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Differences in Efficacy Among New and Old Potassium Binders in Dialysis Patients: A Systematic Review and Meta-Analysis

In depth review

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ABSTRACT

Introduction. Hyperkalemia is a common and serious complication in dialysis patients, with increased incidence and severity over time. Newer potassium binders, patiromer and sodium zirconium cyclosilicate (SZC), offer improved tolerability compared to older agents. This meta-analysis aims to evaluate the efficacy and safety of these newer binders in dialysis patients.

Methods. This systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted, adhering to PRISMA guidelines. Searches were performed in MEDLINE, PubMed, CINAHL, and EMBASE up to November 1, 2024. RCTs comparing patiromer or SZC to placebo, sodium polystyrene sulfonate (SPS), or calcium polystyrene sulfonate (CPS) in dialysis patients were included. Primary outcomes were differences in serum potassium levels. Secondary outcomes included adverse events (AEs) and mortality. Data were analyzed using fixed and random-effects models, and heterogeneity was assessed.

Results. Six RCTs, involving 3155 patients, were included. SZC and SPS significantly reduced pre-HD potassium levels compared to placebo (mean difference -0.68 mmol/L and -0.62 mmol/L, respectively; $p<0.0001$). Patiromer did not show a significant difference compared to placebo (mean difference -0.17 mmol/L; $p=0.16$). All treatments demonstrated a reduction in hyperkalemia events compared to placebo. Adverse event data were limited and not statistically analyzable, but no significant differences in total AEs were observed. Mortality data were sparse, with only one death reported in the placebo group. High heterogeneity was observed in the comparison between new and old binders/placebo.

Conclusion. SZC and SPS effectively reduce pre-HD potassium levels in dialysis patients compared to placebo. Patiromer's effect was not statistically significant. All binders reduced hyperkalemia events. Safety profiles appeared comparable, but data were limited. The lack of sufficient RCTs, especially those directly comparing newer binders, highlights a significant knowledge gap. Further studies are needed to evaluate long-term outcomes, including quality of life and cardiovascular effects, and to directly compare the efficacy and safety of different potassium binders in this population.

KEYWORDS: Dialysis, Patiromer, Potassium, sodium zirconium cyclosilicate, Sodium polystyrene sulphonate

Introduction

The incidence of hyperkalemia is one of the most common complications of kidney disease. Its incidence increases in patients who previously experienced hyperkalemia, with successively shorter time between the episodes [1].

Patiromer and Sodium Zirconium Cyclosilicate (SZC), new exchange ions polymer resin and exchange ions microporous resin, were recently developed reducing adverse events and improving palatability compared to old potassium binders [2–4].

Furthermore, many studies in conservative CKD demonstrated that these new drugs reduce hyperkalemia in patients treated with RAASIs [5].

Many systematic reviews compared new potassium binders with old potassium binders or placebo, but no one performed it in dialysis patients [6].

The main objective of our metanalysis is to evaluate the difference in serum potassium levels after treatment with SZC and Patiromer compared to placebo, sodium polystyrene sulfonate or calcium polystyrene sulfonate. Furthermore, the safety needs to be evaluated among these potassium binders in this population, due to the different pharmacokinetics that improve them.

Methods

Data source and search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7] and was conducted according to a pre-published protocol (CRD42024608049) [8, 9]. The literature search was designed and performed by two Authors (V.C. and A.P.). We performed a systematic, highly sensitive search in MEDLINE, PubMed, CINAHL and EMBASE for English-language articles without time or sex restriction up to November 1, 2024. Grey literature was screened through Google Scholar, SCOPUS and clinicaltrials.gov.

Study selection and data extraction

We included any randomized controlled trials (RCTs) testing the effects of potassium binders without sex restriction. Studies were included if provided information on outcomes of interest, such as 1) Differences in serum potassium concentration, 2) Adverse events (AEs), and 3) Mortality.

Studies were excluded if they included oncological patients, acute dialysis or CKD in conservative treatment. Articles were screened by titles and abstracts by two independent investigators (V.C. and A.F.), excluding studies not pertinent to the topic and, subsequently, assessed the full texts to determine eligibility according to the pre-specified inclusion/exclusion criteria. Any disagreement on study judgments was discussed with a third author (V.M.) who was not involved in the selection process.

Reviews, letters, case reports and studies performed on children (age<18) were excluded from analyses but screened for potential additional references. Ongoing, unpublished trials were searched on the clinicaltrials.gov website. Authors of some of the included studies were contacted for additional information about study methods and unreported data.

Data analysis

Primary analysis will compute serum potassium differences between a network meta-analysis comparing each potassium binder/placebo. Secondary analysis will consist of a comparison between SZC/Patiromer and placebo/sodium polystyrene sulfonate or calcium polystyrene sulfonate.

All data will be analyzed with fixed-effect model or random-effect model based on the heterogeneity of the studies. Mean differences, and 95% confidence interval (CI), will be calculated for continuous outcomes. For dummy outcomes, the Odds Ratio (OR), computing 95% confidence interval (CI), will be computed. Data were pooled using the fixed-effects model and also analyzed with the random-effects method to guarantee the strength of the model. We plan to test for heterogeneity using the χ^2 statistic related to the degrees of freedom, with a p value of 0.05 used as the cut-off value to determine statistical significance. In addition, the degree of heterogeneity will be investigated by calculating the I^2 statistics. We will consider I^2 low if <25%, moderate if 25-50%, moderate-high if 50-75% and very high if >75%. In case of high heterogeneity, we will perform sensitivity analyses to explore sources of heterogeneity, such as study quality, year of publication, intervention or control variables, participants characteristics, and risk of bias. In addition, sub-group analyses will be conducted.

We will assess funnel plot asymmetry and the contour-enhanced funnel plot to explore publication bias, if the number of studies allows it. GRADE System will be used to evaluate the certainty of the evidence and to summarize the study conclusions. We planned to construct a summary table via the GRADEpro-GDT (GRADEpro GDT 2015) [10], reporting a summary of the available outcomes' findings and the quality of the evidence supporting each outcome.

Statistical analyses were performed using Review Manager (RevMan; Version 5.4.) software and R4.4.0 software to perform the Network meta-analysis of all outcomes.

Quality and risk of bias assessment

The quality of RCTs was assessed by using the checklist developed by the Cochrane Renal Group which evaluates the presence of potential selection bias (random sequence generation and allocation concealment), performance bias (blinding of investigators and participants), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting) and possible other sources of bias.

Results

Search results

The selection process has been summed up in the flowchart (Figure 1). Two hundred and twenty-two references were retrieved. Among these, 95 were duplicates. By screening titles and abstracts, a total of 16 citations were selected for full-text evaluation. Among these, 6 articles were excluded because: 1) dealing with other populations or not reporting outcomes pertinent to the topic (n=7), 2) wrong intervention or no comparator (n=2), 3) duplicate (n=0), 4) various reasons (n=2). One study has been retrieved by Clinicaltrial.gov. Six articles referring to 5 full studies were reviewed in detail and included in the review [11, 15].

Study characteristics

All RCTs employed a parallel design. All studies were published after 2019. The final population analyzed in this review included 3155 patients, but the study sample sizes were variable, ranging from 33 [11] to 2690 [13]. The percentage of male participants varied from 49.3% [14] to 73% [15]. The mean age of patients ranged from 54 [11] to 66 [15] years. Three studies compared SZC to placebo, one study compared Patiromer to placebo, and one crossover study compared Patiromer to both placebo and SPS. The main characteristics of the eight RCTs reviewed are summarized in Table 1.

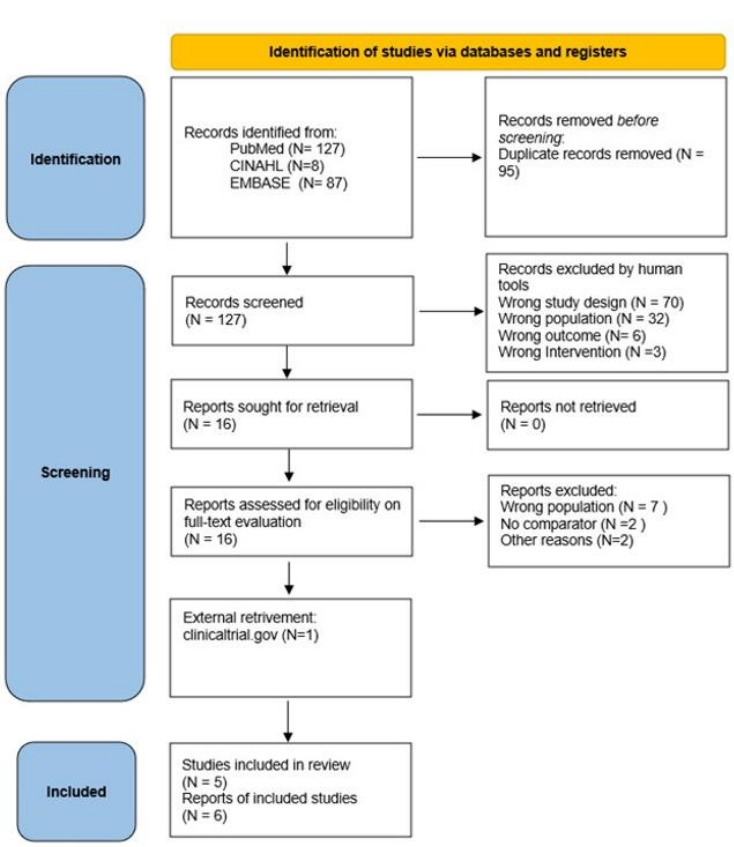

Figure 1. Study selection flow.

Trial reference	Study population and its characteristics	Intervention	Comparator	Study duration	Outcome(s)	Results	Notes
NCT03781089	Thrice weekly HD, adults Exclusion: Pregnancies -N=33 -Age (yr)= ~54 – Men (%)= 54.5% – Hispanic = 18.2% Countries= United States (single centre)	Patiromer (8.4mg/die) N=17	SPS (15g) N=16	7 weeks	Delta K	Not reported	Patients were checked up at 3, 5, 10, 14 and 27 weeks after initiation of treatment
					hypekalemia events*	13 in patiromer group vs 41 in SPS group	
					AEs	Death: 0 in patiromer group vs 0 SAE: 2 in patiromer group vs 2 (Arrhythmia: 0 in patiromer group vs 1 Infection: 0 in patiromer group vs 1 FAV thrombosis: 1 in patiromer group vs 0 Hospitalization: 1 in patiromer group vs 0)	
NCT03 303521	Thrice weekly HD, adults Exclusion: Hemoglobin <9 g/dl Pregnancies -N= 196 -Age (yr)=58 -Men (%)= 58.7%	SZC (5-10 mg) N=97	Placebo N=99	11 weeks	Delta K*	Mean difference between SZC and Placebo groups: − 0.74 mmol/L (95% CI − 0.97/− 0.52)	It is a post-Hoc analysis

	-Hispanic (%)= 52% -Countries= Japan, Russia, US, UK				hyperkalemia events	Not reported	
					AEs	Hypokalemia (k<2 mmol/L) was not registered in either SZC group or the placebo group	
NCT03303521	Thrice weekly HD, adults Exclusion: Hemoglobin <9 g/dl Pregnancies -N= 196 -Age (yr)=58 -Men (%)= 58.7% -Hispanic (%)= 52% -Cauntries= Japan, Russia, US, UK	SZC (5-10 mg) N=97	Placebo N=99	11 weeks	Delta K	Not reported	
					hyperkalemia events*	6/97 in SZC group vs 13/99 in placebo group	
					AEs	Total AEs: 40/97 vs 46/99 in placebo group GI disorders: 19/97 vs 17/99 in placebo group Infection: 12/97 vs 9/99 in placebo group SAEs: 7/9 vs 8/99 in placebo group	
NCT04847232	Recurrent serum K > 5.5 mmol/L in adults thrice weekly HD patients. Exclusion: -Pregnancies -Arrhythmias within 7 days before screening N= 2690 -Age (yr)=56 -Men (%)= NS Countries=Argentina, Austria, Brazil, Bulgaria, Canada, China, Czechia, Germany, Hungary, Italy, Japan, Malaysia, Mexico, Peru, Poland, Russian Federation, Slovakia, Spain, Taiwan, Thailand, Turkey, Ukraine, the UK, the USA and Vietnam	SZC (5-10mg) N= 1349	Placebo N=1341		Delta K	Not reported	Although the RCT results were completed, data are published but available partially on clinicaltrial.gov
					hyperkalemia events*	125 in SZC group vs 280 in placebo group	
					AEs	GI disorders: 251 vs 260 in placebo group Infection: 295 vs 252 in placebo group SAEs: 7/9 vs 8/99 in placebo group	
NCT04217590	China adults thrice weekly HD patients with preHD K >5.4 mmol/L Exclusion: Pregnancies -N= 134 -Age (yr)=55 -Men (%)= 49.3%	SZC (5-10 mg) N=67	Placebo N=67	11 weeks	Delta K	Mean difference between SZC and Placebo groups: –0.65 mmol/L (95% CI, –0.81 to –0.48; P < 0.001).	
					hyperkalemia events*	40/67 in SZC group vs 56/67 in placebo group	
					AEs	No severe hyperkalemia	

						has been registered hypokalemia 2/67 in SZC group vs 0/67 in placebo group AEs 42/67 in SZC group vs 44/67 in placebo group SAEs 6/67 in SZC group vs 8/67 in placebo group Infection 0 in SZC group vs 1/67 in placebo group Death 0 in SZC group vs 1/67 in placebo group GI 6/67 in SZC group vs 9/67 in placebo group	
SNCTP00000391 2	Swiss adults thrice weekly HD patients Exclusion: Pregnancies -N= 51 -Age (yr)=66 -Men (%)= 73% – Caucasian= 82% – Countries= Switzerland (multicentric)	Patiromer (8.4mg/die) N=51	Placebo N=51	8 weeks	Delta K	0.15+0.16 mmol//l in patiromer group vs 0.32+0.06 in placebo group	unblinded two-arm crossover RCTs
					hyperkalemia events*	17% in patiromer group vs 34% in placebo group	
					AEs		
SNCTP00000391 2	Swiss adults thrice weekly HD patients Exclusion: Pregnancies -N= 51 -Age (yr)=66 -Men (%)= 73% – Caucasia= 82% -Countries= Switzerland (multicentric)	Patiromer (8.4mg/die) N=51	SPS (15g) N=51	8 weeks	Delta K	0.15+0.16 mmol//l in patiromer group vs -0.3+0.05 in SPS group	unblinded two-arm crossover RCTs
					hyperkalemia events*	17% in patiromer group vs 12% in SPS group	
					AEs	GI 26% in Patiromer group vs 24% in SPS group	

Table 1. Summary of main characteristics and findings of the RCTs reviewed.

Study quality and risk of bias

Random sequence generation and allocation concealment were detailed in all trials. Three RCTs were double-blind, and one was open-label [15]. Blinding of participants, investigators and outcome assessors was specified in all studies. Attrition bias was low in all studies. The overall dropout rate was lower than 10 % for each study. Reporting bias was high in all studies. No other potential sources of bias were observed in the majority of studies (Figure 2).

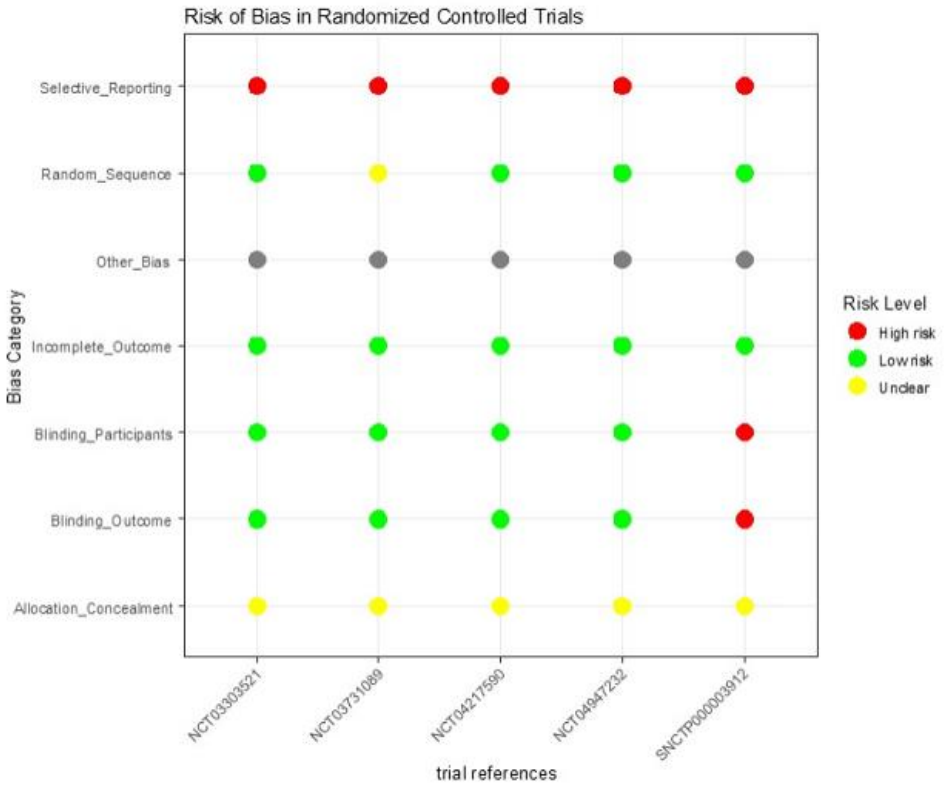

Figure 2. Risk of bias.

<u>Outcome data</u>

Mortality

The three studies that compared SZC to placebo reported 114 deaths in the placebo group and 120 in the SZC group, and data on mortality were available.

Differences in potassium level

Data on pre-HD potassium value as a continuous variable were reported by 3 studies [12, 14, 15]. a pooled analysis involving 432 patients, both SPS and SZC showed a significant reduction in serum potassium levels compared to placebo, with a mean difference of –0.6200 (95% CI: [–0.89 / –0.35]; $p < 0.0001$) and –0.68 (95% CI: [–0.81 / –0.55]; $p < 0.0001$), respectively. Conversely, no differences between Patiromer and placebo were found (mean difference -0.17, 95%CI [-0.41/0.07], p=0.16). This collective analysis was not affected by heterogeneity (I^2=0%) (Figure 3). The GRADE quality of this analysis was low after downgrading for the small number of the included studies.

Similarly, a meta-analysis comparing the new agent to the old agent/placebo showed a significant reduction of serum potassium in the new binders group (-0.47, 95%CI [-0.91/-0.02], p=0.04), but it revealed the highest heterogeneity (I^2=94%).

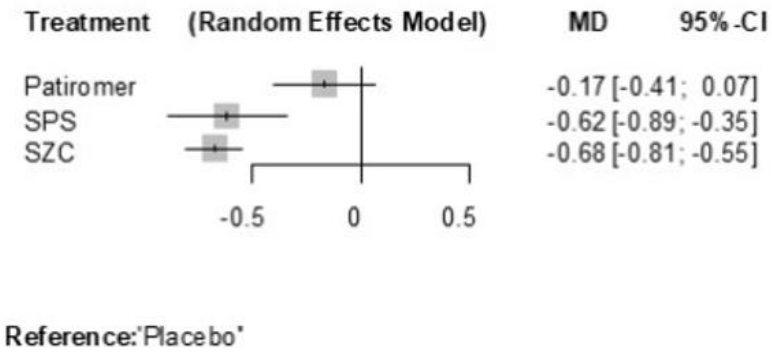

Figure 3. Forest plot. Comparison between potassium binders on mean difference in serum potassium.

Hyperkalemia events

Hyperkalemia has been reported in all studies. In this case, differences have been found in each group compared to placebo (Patiromer -0.791, 95%CI:[-1-0.078], p=0.030; SPS -0.998, 95%CI [-1-0.250], p=0.009; SZC -0.620, 95%CI [-1-0.220], p=0.002). According to these results, all treatments can avoid pre-dialysis hyperkalemia (K>5.5 mmol/L) compared to placebo (Figure 4). However, it revealed the highest heterogeneity (I^2=99%).

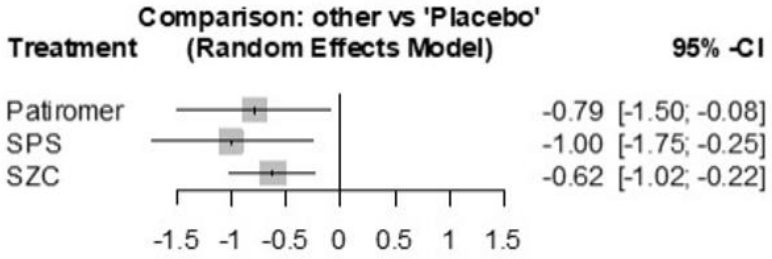

Figure 4. Forest plot. Comparison between potassium binders on hyperkalemia incidence.

Adverse Events

Adverse events cannot be statistically analyzed since they are not reported in each study and, where reported, as non-aggregable data. However, no difference has been found for total AEs in the included studies. The same can be assessed either for gastrointestinal events, for infectious or for SAEs. They are detailed in Table 1.

Discussion

Our analysis showed a significant difference in the management of hyperkalemia for each potassium binder compared to the only dialytic treatment with a lower pre-HD potassium concentration for SZC and SPS, without significant hypokalemia recurrence. At the same time, the recurrence of AEs not seem to be higher than only dialytic treatment.

Intradialytic hyperkalemia has been related to mortality and comorbidity, as well as hyperkalemia in conservative CKD [17–19]. Furthermore, the worst management of potassium worsens the intradialytic cardiovascular risk due to the speediest correction, almost obliged in patients with kalemia higher than 6.5 mmol/L. Although diet education, disionemia is not easy to manage in dialysis patients, often due to the lack of alimentary compliance [20].

The higher reduction of serum potassium in SZC patients than in patiromer patients can be easily explained by the speedier efficacy of the first. Indeed, SZC results are speedier in the first 48h than

patiromer, and serum potassium in dialysis patients needs management into the 48/72h without dialysis [21]. This difference in speed could be crucial in patients with acute hyperkalemia or those requiring rapid potassium normalization for urgent medical procedures.

As reported in the published protocol, highlighting possible gaps in actual knowledge was one of the aims and this systematic review revealed an important gap: the lack of sufficient RCTs. The crucial relevance of knowing the efficacy and the safety of these new drugs for clinicians should be juxtaposed with enough structured and dialysis-based RCTs. In particular, the lack of studies directly comparing the different potassium binders with each other makes it difficult to establish which is the optimal choice for dialysis patients. Future studies should focus on direct comparisons to provide more robust evidence.

The lack of a sufficient number of RCTs has been reported since the first decade of this century, highlighting the phenomenon of the “Invisible trial” [22]. Even though the Restoring Invisible & About palatability and adherence, no data available from RCTs exist even though the APPETIZE study ended in 2022 [23]. Abandoned Trials (RIAT) initiative on Cochrane evidence products showed a possible solution to this problem, trials for smaller populations are often not enough to generate evidence. Furthermore, the variability of dialysis patient populations, with different comorbidities and dialysis regimens, makes it difficult to generalize the results of existing studies. A personalized approach to hyperkalemia management is needed, taking into account the specific needs of each patient.

Furthermore, some studies compared the cost-effectiveness of new and old potassium binders, with evidence of slightly lower cost in the new K binders, often due to the reduction of hospitalisation [24, 25].

Nowadays, the small number of performed trials on dialysis patients represents the major limit of this systematic review. Indeed, the lack of RCT on hemodialysis did not allow us to give a clear opinion about the use of these drugs on dialysis patients, preventing us from fully understanding if there is one potassium binder more efficient or secure. It is a serious gap in our acknowledgement that needs to be solved. Also, hypokalemia, one of the major adverse events of these drugs, is not reported enough to compute a real risk. The lack of detailed data on adverse events, particularly hypokalemia, limits our ability to fully assess the safety profile of these drugs. Future studies should include a systematic assessment of adverse events, with particular attention to hypokalemia and its clinical consequences. One of the limitations of this systematic review is the highest heterogeneity, perhaps due to the small sample, the small number of included studies and the heterogeneity of the comparisons (SPS and Placebo).

Conclusion

In conclusion, according to our analysis, all potassium binders seem to have more efficacy than placebo and seem to have high safety. However, the knowledge gap cannot be solved due to the need for more RCTs, paying attention that all outcomes are evaluated and reported. Furthermore, it is essential that future studies focus on evaluating the long-term impact of these drugs on the quality of life of dialysis patients and on cardiovascular outcomes. The management of hyperkalemia must be integrated into a comprehensive approach to the care of the dialysis patient, taking into account their specific needs and comorbidities.

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