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Pro/Con Debate

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When comparing the safety of drugs, don't forget the exposure dimension

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Hyperkalemia can have serious health consequences if left untreated. Over the last decade, there has been an increase in the availability of treatments for hyperkalemia, including the new cation exchange polymers, patiromer and sodium zirconium cyclosilicate (SZC).

As healthcare costs continue to rise, it is essential to consider the affordability of treatments in addition to their efficacy. Sodium Polystirene Sulphate (SPS), available since the 1960s, has a significantly lower price than the recent alternatives, patiromer and SZC. This difference in cost is important for patients, healthcare providers and insurance companies, all of whom bear the financial burden of medical expenses.

Comparing the costs of these treatments, SPS has a distinct advantage. A month's supply of SPS can be as low as $20–$30, whereas patiromer and SZC costs can range from $600 to $1000 monthly.

SPS has been in use for over six decades. In countries participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) 2002–11 study, on average, 20% of patients were chronically on SPS or calcium polystyrene sulphate (CPS), a calcium-based resin with low cost, and the use of these resins was not associated with an excess risk for mortality [1]. About 40%–50% of dialysis patients in France use these drugs chronically [1]. Since the policy of using SPS and CPS in dialysis patients in France is long-standing (at least 40 years), it appears logical to surmise that no dramatic excess risk for major gastrointestinal (GI) problems attributable to the same drugs has emerged in the French pharmacovigilance program, which is very well organized [2]. In a large, nationwide French study including over 40 000 SPS and CPS users, the incidence of adverse GI events in patients undergoing dialysis was low. Neither SPS nor CPS was associated with increased GI events risk [3]. Incidentally, it remains unclear whether severe GI problems reported in past surveys are causally related to SPS and CPS or are the mere expression of the high risk for GI complications in these patients, including ischemic colitis due to hypotensive episodes during dialysis [4]. Nonocclusive hemorrhagic necrosis of the intestine is a well-known complication of congestive heart failure [5], another condition where SPS and CPS are frequently used. As of 31 December 2019, over 50 000 patients were on chronic dialysis in France, and 20 000 to 25 000 were on chronic treatment with cation exchange resins. Globally, this country's exposure to SPS and CPS in the dialysis population has been massive. This extensive use has allowed nephrologists to accumulate a wealth of knowledge and experience in administering SPS and CPS as a treatment for hyperkalemia. Patiromer and SZC are relatively new, having been approved by the Food and Drug Administration in 2015 and 2018, respectively. The estimated global exposure in participants of trials that tested patiromer (AMETHYST-DN and OPAL-HK trials) is approximately 362 patient-years. For SZC (ZS-003 and HARMONIZE trials), it is approximately 49 patient-years, an extremely small exposure, at the irrelevance limit, compared with that in patients treated with SPS and CPS over the last six decades. Outside clinical trials, patiromer and SZC are still scarcely used. In the Stockholm health database, which includes over 1 million individuals, in 2021 only 47 patients were started on the new drugs vs 1857 started on SPS [6]. Similarly, patiromer and SZC are scarcely used in the USA [7]. Less real-world experience with these drugs may lead to a higher degree of uncertainty regarding their long-term safety and effectiveness. In a way, the old generation resins story is like the hemodialysis story. Hemodialysis treatment has never been tested in a clinical trial. Clinicians accepted the evidence of the efficacy and safety of hemodialysis that emerged

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in clinical practice in the early years of this treatment and confidently applied this treatment. Over the years, particularly in France, nephrologists gathered experience of the efficacy of SPS and CPS as potassium-lowering agents and progressively arrived at an extensive use of these cation exchange resins in pre-dialysis chronic kidney disease and dialysis patients.

Some investigators doubt the efficacy of SPS for lowering serum potassium. Old studies apart, fresh analyses in the Stockholm health database comparing serum potassium in 1879 adults that started treatment with SPS and 147 with novel binders have shown that after 2 weeks of treatment, mean plasma potassium went down to 4.6 and 4.8 mmol/L in patients with cation exchange resins and novel binders, respectively, and was maintained similarly low during the 2 months post-treatment [6].

Regulatory agencies did not consider the global evidence showing the low risk of SPS and CPS and gave the green light to short-term trials comparing the new drugs with a placebo. New treatments should be compared with proven efficacy and safety treatments [8]. Cost-effectiveness analyses of the new drugs did not consider treatment with cation exchange resins as a comparator [9]. The efficacy of SPS and CPS as potassium-lowering agents in clinical practice is now well demonstrated [6]. This moderator believes that the safety of these drugs is testified to by the low risk for severe GI problems in a very high-risk population like the dialysis population.

CONFLICT OF INTEREST STATEMENT

C.Z. is member of the *CKJ* editorial board.

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