8 ± 0.5	Not provided Not provided
Wang et al[46] Randomized controlled trial of crossover design	CPS 5 g PO TID	Placebo	No—patients on diuretics and insulin were included	7 wk total, 3 wk intervention × 2 for crossover with 1 wk washout	Primary Change in potassium after treatment	CPS Group 5.93 ± 0.38 Placebo 5.97 ± 0.51	CPS Group 5.29 ± 0.51 Placebo 5.61 ± 0.65	CPS Group −0.48 (−0.75, −0.16) Placebo −0.1 (−0.49, 0.32)
Batterink et al[49] Retrospective cohort study	Sorbitol containing SPS—single dose	Matched controls—Not treated with SPS	No	6-24 hr	Primary Change in serum potassium	Intervention 5.3 ± 0.2 Control 5.1 ± 0.2	Not provided Not provided	Intervention −0.58 ± 0.39 Control −0.44 ± 0.5
Chernin et al[52] Retrospective cohort single-arm study	15 g SPS once daily	None	Probably No	14.5 mo (median)	Primary Pre and post SPS serum potassium	6.4 ± 0.3	4.6 ± 0.6	Not provided
Fordjour et al[53] Prospective chart review	SPS of varying doses (low, med, high)—mostly single dose	SPS of varying doses	Yes Insulin in 21% However, data presented is for SPS monotherapy	88.8% within 24hrs, 100% within 48hrs	Primary Change in serum potassium	SPS 10-20 g 5.6 ± 0.4 SPS 30-40 g 5.7 ± 0.6 SPS 45-120 g 6.1 ± 0.1	Not provided Not provided Not provided	SPS 10-20 g −0.7 ± 0.5 SPS 30-40 g −0.9 ± 0.5 SPS 45-120 g −1.1 ± 0.6
Georgianos et al[54] Retrospective single-arm cohort study	Low dose SPS (15 g daily mixed in a glass of water)	None	Yes Insulin (7.7%) Loop diuretics (34.6%)	15.4 mo (median) Minimum 2 wk	Primary Pre and post SPS serum potassium (1 mo and mean post-SPS)	5.9 ± 0.4	4.9 ± 0.7 (1 mo) 4.8 ± 0.5 (average)	Not provided
Hagan et al[48] Retrospective single-arm cohort study (chart review)	Single dose SPS (mean 32.4 g)	None	Yes IV Calcium (27%) Insulin (30%) Loop diuretic (18%) Bicarbonate (21%) Hemodialysis (11%)	Mean: 8.45 hr	Primary Pre and post SPS serum potassium	5.8 (95% CI: 5.81-5.86)	4.87 (95% CI: 4.76-4.98)	−0.93 (SD not provided)
Hunt et al[28] Retrospective single-center cohort	Single dose SPS (30 or 15 g)	None	No	15 hr (IQR: 11-19 hr) 14 hr (interquartile range 10-18h)	Primary Pre and post SPS serum potassium Change in serum potassium	SPS 15 g: 5.6 (IQR: 5.5-5.7) SPS 30 g: 5.7 (IQR: 5.5-5.8)	SPS 15 g: 5.1 (IQR: 4.8-5.4) SPS 30 g: 4.9 (IQR: 4.7-5.2)	SPS 15 g: −0.5 (IQR: −.2, −0.9) SPS 30 g: −0.8 (IQR: −0.4, −1.1)
Kessler et al[50] Retrospective cohort single arm	Single dose of SPS of varying doses (15, 30, 45, 60 g)	None	No	Mean: 10 hr	Primary Pre-SPS, Post-SPS and Mean Serum Potassium change	5.57 ± 0.35	4.59 ± 0.46	−0.99 ± 0.51

(continued)

Table 4. (continued)

Study ID and design	Intervention group	Control/comparator	Co-intervention allowed	Duration of follow-up	Study outcomes (primary/secondary)	Primary outcome		
						Starting [K], mmol/L	Postresin [K], mmol/L	Change in [K], mmol/L
Mikrut and Brockmiller-Sell[34] Retrospective and prospective single arm cohort study	Single-dose Oral SPS	None	No	At least 12 hr	Primary Pre-SPS, post-SPS and Serum Potassium change	Retrospective 30 g 5.63 Retrospective 60 g 6.24 Prospective 30 g 5.69 Prospective 60 g 6.67	Retrospective 30 g 4.64 Retrospective 60 g 4.51 Prospective 30 g 4.68 Prospective 60 g 4.40	Retrospective 30 g −0.99 ± 0.64 Retrospective 60 g −1.73 ± 0.87 Prospective 30 g −1.01 ± 0.67 Prospective 60 g −2.25 ± 0.82
Mistry et al[35] Retrospective single-arm cohort study (chart review)	Oral and rectal SPS—single dose	None	No	6.5 hr	Primary	Oral SPS 15 g 5.51 ± 0.39 Oral SPS 30 g 5.64 ± 0.43 Oral SPS 60 g 5.58 ± 0.33 Rectal SPS 30 g	Oral SPS 15 g 5.12 ± 0.67 Oral SPS 30 g 4.95 ± 0.72 Oral SPS 60 g 4.67 ± 0.43 Rectal SPS 30 g	Oral SPS 15 g −0.39 Oral SPS 30 g −0.69 Oral SPS 60 g −0.91 Rectal SPS 30 g −0.22
Nakamura et al[36] Retrospective cohort study	Change group (Ca-resin to Na-resin)	New Start of Na-Resin (SPS)	Probably No	Averaged over 4-wk period	Pre and Post potassium levels for both groups	Change group 5.5 ± 0.6 New Start group 5.9 ± 0.4	Change group 4.9 ± 0.6 New Start group 4.7 ± 0.6	Change group Not provided New Start group Not provided
Sandal et al[42] Retrospective cohort study	SPS 15 g in 20 g sorbitol outcomes only post-first dose	None	No	Five intervals from 0 to >18 hr	Pre-resin potassium Post-resin potassium	5.59 ± 0.45 Statistically significant within 0-4 hr strata See paper for trend over 18 hr	Not provided	16.7% decrease (0.93)
Yousaf and Spinowitz[55] Retrospective single-arm cohort study	SPS 30 g (99 doses) SPS 15 g (7 doses)	None	Yes—unclear what proportion	637 ± 423 min	Pre-resin potassium, Post-resin potassium	5.37 ± 0.26	4.84 ± 0.66	Not provided
Yu et al[45] Retrospective single-arm cohort study	CPS 2.5-15 g/d (mean dose 8 g/d)	None	Unclear	5.6 ± 8.7 mo	Pre-resin potassium, post-resin potassium	5.8 ± 0.3	4.9 ± 0.7	Not provided
Flinn et al[15] Quasi-experimental design	Oral: 15 g SPS QID prn with 5 g QID regular with sorbitol titrated to diarrhea Rectal: 40 g SPS with 200mL of 25% sorbitol	Sorbitol alone	None Unclear effect of D50 500-700mL IV daily	5 d	Primary Pre and post SPS serum potassium	Oral SPS + sorbitol 6.7 ± 0.4 Sorbitol 6.3 ± 0.2 Rectal SPS + sorbitol 7 ± 0.3	Oral SPS + sorbitol 5.2 ± 0.5 Sorbitol 4.6 ± 1.3 Rectal SPS + sorbitol 4.5 ± 1.3	Oral SPS + sorbitol −1.6 ± 0.3 Sorbitol −1.7 ± 1.5 Rectal SPS + sorbitol −2.6 ± 1.1
Johnson et al[30] Quasi-experimental study	SPS candy TID (15 g/d)	Placebo candy	Probably No	2 wk total study, 1 wk placebo candy, 1 wk SPS candy	Primary Pre and post SPS serum potassium	Treatment 5.11 ± 0.7 Control 5.81 ± 0.6	Treatment 4.81 ± 0.5 Control 5.55 ± 0.9	Treatment −0.3 ± 0.73 Control −0.2 ± 0.64
Ng et al[39] Quasi-experimental study design	SPS 10 g PO TID × 3 d	None	Probably No	3 d (days 1, 2, 3 and postresin)	Daily serum potassium concentration	4.9 ± 0.8	4.6 ± 0.7 (day 1) 4.2 ± 0.7 (day 2) 4.0 ± 0.4 (day 3) 4.0 ± 0.5 (post)	−0.95 ± 0.8
Scherr et al[10] Quasi-experimental study design	SPS 20-60 g/d in divided doses (median 40 g)	None	Yes (in cases 23 and 25)	1-6 d, mean 3 d	Pre-resin potassium Post-resin potassium	Oral SPS 6.3 ± 1.0 Rectal SPS 6.5 ± 1.1 Long-term oral SPS 7.0 ± 0.4	Oral SPS 4.6 ± 1.3 Rectal SPS 5.9 ± 1.5 Long-term oral SPS Not provided	Oral SPS −0.9 ± 0.6 Rectal SPS −0.7 ± 0.8 Long-term oral SPS −5.25 ± 1.5
Tomino et al[44] Quasi-experimental study design	CPS jelly preparation 5 g PO daily, increased by 5 g per month up to 15 g/d	None	Probably No	3 mo	Serum potassium concentration at baseline, 1, 2, 3 mo	5.7 ± 0.1	Not provided	−1.33 ± 0.18

Note. SPS = sodium polystyrene sulfonate; CI = confidence interval; CPS = calcium polystyrene sulfonate; HD = hemodialysis; ESRD = End-stage renal.

Table 5. Secondary Outcome Data on Polystyrene Exchange Resins.

Study ID and design	Number of participants	Intervention group	Control/comparator	Duration of follow-up	Secondary outcome (GI adverse events, recurrent hyperK, etc)
Lepage et al[32] Randomized control trial	SPS: 16 Placebo: 17	SPS 30 g PO daily × 7 d	Placebo	6.9 d	Higher proportion achieved normokalemia with SPS (73% vs 38%) Three patients became hypokalemic with the lowest K = 3.0, nonstatistically significant No colonic necrosis, similar prevalence of GI side effects in both groups No hypernatremia, no hyperphosphatemia, 3 episodes of hypocalcemia (18.5%), and 5 episodes of hypomagnesemia (31.2%) compared with 1 episode of hypomagnesemia in control group—considered not statistically significant
Nakayama et al[37] Prospective open labeled randomized crossover trial	SPS: 10 CPS: 10	SPS 5 g TID	CPS 5 g TID	4 wk + crossover of 4 wk	SPS drop out due to edema (3), headache (1) and diarrhea (1). No other adverse events. Decrease in serum Ca and Mg with SPS and iPTH increased with SPS and decreased with CPS
Nasir and Ahmad[38] Randomized control trial	SPS: 47 CPS: 50	SPS 5 g PO TID × 3 d	CPS 5 g PO TID × 3 d	3 d	Adverse events included nausea and anorexia more so in SPS than CPS group (42.5% vs 18%) and (34% vs 14%). No change in serum calcium, sodium or phosphate
Wang et al[46] Randomized control trial of crossover design	CPS: 29 Placebo: 29	CPS 3 × 5 g/d	Placebo	7 wk total, 3 wk intervention × 2 for crossover with 1 wk washout	4/58 in the control group and 5/58 in the CPS group became hypokalemic after 3 wk No change in interdialytic weight gain. No hypercalcemia. Mild-to-moderate constipation was the most common GI side effect. Overall prevalence of adverse events was not statistically different. Improved normokalemia (60% vs 31%)
Arroyo et al[51] Prospective single-arm study	7	Withdrawal of CPS	None	3 mo	Increase in serum calcium of 0.96 ± 0.46
Batterink et al[49] Retrospective cohort study	SPS: 66 Control: 72	Sorbitol containing SPS	Matched controls—Not treated with SPS	6-24 hr	Bowel obstruction, nonfatal not related to SPS
Chernin et al[52] Retrospective cohort single-arm study	SPS: 14	15 g SPS once daily	None	14.5 m (median)	One death due to sepsis, zero cases of colonic necrosis, abdominal pain and constipation that resolved while using SPS No change in serum sodium Two mild cases of asymptomatic hypokalemia (3.1, 3.0), dose of SPS reduced to every other day
Fordjour et al[53] Prospective chart review	SPS 10-20 g: 26 SPS 30-40 g: 66 SPS 45-120 g: 18 154 total including co-intervention groups	SPS of varying doses (low, med, high)	SPS of varying doses	88.8% within 24 hr, 100% within 48 hr	No data on GI adverse events. Nonresponders (<0.5 mmol/L decrease in serum K) between 17% and 35%. Least effective in low doses and low initial serum potassium
Georgianos et al[54] Retrospective single-arm cohort study	SPS: 26	Low dose SPS (15 g daily mixed in a glass of water)	None	15.4 mo (median) Minimum 2 wk	Recurrent hyperkalemia in 7 patients (10 episodes). No serious adverse GI events. Statistically significant increase in serum sodium 139.5 ± 2.9 to 141.2 ± 2.4 mmol/L
Hagan et al[48] Retrospective single-arm cohort study (chart review)	SPS: 501	Single-dose SPS (mean 32.4 g)	None	Mean: 8.45 hr	Two cases of necrotic bowel perforation within 3 d and 24 hr of SPS administration 31 cases of hypokalemia with a mean serum potassium of 3.11 mEq/L 10 cases of new onset hypernatremia with a mean of 148.5 mmol/L
Hunt et al[28] Retrospective single-center cohort	SPS 15 g: 53 SPS 30 g: 61	Single-dose SPS (30 or 15 g)	None	15 hr (IQR = 11-19 hr) 14 hr (IQR = 10-18 hr)	GI Adverse events Two "Possible" WHO-UMC Classification—ischemic colitis and perforated duodenal ulcer
Jadoul et al[29] Database prospective cohort study (DOPPS)	SPS: 2296 Control: 9113	SPS (most common were 15 g daily, 15 g weekly and 15 g 4 times per week)	Patients not on SPS	Median: 18.5 mo (IQR: 9.3-28.0 mo)	SPS was associated with reduced mortality, but signal was likely due to confounders. Associated with a increased in 250 g of IDWG and 0.2-0.3 mg/dL higher phosphate
Kessler et al[50] Retrospective cohort single arm	SPS: 122	Single dose of SPS of varying doses (15, 30, 45, 60 g)	None	Mean: 10 hr	No data on GI events No change in serum calcium, mild increase in serum sodium (0.89 ± 3.33)
Laureati et al[31] Retrospective cohort study (SRR) Swedish Renal Registry	SPS exposed: 19530	SPS exposure (single dispensation or chronic usage)	Compared with nonexposed	Follow-up period of 2006-2016	Serious GI Adverse Event (ulcer and perforation, ischemia/thrombosis) SPS: HR = 1.25 SPS per label dose: HR = 1.54
McGowan et al[33] Retrospective single-arm chart review of pathology database	Intestinal ischemia: 11	Intestinal ischemia with SPS-sorbitol exposure Mean dose of SPS was 92 g—all oral	None	Range: <1-11 d Median: 2 d	9/11 were admitted for medical diagnoses, 2/11 had surgical procedures, 9/11 were female, 4/11 had ESRD requiring HD, 2/11 had uremia
Mikrut and Brockmiller-Sell[34] Retrospective and prospective single-arm cohort study	SPS Retrospective 30 g: 30 SPS Retrospective 60 g: 7 SPS Prospective 30 g: 24 SPS Prospective 30 g: 4	Single-dose Oral SPS	None	At least 12 hr	No adverse GI events, decrease in serum calcium by overage of 0.6 mg/dL (0.15 mmol/L) and stable serum sodium levels

(continued)

Table 5. (continued)

Study ID and design	Number of participants	Intervention group	Control/comparator	Duration of follow-up	Secondary outcome (GI adverse events, recurrent hyperK, etc)
Mistry et al[35] Retrospective single-arm cohort study (chart review)	Oral SPS 15 g: 50 Oral SPS 30 g: 50 Oral SPS 60 g: 13 Rectal SPS 30 g: 5	Oral and rectal SPS	None	6.5 hr	No data on adverse GI events. Persistent hyperkalemia was noted in 50%, 30 and 23.1% in the 15, 30, and 60 g, group, respectively. All patients in the rectal group remained hyperkalemic
Nakamura et al[36] Retrospective cohort study	Change group (Ca-resin to Na-resin): 11 New Start (Na-resin): 29	Change group (Ca-resin to Na-resin)	New start of Na-Resin (SPS)	Averaged over 4-wk period	3/29 in new start group experienced constipation, no change in constipation in change group. Increase in serum Na from 137 ± 2.3 to 139.0 ± 2.5. Otherwise no change in weight gain or blood pressure. Also increase in phosphate from 5.6 ± 0.7 to 6.5 ± 1.5 mg/dL
Noel et al[40] Population-based retrospective matched cohort study	27 704 exposed to 27 704 nonusers	SPS exposure	Matched and nonmatched	30 d	Adverse GI events (intestinal ischemia/thrombosis, GI ulceration/perforation or resection/ostomy) SPS: 22.97 per 1000 person-years Nonusers: 11.01 per 1000 person-years No change after 2007 Food and Drug Administration Warning against sorbitol use Hazard ratio associated with SPS use = 1.94
Rossignol et al[41] Prospective Multicenter Registry Study	527	SPS (72%) CPS (4%)	None	1, 2, and 3 mo	Recurrence of hyperkalemia at 1, 2, 3 mo remained high 59.7% (recurrence equal or high than initial level)
Sandal et al[42] Retrospective cohort study	SPS: 135	SPS 15 g in 20 g sorbitol only post-first dose	None	Five intervals from 0 to >18 hr	Thirteen deaths were reported, one was ischemic colitis, but no postmortem completed. No data on other adverse events
Sevitt and Wrong[43] Retrospective single-arm cohort study	CPS: 10	CPS	None	8.3 ± 7.11 mo	Pre- vs post-calcium 2.43 ± 0.25 vs 2.715 ± 0.335 mmol/L 50% of patients became hypercalcemia at some point during therapy (days to years)
Watson et al[47] Retrospective cohort study	2194 compared with 121 197 unexposed	SPS exposed	Not exposed	Within 30 d (September 1, 2001 to October 31, 2010)	Colonic necrosis 9-y cumulative incidence: 0.14% vs 0.07%. RR = 2.10 Three cases were identified—all in advanced care/ICU settings with age >65 and eGFR <30 mL/min/1.73 m^2, median dose was 45 g—only one had SPS crystal in situ
Yu et al[45] Retrospective single-arm cohort study	CPS: 247	CPS 2.5 g-15 g/d (mean dose 8 g/d)	None	5.6 ± 8.7 mo	Unpleasant taste of CPS, constipation in 7.7, no serious adverse events
Flinn et al[15] Quasi-experimental design	Oral SPS + sorbitol: 5 Sorbitol: 3 Rectal SPS + sorbitol: 2	Oral: 15 g SPS QID prn with 5 g QID regular with sorbitol titrated to diarrhea Rectal: 40 g SPS with 200 mL of 25% sorbitol	None	5 d	Increase in serum sodium from a mean of 134 to 143 One patient in the oral resin group became hypokalemic. Another patient in the retention enema group became hypokalemic—trough level not provided and unclear whether symptomatic. The latter was deemed to have EKG changes consistent with digitalis intoxication
Ng et al[39] Quasi-experimental study design	SPS: 7	SPS 10 g PO TID × 3 d	None	3 d (days 1, 2, 3 and postresin)	One patient became hypokalemic and had a post-resin K = 3.2 with a starting K = 5.0, no comment on symptoms
Scherr et al[10] Quasi-experimental study design	Oral SPS: 22 Rectal SPS: 8 Long-term oral SPS: 2	SPS	None	1-6 d, mean = 3 d	Five patients became hypokalemic with oral SPS, with a mean of 2.72 mEq—no comment on symptoms
Tomino et al[44] Quasi-experimental study design	CPS: 23	CPS jelly preparation 5 g PO daily, increased by 5 g per mo up to 15 g/d	None	3 mo	No adverse reactions, no weight or blood pressure changes noted. No change in sodium, calcium, magnesium phosphate or chloride levels

Note. GI = gastrointestinal; HD = hemodialysis; ESRD = End-stage renal disease; SPS = sodium polystyrene sulfonate; CPS = calcium polystyrene sulfonate.

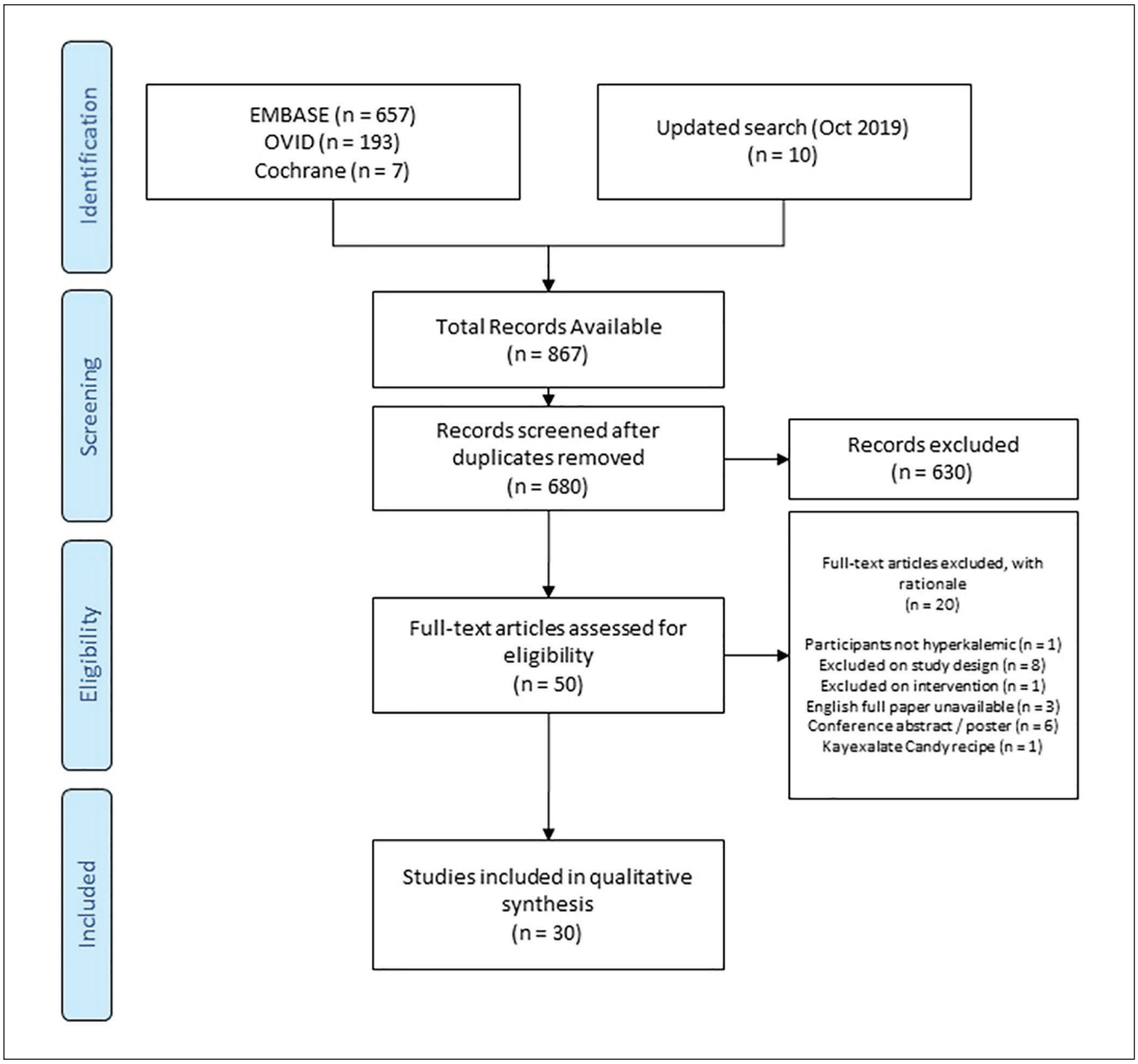

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Material. The protocol was not published or registered prior to completion of the systematic review. Two independent reviewers (S.W.S.W. and G.Z.) screened the titles, abstracts, and full papers against eligibility criteria.

Eligibility Criteria

We conducted a systematic review and meta-analysis of primary research literature that included full-text, English language, original RCTs, and observational studies. Our population of interest was adult patients above 18 years of age who received a polystyrene sulfonate resin for the treatment of hyperkalemia. Supplemental Table 1 summarizes the inclusion and exclusion criteria of our review. Studies were included that examined the management of hyperkalemia in adult patients with SPS or CPS with outcome data on reduction of serum potassium level and/or adverse events. Hyperkalemia was defined as a serum potassium >5.0 mEq/L. A lower threshold for defining hyperkalemia allows this review to capture a broader scope of literature including mild hyperkalemia. Studies without controls, with placebo controls and with active controls, were included. Literature reviews, systematic reviews, case studies, case series, and editorial pieces were

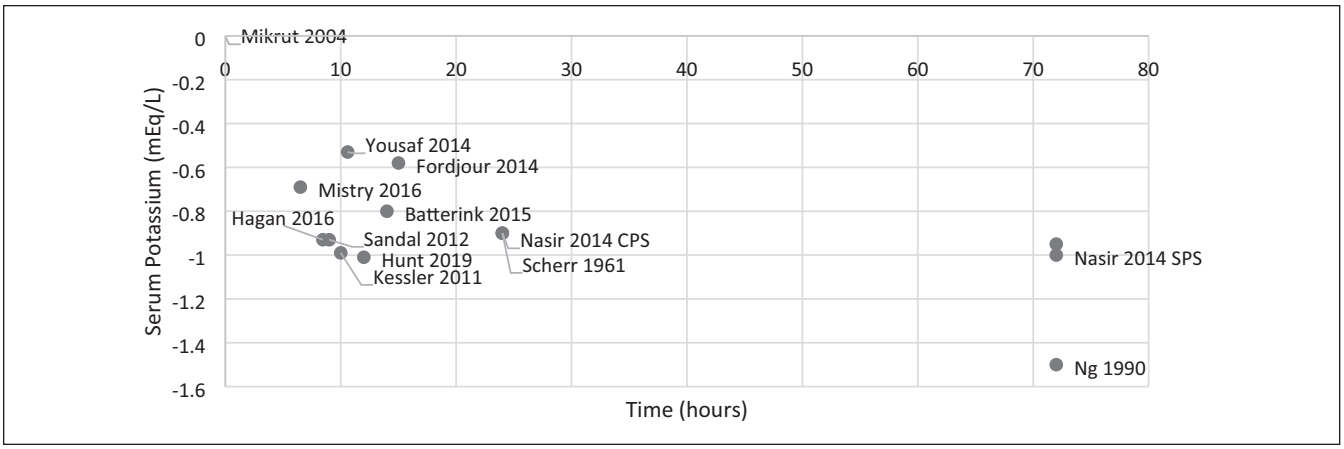

Figure 2. Change in serum potassium in intervention group of studies examining primary outcome within 72 hours.
Note. SPS = sodium polystyrene sulfonate; CPS = calcium polystyrene sulfonate.

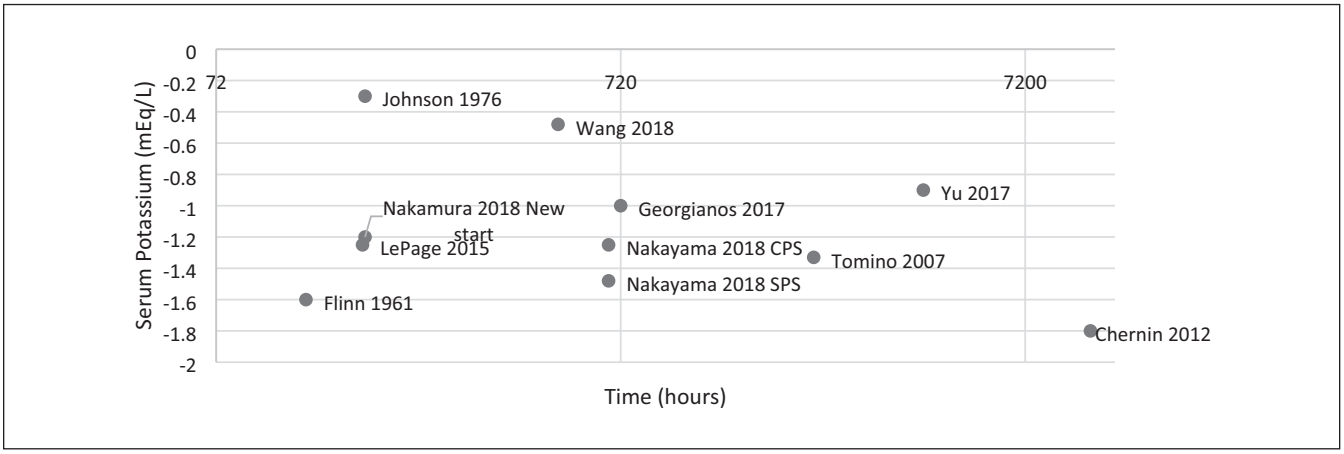

Figure 3. Change in serum potassium in intervention group of studies examining primary outcome after 72 hours.
Note. SPS = sodium polystyrene sulfonate; CPS = calcium polystyrene sulfonate.

excluded. For this study, nonrandomized interventional study designs were categorized as quasi-experimental studies and were included. Discrepancies were resolved by consensus.

Data Extraction and Outcome Measures

All included studies were assessed by 2 authors for data extraction. The primary outcome was the change serum potassium. The secondary outcomes were the incidence of adverse GI events associated with the use of polystyrene resins, hypokalemia, hypercalcemia, and rates of recurrent hyperkalemia. A broad definition of adverse GI events was used, including intestinal necrosis, ischemia, perforation, or ulceration. Additional post hoc secondary outcomes were added including hypernatremia, hypomagnesemia, weight gain, and funding sources.

Study characteristics were also collected including type of intervention, dose of resin, single dose or multidose, time to outcome, and number of included study participants.

Bias Assessment

Articles were independently assessed by each reviewer (S.W.S.W. and G.Z.) and dichotomized to low/high risk of bias based on standardized scoring systems. An RCT was considered low risk if it satisfied a score of 8 or more based on the Cochrane Risk of Bias Tool 2.0.[24] An observational study was considered low risk if it satisfied a score of 8 or more based on the Newcastle-Ottawa Criteria.[25] All nonrandomized interventional study designs (Quasi-experimental)

were assessed using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) assessment tool.[26]

Statistical Analysis

The data abstracted from this systematic review were not amenable to meta-analysis due to significant heterogeneity in populations, intervention, and measurement of effects. A sensitivity analysis could not be performed due to the low number of studies considered to be at low risk of bias. To determine the direction of effect, vote counting and a corresponding sign test were performed according to the Cochrane Handbook of Systematic Reviews of Interventions Version 6.0.[27] Studies considered in favor of intervention if a reduction of greater or equal to 0.5 mEq/L was achieved. There is no consensus on a clinically relevant reduction in serum potassium and so this value was set by the authors of this study. Qualitative analyses were performed on the study characteristics and secondary outcomes. A post hoc analysis was performed on the effect of potassium binding resins on weight gain, serum sodium, and magnesium.

Results

We identified 867 relevant articles (Figure 1). After applying the exclusion criteria and removal of duplicates, 30 articles were eligible for inclusion (Table 1).[10,12,15,28-54] Of the included studies, 4 studies were RCTs, 21 were observational studies (Table 2), and 5 studies were nonrandomized interventional study designs (quasi-experimental study designs) (Table 3). Most of the literature was published since 2010: 4 articles were published before 1990, 1 between 1990 and 2000, 3 between 2000 and 2010, and 22 were published since 2010. A total of 212 351 patients were included in these studies with 208 patients within the RCTs, 1766 patients in observational studies investigating the primary outcome, 210 293 patients in observational studies investigating secondary outcomes, and 84 patients in quasi-experimental study designs. In total, 2058 patients were included in studies investigating the primary outcome and 210 293 patients in studies investigating the secondary outcomes.

Study Characteristics

Included Study Designs

This systematic review identified 4 RCTs investigating the use of polystyrene resins in the setting of hyperkalemia.[32,37,38,46] Lepage et al and Wang et al studied the efficacy of polystyrene resins in placebo-controlled trials. Nakayama et al and Nasir and Ahmad compared SPS with an active comparator, CPS. These 2 trials were included as they provided valuable data on the magnitude of reduction in serum potassium with both CPS and SPS. However, it was felt to be of similar quality to the other data in this review and thus was included. The inclusion of such data does not change the overall conclusions of the review. All RCTs studied outpatients exclusively. Nasir and Ahmad specifically studied patients presenting to the emergency department. Only Wang et al conducted an RCT examining the effect of polystyrene exchange resins in patients treated with hemodialysis.

Setting

Of the included studies, 14 (46%) studied outpatients exclusively, 2 (6.7%) articles studied patients in the emergency department. Nine (30%) studies investigated inpatients exclusively. Only 1 (3.3%) study conducted by Watson et al included both inpatients and outpatients. Four (13%) studies provided no data on the setting.

Population Characteristics

Most studies provided data on elderly patients with documented renal dysfunction in the outpatient setting. However, there was significant heterogeneity. In studies investigating the primary outcome, the mean age of participants was 66.2 years. The mean age of participants in studies investigating secondary outcomes was 49.0 years; however, the mean age was significantly affected by the younger matched control group in the article by Watson et al.[47] The mean age of participants of articles investigating secondary outcomes excluding Watson et al is 70 years. Seventeen (57%) studies included patients with a mean age above 65 years, 4 (13%) studies included no information about the age of their study population.

Four (13%) studies included both patients on hemodialysis and those without. Six (20%) studies investigated the effect of polystyrene resins exclusively in patients on maintenance dialysis, 19 (63%) articles were included that studied nondialysis patients. The observational study by Watson et al did not specify the inclusion of patients on hemodialysis.

Of the 23 studies that included patients not on hemodialysis, 3 (13%) reported no data on renal function, 4 (17%) articles reported mean serum creatinine >200 μmol/L, 8 (35%) studies reported estimated glomerular filtrate rate (eGFR), creatinine clearance (CrCl), or CKD staging consistent with a mean CrCl less than 30 mL/min/1.73 m^2. Six (26%) studies reported either eGFR or CrCl between 30 and 60 mL/min/1.73 m^2. Flinn et al reported that patients were oliguric, with no further details on renal function.[15] Nasir and Ahmad 2014 reported that patients had a range of CKD stages from I to IV.[38] Overall, most articles that reported either renal function studied patients with a CrCl or eGFR of less than 60 mL/min/1.73 m^2.

Interventions

Ten studies (45%) investigating the primary outcome utilized a single-dose resin. Seventeen (57%) of studies investigated

the primary outcome using SPS and 3 (10%) using CPS. Both Nakayama et al and Nasir and Ahmad studied both SPS and CPS. Sodium polystyrene sulfonate dosing was studied between 15 g daily up to 60 g per day. Calcium polystyrene sulfonate was studied at lower doses ranging from starting doses of 5 to 15 g per day.

Time to Outcome

The reported time to effect of polystyrene sulfonate resins was variable between studies. Of the 22 included studies investigating the primary outcome, 5 (23%) reported outcomes in less than 12 hours, 5 (23%) reported outcomes within 12 to 24 hours, 5 (23%) reported outcomes within 1 to 7 days, and 7 (32%) reported outcomes assessed beyond 7 days.

Co-intervention

Hyperkalemia is often treated with multiple agents concomitantly including insulin, beta-agonists, and diuresis. These confounders may result in overestimation of the effect of cation resins. Of the 13 observational studies studying the primary outcome, 7 excluded co-intervention, 4 studies likely did not have co-intervention but did not explicitly exclude co-intervention (Chernin et al, Georgianos et al, Nakamura et al, Yu et al), and 2 studies (Hagan et al, Yousaf et al) included co-intervention. Of the quasi-experimental study designs, only Scherr et al documented co-intervention. The remaining 4 studies did not explicitly exclude co-intervention but were unlikely to co-administer other agents for hyperkalemia.

Risk of Bias

In the included RCTs, risk of bias overall was low as assessed by the Cochrane Risk of Bias Tool. Studies were largely well-designed albeit with small sample sizes. However, only the trials by Lepage et al and Wang et al were considered strictly to be at low risk of bias. Both Nakayama et al and Nasir and Ahmad compare SPS with an active comparator CPS. Therefore, its effect compared with placebo is not able to be elucidated. In addition, the open-label nature of trial by Nakayama et al could introduce bias. Furthermore, the randomization process was also not clearly outlined by Nasir and Ahmad. Despite these, the objective measure of serum potassium was protective in ensuring the validity of these findings.

Observational studies were assessed by the Newcastle-Ottawa Criteria and only 6 studies were low risk of bias. Only 2 observational studies examining the primary outcome, Batterink et al and Nakamura et al were at low risk of bias. The remaining 3 studies investigated secondary outcomes at a population level (Jadoul et al, Noel et al, Rossignol et al, Watson et al). The high-risk studies were designated as such largely due to the lack of comparator groups.

The quasi-experimental studies were assessed using the ROBINS-I tool. All studies were at serious or critical risk of bias. Overall, the studies included few participants, had missing demographic data, or lacked comparator groups.

Outcomes

Primary Outcome

Reduction in serum potassium. This systematic review demonstrates that the current evidence for polystyrene use in hyperkalemia is heterogeneous and has a paucity of high-quality placebo-controlled studies (Table 4). Current literature from observational studies largely support the use of SPS/CPS for lowering serum potassium. There is no consensus on a clinically significant reduction in serum potassium, we defined a clinically significant difference as a reduction in serum potassium of 0.5 mEq/L. In total, 88% of the 25 included studies favored intervention ($P < .001$). Notably, of the 23 studies that reported an outcome as a reduction in serum potassium 2 of 4 (50%) RCTs, all 13 observational studies and 4 of 5 (80%) quasi-experimental studies demonstrated a reduction of >0.5 mEq/L during the study period (Figure 2 and 3).

A dose-dependent reduction of serum potassium was also observed in 5 observational studies (Fordjour et al, Hunt et al, Kessler et al, Mistry et al, and Yu et al). Four studies investigated the effect of SPS/CPS over time. Sandal et al observed a progressive decline reaching a minimum serum potassium at 18 to 24 hours. Flinn et al and Ng et al reported a continued decline in serum potassium at 6 and 3 days, respectively. In contrast, Tomino et al demonstrated a continued decline in potassium 3 months after initiation of treatment; however, there were monthly increases in doses.

A sensitivity analysis including only low-risk studies revealed that only the study by Lepage et al demonstrated a reduction of greater than 0.5 mEq/L (1.04 mEq/L) when compared with placebo. Both other low-risk studies by Wang et al and Batterink et al demonstrated an additional reduction in serum potassium of 0.38 and 0.14 mEq/L compared with placebo or matched controls. While both differences were statistically significant, the clinical significance of small reductions in serum potassium is unclear. Notably, the Wang et al trial used a low dose of CPS, 5 g 3 times a day over the study period. Of the participants in the Batterink et al study, 47% received a single dose of 30 g of SPS dose and 48.5% received a single 15-g dose.

In summary, the data from the 2 low risk of bias studies suggest a serum potassium reduction of 0.14 mEq/L in 6 to 24 hours and 0.38 mEq/L in 3 weeks.[8,46] Other data from observational data and RCTs with active comparators estimate a more generous effect on potassium reduction. The reduction in serum potassium ranges from 0.3 to 2.25 mEq/L with the effect varying with dose and duration of therapy.[10,34] Several studies support a dose-dependent reduction in serum potassium with escalating resin

doses.[28,35,45,50,53] Overall, the current evidence supports a small reduction in serum potassium with the use of polystyrene sulfonate resins. Most of the current literature is observational and lacks appropriate controls. The results of this review do not change in the direction of effect after a sensitivity analysis excluding studies at high risk of bias.

Secondary Outcomes

GI adverse events. The risks of polystyrene resin use have been better elucidated in observational data in recent years (Table 5). In 2012, Watson et al published a retrospective cohort study providing the first estimations of relative risk and absolute risk of pathologically demonstrated colonic necrosis in SPS use. The reported 9-year cumulative incidence of colonic necrosis was 0.14% with a relative risk of 2.10 that was not considered significant. The number needed to harm was 1395 in the entire cohort and 631 in patients above the age of 65 years. The authors concluded that there was no increased risk associated with SPS use. Subsequent studies by Laureati et al and Noel et al expanded the scope to include other serious adverse GI events including ulcer, perforation, and ischemia. They reported an overall increase in serious adverse GI events associated with SPS use. The reported hazard ratios were 1.25 and 1.94 and incidence rates per 1000 person-years were 16 and 22.97 in Laureati et al and Noel et al, respectively. Current observational data from these 3 studies as well as data from a systematic review of case reports suggest that adverse GI events occur from days 2 to 14 after SPS administration. In addition, Noel et al noted no difference in event rate before and after the 2009 FDA recommendation to avoid coadministration with sorbitol. None of the participants in Laureati et al were exposed to sorbitol. While there are no studies specifically examining the risk of adverse events with CPS use, we expect the adverse event profile to be similar to SPS. All 3 studies had a follow-up period of 30 days following polystyrene resin exposure. Noel et al noted an increased risk in GI adverse events being detected afer 10 days and persisting during the entire follow-up period.

These observational studies represent the best evidence to date for the effect of polystyrene resins on GI events and are the only studies that are adequately powered to study the rare adverse GI events. In summary, SPS use is associated with increased adverse GI events with an estimated hazard ratio of 1.25 to 1.94 and an incidence rate of 16 to 23 per 1000 person-years.[31,40] This increased risk of rare but serious adverse GI events should be considered when prescribing polystyrene sulfonate resins.

Weight gain. Several studies have reported the effect of polystyrene resins on weight in both dialysis and nondialysis groups. Data from the DOPPS (Dialysis Outcomes and Practice Patterns Study) as analyzed by Jadoul et al suggest that there is a 250 mL increase in interdialytic weight gain in patients treated with maintenance dialysis prescribed a sodium-based potassium resin. In contrast, Nakamura et al demonstrated no change in weight in patients on hemodialysis in the SPS new start or resin change groups. Wang et al also demonstrated no change in weight with the use of CPS.

Three studies reported on the effect of resins on weight in patients not on hemodialysis (Chernin et al, Nakayama et al, and Nasir and Ahmad) report no statistically significant change in weight associated with polystyrene resin use. Nakayama et al did identify a nonstatistically significant trend to increased weight and a statistically significant association between weight and serum sodium.

Electrolyte abnormalities. Hypokalemia was reported in 7 studies. Both placebo-controlled RCTs reported hypokalemia; however, neither found that the rate was statistically different between treatment and placebo arms within the follow-up period of 6.9 days to 3 weeks.[32,46] Two studies studied hypercalcemia while using CPS (Arroyo et al and Sevitt and Wrong). The follow-up time was 3 and 8.3 months, respectively. Neither reported patients who were symptomatic from hypercalcemia. The 7 patients in Arroyo et al showed an increase in serum calcium of 0.91 $\pm$ 0.46 mg/dL (0.22 $\pm$ 0.46 mmol/L) after starting CPS. The mean CPS dose was 8.93 g per day which conferred a total of 713 mg of elemental calcium daily. Of the 10 participants in the Sevitt and Wrong study, 5 patients became hypercalcemic with an average dose of elemental calcium being 1963 mg per day. However, the overall incidence of hypercalcemia has not been studied. Other studies (Tomino et al, Wang et al, Nasir and Ahmad) demonstrated no change in serum calcium with the use of CPS. Of the 6 studies that reported on serum calcium with SPS use, only Lepage et al reported a reduction in serum calcium. Three of 16 participants (18.8%) had hypocalcemia compared with placebo, which had no episodes of hypocalcemia.

Of the 9 studies that reported on serum sodium with SPS usage, 3 noted an increase in serum sodium ranging from 0.89 to 9 mEq/L (Flinn et al, 9 mEq/L; Georgianos et al, 0.89 mEq/L; Nakayama et al, 1.6 mEq/L). One case of hypernatremia was reported by Flinn et al with a serum sodium of 148 mEq/L from 143 pre-resin. Hagan et al reported 10 cases of new onset hypernatremia (2%) with a mean serum sodium of 148.5 mEq/L. A mean change in serum sodium was not provided. Out of the 3 studies that reported sodium with CPS use, there was no change in serum sodium.

Three studies (Lepage et al, Nakayama et al, and Tomino et al) reported serum magnesium levels. Lepage et al reported 5 of 16 participants (31.2%) had hypomagnesemia compared with one in the placebo group. The other 2 studies noted no change in rates of hypomagnesemia.

Electrolyte disturbances are common, and the attributability of these abnormalities to polystyrene resin use is unclear without control data. There is conflicting evidence on the association of CPS with hypercalcemia. Recent studies have identified no change or modest changes to serum calcium.

Other than in the study by Lepage et al, SPS was not shown to have a statistically significant association with hypocalcemia and hypomagnesemia. Modest increases in serum sodium were observed with SPS use ranging from 0.89 to 9 mEq/L with more recent estimations being low.

Funding sources. Of the 30 included studies, 23 (77%) had no funding or conflict of interest to declare. Two studies investigating secondary outcomes disclosed funding support from pharmaceutical industry. Three studies had one author who received a research chair, an honoraria, and personal fees from pharmaceutical industry. Finally, Noel et al and Wang et al were both funded by nonindustry groups: Institute for Clinical Evaluative Sciences and Liaoning Province Translational Medicine Centre, respectively. Overall, the data included in this systematic review appear to be largely free of significant conflicts of interest. The results and conclusions do not change when studies with a funding source are excluded.

Discussion

The primary objective of this systematic review was to identify the currently available evidence for the efficacy and safety of polystyrene exchange resins in adults with hyperkalemia. To our knowledge, this study is the first systematic review to include and assess RCTs, observational data, and nonrandomized interventional studies. Previous systematic reviews investigating efficacy have previously only included RCTs, of which there are few studies.[7,8,23] Previous reviews on the safety profile of polystyrene resins have focused on the adverse GI events and examined the case series and case report literature. This review builds on that knowledge by including data regarding the safety profile of polystyrene resins from large observational studies and by including additional safety endpoints.

This systematic review identified several themes as outlined in the following sections.

Key Point 1: Highly Variable Timeline Studied—Poor Evidence for Use in Acute Hyperkalemia

The majority and highest quality evidence for the use of polystyrene resins is for periods of time greater than 24 hours. Ten studies investigated the effects of single-dose polystyrene resins within 24 hours, none of which are RCTs. While all studies reported a reduction in serum potassium, these studies were subject to significant confounders. The variable timelines studied likely reflect the ongoing uncertainty of the role of SPS/CPS in acute and chronic hyperkalemia—terms that are not well-defined in the literature. In contrast, 12 studies investigated the role of polystyrene resins beyond 24 hours. Ten of 12 demonstrated a reduction of greater than 0.5 mEq/L. However, only 1 of 3 low-risk studies demonstrated this reduction when compared with a matched control or placebo group. This difference in serum potassium reduction may be a result of the comparatively high dose of resin used in the study conducted by Lepage et al when compared with Wang et al and Batterink et al. While the paucity of high-quality evidence does not exclude the possibility of benefit, it is important to note that the use of potassium resins in acute hyperkalemia is not robustly supported by the evidence. The use in chronic hyperkalemia is somewhat mixed and may depend on the dose of resin provided.

Key Point 2: Patient-Centered Outcomes Such as Recurrence of Hyperkalemia and Mortality are Under-Studied

This study reviews the data available for the potassium-lowering effects of polystyrene resins. This endpoint, however, does not necessarily represent patient-important outcomes. Several studies have demonstrated that chronic hyperkalemia is well tolerated in patients with CKD and that mortality from hyperkalemia is highest in those with normal or lower grade CKD.[3-6] Furthermore, data from Rossignol et al suggest that the use of polystyrene resins does not prevent recurrence of hyperkalemia at a population level.[41] At the present time, it remains unclear whether the use of polystyrene resins produces an effect on patient-centered outcomes including hospitalization, morbidity, and mortality; this is especially relevant in the setting of chronic use.

Key Point 3: Safety Profile—Interdialytic Weight Gain and Electrolyte Disturbances Have Limited Data

Within the current body of literature, complications of polystyrene use included interdialytic weight gain in SPS, hypercalcemia in CPS, and adverse GI events. Recent literature has provided data on the adverse GI events; however, the other adverse effect profiles of these medications remain poorly studied. Specifically, interdialytic weight gain and electrolyte disturbances including hypercalcemia are potential adverse effects that have been minimally studied.

Strengths/Limitations

The present review is the first systematic review of the current literature on polystyrene sulfonate resins in hyperkalemia that closely examines RCT data, observational, and nonrandomized experimental study data. This study included both commonly available preparations of SPS and CPS. In contrast, a previous review included 18 studies on SPS and CPS and previous Cochrane reviews have only included at most one RCT.[7,8,23]

We acknowledge several limitations in this study. Case studies and case series were excluded from the search results. Large case series may have been excluded despite having comparable sample sizes to studies included due to lack of a

comparator and calculated estimates. Due to the heterogeneity of the studies, the data were unable to be meta-analyzed and as such the potassium-lowering effect of polystyrene sulfonate resins remains founded on small studies with potential confounders. As with any review the validity of the results is limited by publication bias. We were not able to quantify this given study heterogeneity. However, there was adequate dispersion of sample sizes and estimates that we capture in our review that would minimize such bias.

Conclusions

The current literature suggests that polystyrene sulfonate resins may have a modest effect on lowering potassium in the setting of hyperkalemia. The magnitude of effect remains unclear as most of the available evidence is at high risk of bias. The best evidence for its use is for longer term treatment of hyperkalemia, typically greater than 72 hours and with multiple doses of resin. It remains unclear whether there is a role for polystyrene resins in the acute management of hyperkalemia. The most well-recognized complication of polystyrene sulfonate use are adverse GI events including ischemia with an estimated hazard ratio between 1.25 and 1.94 and incidence rates per 1000 person-years between 16 and 22.97. The adverse effect profile has not yet been clearly elucidated; however, current evidence suggests that hypercalcemia, hypernatremia, and hypomagnesemia may not be clinically relevant adverse outcomes with polystyrene resin use. There also remains little evidence on the effect of polystyrene sulfonate resins on patient-important outcomes such as hospitalization, morbidity, and mortality. Future research should be directed at determining the magnitude of effect of polystyrene resin use compared with placebo in both acute and chronic hyperkalemia with a focus on patient-important outcomes.

List of Abbreviations

SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate; RCT, randomized control trial; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GI, gastrointestinal.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors consented to the publication of this manuscript.

Availability of Data and Materials

All data is presented in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sheung Wing Sherwin Wong https://orcid.org/0000-0003-1517-7709

Supplemental Material

Supplemental material for this article is available online.

References

1. Belmar Vega L, Galabia ER, Bada da Silva J, et al. Epidemiology of hyperkalemia in chronic kidney disease. *Nefrologia*. 2019;39(3):277-286.
2. Montford JR, Linas S. How dangerous is hyperkalemia? *J Am Soc Nephrol*. 2017;28:3155-3165.
3. Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study. *Am J Nephrol*. 2016;44(3):179-186.
4. Torlén K, Kalantar-Zadeh K, Molnar MZ, Vashistha T, Mehrotra R. Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. *Clin J Am Soc Nephrol*. 2012;7(8):1272-1284.
5. Khanagavi J, Gupta T, Aronow WS, et al. Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. *Arch Med Sci*. 2014;10:251-257.
6. Luo J, Brunelli SM, Jensen DE, Yang A. Association between serum potassium and outcomes in patients with reduced kidney function. *Clin J Am Soc Nephrol*. 2016;11:90-100.
7. Mahoney BA, Smith WAD, Lo D, Tsoi K, Tonelli M, Clase C. Emergency interventions for hyperkalaemia. *Cochrane Database Syst Rev*. 2016;2005:CD003235.
8. Batterink J, Cessford TA, Taylor RAI. Pharmacological interventions for the acute management of hyperkalaemia in adults. *Cochrane Database Syst Rev*. 2015;10. doi: 10.1002/14651858.CD010344.pub2.
9. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol*. 2014;10(11):653-662.
10. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL. Management of hyperkalemia with a cation-exchange resin. *N Engl J Med*. 1961;264:115-119.
11. Long B, Warix JR, Koyfman A. Controversies in management of hyperkalemia. *J Emerg Med*. 2018;55:192-205.
12. Watson M, Abbott KC, Yuan CM. Damned if you do, damned if you don't: potassium binding resins in hyperkalemia. *Clin J Am Soc Nephrol*. 2010;5(10):1723-1726.
13. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective. *J Am Soc Nephrol*. 2010;21(5):733-735.
14. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med*. 2013;126(3):P264.E9-P264.E24.
15. Flinn RB, Merrill JP, Welzant WR. Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. *N Engl J Med*. 1961;264:111-115.

16. Gerstman BB, Platt R. Use of sodium polystyrene sulfonate in sorbitol in the United States, 1985–1989. *Am J Kidney Dis*. 1991;18(5):619-620.
17. Food and Drug Administration. *Kayexalate ® SODIUM POLYSTYRENE SULFONATE, USP Cation-exchange Resin*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/011287s023lbl.pdf
18. Ayoub I, Oh MS, Gupta R, McFarlane M, Babinska A, Salifu MO. Colon necrosis due to sodium polystyrene sulfonate with and without sorbitol: an experimental study in rats. *PLoS ONE*. 2015;10(9):e0137636. doi:10.1371/journal.pone.0137636.
19. Lillemoe KD, Romolo JL, Hamilton SR, Pennington LR, Burdick JF, Williams GM. Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery*. 1987;101(3):267-272.
20. Weisberg LS. Management of severe hyperkalemia. *Crit Care Med*. 2008;36:3246-3251. doi:10.1097/CCM.0b013e31818f222b.
21. Kovesdy CP. Management of hyperkalemia: an update for the internist. *Am J Med*. 2015;128(12):1281-1287.
22. Gruy-Kapral C, Emmett M, Santa Ana CA, Porter JL, Fordtran JS, Fine KD. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol*. 1998;9:1924-1930.
23. Palaka E, Leonard S, Buchanan-Hughes A, Bobrowska A, Langford B, Grandy S. Evidence in support of hyperkalaemia management strategies: a systematic literature review. *Int J Clin Pract*. 2018;72:e13050. doi:10.1111/ijcp.13052.
24. Sterne J, Savović J, Page M, et al. RoB 2: a revised Cochrane risk-of-bias tool for randomized trials. *Cochrane Methods Bias*. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials. Published 2011. Accessed April 20, 2020.
25. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2017. The Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
26. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355. doi:10.1136/bmj.i4919.
27. Higgins Julian PT, Green S. Cochrane Handbook for Systematic Reviews of interventions—Cochrane training. *Handbook*. 2011;649.
28. Hunt TV, Demott JM, Ackerbauer KA, Whittier WL, Peksa GD. Single-dose sodium polystyrene sulfonate for hyperkalemia in chronic kidney disease or end-stage renal disease. *Clin Kidney J*. 2019;12:408-413. doi:10.1093/ckj/sfy063.
29. 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(3):252-259.
30. Johnson K, Cazee C, Gutch C, Ogden D. Sodium polystyrene sulfonate resin candy for control of potassium in chronic dialysis patients. *Clin Nephrol*. 1976;5(6):266-268.
31. Laureati P, Xu Y, Trevisan M, 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*. 2020;35:1518-1526. doi:10.1093/ndt/gfz150.
32. 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;10:2136-2142.
33. McGowan CE, Saha S, Chu G, Resnick MB, Moss SF. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. *South Med J*. 2009;102(5):493-497.
34. Mikrut M, Brockmiller-Sell H. Sodium polystyrene sulfonate dosing guidelines for the treatment of adult hyperkalemia. *Hosp Pharm*. 2004;39:765-771.
35. Mistry M, Shea A, Giguère P, Nguyen ML. Evaluation of sodium polystyrene sulfonate dosing strategies in the inpatient management of hyperkalemia. *Ann Pharmacother*. 2016;50(6):455-462.
36. Nakamura T, Fujisaki T, Miyazono M, et al. Risks and benefits of sodium polystyrene sulfonate for hyperkalemia in patients on maintenance hemodialysis. *Drugs R D*. 2018;18(3):231-235.
37. Nakayama Y, Ueda K, Yamagishi S, et al. Compared effects of calcium and sodium polystyrene sulfonate on mineral and bone metabolism and volume overload in pre-dialysis patients with hyperkalemia. *Clin Exp Nephrol*. 2018;22(1):35-44.
38. Nasir K, Ahmad A. Treatment of hyperkalemia in patients with chronic kidney disease: a comparison of calcium polystyrene sulphonate and sodium polystyrene sulphonate. *J Ayub Med Coll Abbottabad*. 2014;26(4):455-458.
39. Ng YY, Wu SC, Cheng CT, Yang WC, Chung HM, Huang TP. Reduction of serum calcium by sodium sulfonated polystyrene resin. *J Formos Med Assoc*. 1990;89(5):399-402.
40. 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;179:1025-1033.
41. 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;32:2112-2118.
42. Sandal S, Karachiwala H, Noviasky J, Wang D, Elliott WC, Lehmann DF. Clinical study to bind or to let loose: effectiveness of sodium polystyrene sulfonate in decreasing serum potassium. *Int J Nephrol*. 2012;2012:940320. doi:10.1155/2012/940320.
43. Sevitt LH, Wrong OM. Hypercalcaemia from calcium resin in patients with chronic renal failure. *Lancet*. 1968;2:950-951.
44. Tomino Y, Yamazaki T, Shou I, et al. Dose-response to a jelly preparation of calcium polystyrene sulfonate in patients with hyperkalemia—changes in serum potassium levels with or without a RAAS inhibitor. *Clin Nephrol*. 2007;68:379-385.
45. Yu MY, Yeo JH, Park JS, Lee CH, Kim G.-H. Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients. *PLoS ONE*. 2017;12:e0173542. doi:10.1371/journal.pone.0173542.
46. Wang J, Lv M-M, Zach O, et al. Calcium-polystyrene sulfonate decreases inter-dialytic hyperkalemia in patients undergoing maintenance hemodialysis: a prospective, randomized, crossover study. *Ther Apher Dial*. 2018;22(6):609-616.
47. Watson MA, Baker TP, Nguyen A, et al. Association of prescription of oral sodium polystyrene sulfonate with sorbitol in an inpatient setting with colonic necrosis: a retrospective cohort study. *Am J Kidney Dis*. 2012;60(3):409-416.

48. Hagan AE, Farrington CA, Wall GC, Belz MM. Sodium polystyrene sulfonate for the treatment of acute hyperkalemia: a retrospective study. *Clin Nephrol*. 2016;85(1):38-43.
49. Batterink J, Lin J, Au-Yeung SHM, Cessford T. Effectiveness of sodium polystyrene sulfonate for short-term treatment of hyperkalemia. *Can J Hosp Pharm*. 2015;68(4):296-303.
50. Kessler C, Ng J, Valdez K, Xie H. The use of sodium polystyrene sulfonate in the inpatient management of hyperkalemia. *J Hosp Med*. 2011;6:136-140.
51. Arroyo D, Panizo N, de Vinuesa SG, et al. Hypercalcaemia as a side effect of potassium binding agents. *Nefrologia*. 2012;32:655-658.
52. Chernin G, Gal-Oz A, Ben-Assa E, et al. Secondary prevention of hyperkalemia with sodium polystyrene sulfonate in cardiac and kidney patients on renin-angiotensin-aldosterone system inhibition therapy. *Clin Cardiol*. 2012;35(1):32-36.
53. Fordjour KN, Walton T, Doran JJ. Management of hyperkalemia in hospitalized patients. *Am J Med Sci*. 2014;347(2):93-100.
54. Georgianos PI, Liampas I, Kyriakou A, et al. Evaluation of the tolerability and efficacy of sodium polystyrene sulfonate for long-term management of hyperkalemia in patients with chronic kidney disease. *Int Urol Nephrol*. 2017;49(12):2217-2221.
55. Yousaf F, Spinowitz B. Management of mild hyperkalemia with sodium polystyrene sulfonate: Is it necessary? *Clin Pract*. 2014;11:501-507.