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Original Research

Protocol for systematic review and meta-analysis for randomized clinical trials on patiromer efficacy and safety in subjects with heart failure

Asim Ahmed Elnour, Abdulla Shehab

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Abstract

Background: We shall assess the efficacy and safety of patiromer in subjects with heart failure (HF) in randomized controlled trials (RCTs). **Methods:** The protocol has been developed supported the PRISMA-P checklist by using (PICO [population, intervention, comparators, and outcome]) items, for adult subjects with HF who have received patiromer in RCTs versus SZC or placebo to attain specific endpoint of control of hyperkalemia. The subjects with HF (population) receiving patiromer (intervention) are compared to placebo or other potassium binders (comparators), like sodium zirconium cyclosilicate (ZS-9, SZC, Lokelma®) for the non-inferiority or superiority in terms of effects on hyperkalemia (outcome) and alter in potassium serum levels. **Results:** Patiromer may provide an efficient treatment for hyperkalemia in subjects with HF receiving angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) and/or mineralocorticoids/aldosterone antagonists (MRA/AA). Patiromer may facilitate the clinical utility of RAAS inhibitors without discontinuation or interruption of therapy in subjects with HF. Patiromer may enable dose titration of AA without the danger of hyperkalemia. Patiromer is anticipated to halt recurrence of hyperkalemia in subjects with HF. **Conclusion:** Patiromer may provide safe and effective therapy for prevention, maintenance, management, and prevent recurrence of hyperkalemia in subjects with HF as compared to the other comparators.

Keywords: efficacy; heart failure; hyperkalemia; meta-analysis; patiromer, randomized controlled trials (RCTs); safety; sodium zirconium cyclosilicate; systematic review

BACKGROUND

Hyperkalemia, is defined as a serum potassium >5 mmol/L, which can keep on with life-threatening consequences like arrhythmia and sudden death.[1-4] Hyperkalemia are often categorized by severity: mild (potassium level 5 to six mmol/L); moderate (potassium level 6.1 to 6.9 mmol/L); and severe (potassium level 7 mmol/L and higher); or electrocardiogram [ECG] changes or symptoms occurring at any level. The marked elevations in serum potassium can cause fatal heart arrhythmias, heart conduction abnormalities, muscle weakness and paralysis (loss of muscle function). Therefore, management of hyperkalemia is crucial to halt life-threatening conditions from higher serum potassium. Hyperkalemia is observed in subjects with comorbidities.[5] like acute kidney injury (AKI) or chronic kidney disease (CKD) or heart failure (HF).[6] Nevertheless, hyperkalemia poses adverse consequences with increased risk of morbidity and mortality, independent of estimated glomerular filtration rate (eGFR) and comorbidities.[7,8] The long-term consequences of hyperkalemia on major cardiovascular events (MACE) and mortality outcomes, remains to be investigated.

Hyperkalemia is especially evident in subjects using renin-angiotensin-aldosterone system inhibitors (RAASi) like angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARBs) and aldosterone antagonist (AA).[9] Patiromer is a sodium-free non-absorbed oral potassium-binding polymer (patiromer, potassium-binding polymer and calcium-sorbitol counter-ion) that has improved efficacy and tolerability in lowering serum potassium levels. The drug binds potassium within the gastrointestinal tract (GIT) and enables fecal elimination of potassium (exchanges calcium ions for potassium in gut).[10] The Food and Drug Administration (FDA) approved patiromer calcium sorbitex (Patiromer-Veltassa®) in 2015 for chronic management of hyperkalemia (onset of 7–48 hours). Patiromer is approved within the United States of America (USA), Europe, and other countries for lowering serum potassium in adult subjects with hyperkalemia[11-12] with diabetes and/or with CKD with or without HF.

However, an identical conger sodium zirconium cyclosilicate (ZS-9) that exchanges sodium and hydrogen ions for potassium (more rapid onset of 1–6 hours) was FDA approved in 2018. Both drugs shouldn't be administered for emergency

Asim Ahmed ELNOUR*. (A A Elnour), shared first authorship, (PhD, MSc), Program of Clinical Pharmacy, College of Pharmacy, Al Ain University-Abu Dhabi campus, Abu Dhabi-UAE, AAU Health and Biomedical research facility, Al Ain University, Abu Dhabi, United Arab Emirates. asim.ahmed@aau.ac.ae
Abdulla SHEHAB. MBChB DipMEd MMEd Ph.D. CCST FACP FRCP FESC FACC FSCAI FAHA FSCCT. Professor of Cardiovascular Medicine. The Royal heart center, Burjeel royal hospital, and Mediclinic Hospitals. Chairman of Education Emirates Medical Association (EMA), Editor in chief Of New Emirates Medical Journal (NEMJ), Vice President of Gulf Intervention Society (GIS), Vice President of Emirates Cardiac Society (ECS), Vice President of Asia Pacific Cardiology (APC). heartdr123@googlemail.com

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management of severe hyperkalemia. Both drugs may offer better GIT adverse effects than former potassium binders. The latter (sodium/calcium polystyrene sulfonate [SPS] and calcium polystyrene sulfonate [CPS]) were reported to be related to colonic necrosis and perforation.[13]

In the UMBER trial (phase 2 multicenter, randomized, double-blind, placebo-controlled study) patiromer (8•4 g once daily) permitted spironolactone use and prevented hyperkalemia in subjects with CKD ([eGFR] 25 to <30 and 30–45 ml/min per 1.73 m2) and uncontrolled resistant hypertension.[14,15] This was also evident in subjects with HF with an eGFR but 60 mL/min per 1•73 m^2 or a history of hyperkalemia that provoked discontinuation of medications blocking the renin–angiotensin–aldosterone system (RAAS), like ACEi, ARBs and AA.

Rationale of the systematic review

Despite the provision of diverse modalities for the management of acute hyperkalemia, opportunities for the management of chronic hyperkalemia, and thereby maintaining ACEi, ARBs and AA clinical utility in subjects with HF, are scarce.

The management of hyperkalemia with traditional polystyrene sulphonate and loop diuretics (furosemide) is related to hypokalemia and other relevant adverse events (AEs). Current treatment options for HF like ACEi, ARBs, and AA are related to hyperkalemia. The hazard of hyperkalemia increases with subjects with CKD and diabetes in HF, limiting the optimal clinical utility of ACEi, ARBs and or AA.

The reduction of dose or discontinuation of ACEi, ARB or AA may have favorable impact on clinical outcomes for such populations of subjects with HF. Consequently, this indicated the need for brand new interventions with improved efficacy and safety to manage hyperkalemia related to HF. The therapy for subjects with HF deserves further exploration for optimum control of hyperkalemia. The efficacy and safety profile of a newly class called novel potassium-binders (patiromer) will assist in optimizing the management of hyperkalemia.

In the current protocol, we will assess subjects (participants) with any type/stage of HF or other cardiovascular diseases receiving patiromer (intervention) versus other potassium binder drugs (comparators) like sodium zirconium cyclosilicate. The non-inferiority or superiority of patiromer are going to be appraised in terms of prevention/control of hyperkalemia and maintenance of normokalemia (outcome). Furthermore, the safety profile for patiromer are assessed as compared to comparators. The differences aligned between patiromer and the other therapies are reported based on the efficacy, and safety profile.

Objective of the review

We shall assess the efficacy and safety of patiromer in subjects with HF using data from published phase II/III randomized controlled trials (RCTs). The aim of this protocol is to explore the pros and cons of patiromer as a completely unique potassium binder in terms of efficacy and safety that delineate its clinical utility in terms of prevention and improving control of hyperkalemia in subjects with HF. The most objective are going to be to assess the efficacy and safety of patiromer in subjects with HF using the available evidence from published RCTs.

METHODS

We will follow the Cochrane library instructions in developing this protocol for systematic review and meta-analysis of the efficacy and safety profiles of patiromer. The primary end-points are going to be clinical responses and treatment improvements in hyperkalemia measured at the tip of intent-to-treat (ITT). This protocol was registered on PROSPERO (Unique ID number CRD42022318564) and was made available fully on the official PROSPERO website, (https://www.crd.york.ac.uk/prospero/#myprospero). The protocol has been developed supported the PRISMA-P checklist.[16] We decide to document important protocol amendments.

Eligibility criteria

We will conduct a scientific review and meta-analysis (participants, interventions, comparisons and outcomes [PICO], Figure 2) of clinical trial and clinical test RCT-s for subjects with HF who have received patiromer. The inclusion criteria are going to be the following: subjects diagnosed with HF (all classes), adult ≥18 years, both gender, history of hyperkalemia, use of ACEi/ARBs or aldosterone antagonist (AA) like spironolactone or eplerenone, hospitalized and non-hospitalized, subjects receiving intervention drug (patiromer) versus comparator, RCT design (phase II or phase III) trials published in English language, full text, primary outcome reported status of hyperkalemia (change in serum potassium level), conducted on humans within the last years (2015-2022). The exclusion criteria are non-RCT, quasi-experiment, trials with primary outcome aside from the efficacy of patiromer, RCT with post-analysis studies, dose-finding RCT-s, retrospective trials, trial on pediatric population, and trials that are conducted on pregnant and transplant subjects. We also exclude trials not fully text, healthy subjects, extension trials, animal studies and non- English language studies. The categories of studies are collected via conducting the search on the Google Scholar, CINAHL, Cochrane library, PubMed (NCBI/NLM), and EMBASE for published RCT in English language reporting the efficacy and safety of patiromer. We are going to conduct the rummage around for published RCT (full text) within the English reporting the efficacy and safety of patiromer on RCTs (phase II and III). The setting is going to be out/in patients (hospitalized or not hospitalized). Trials are retrieved from the year 2015 to the year 2022.

Types of participants, interventions, comparisons and outcomes the participants were subjects diagnosed with HF (any class), and receiving patiromer (intervention) compared to placebo and comparators like sodium zirconium cyclosilicate (comparators) with the end result of prevention, control, maintenance and management of any degree of documented hyperkalemia (change in potassium serum level). The databases are going to be retrieved between the years 2015 to 2022 with the MeSH search terms:

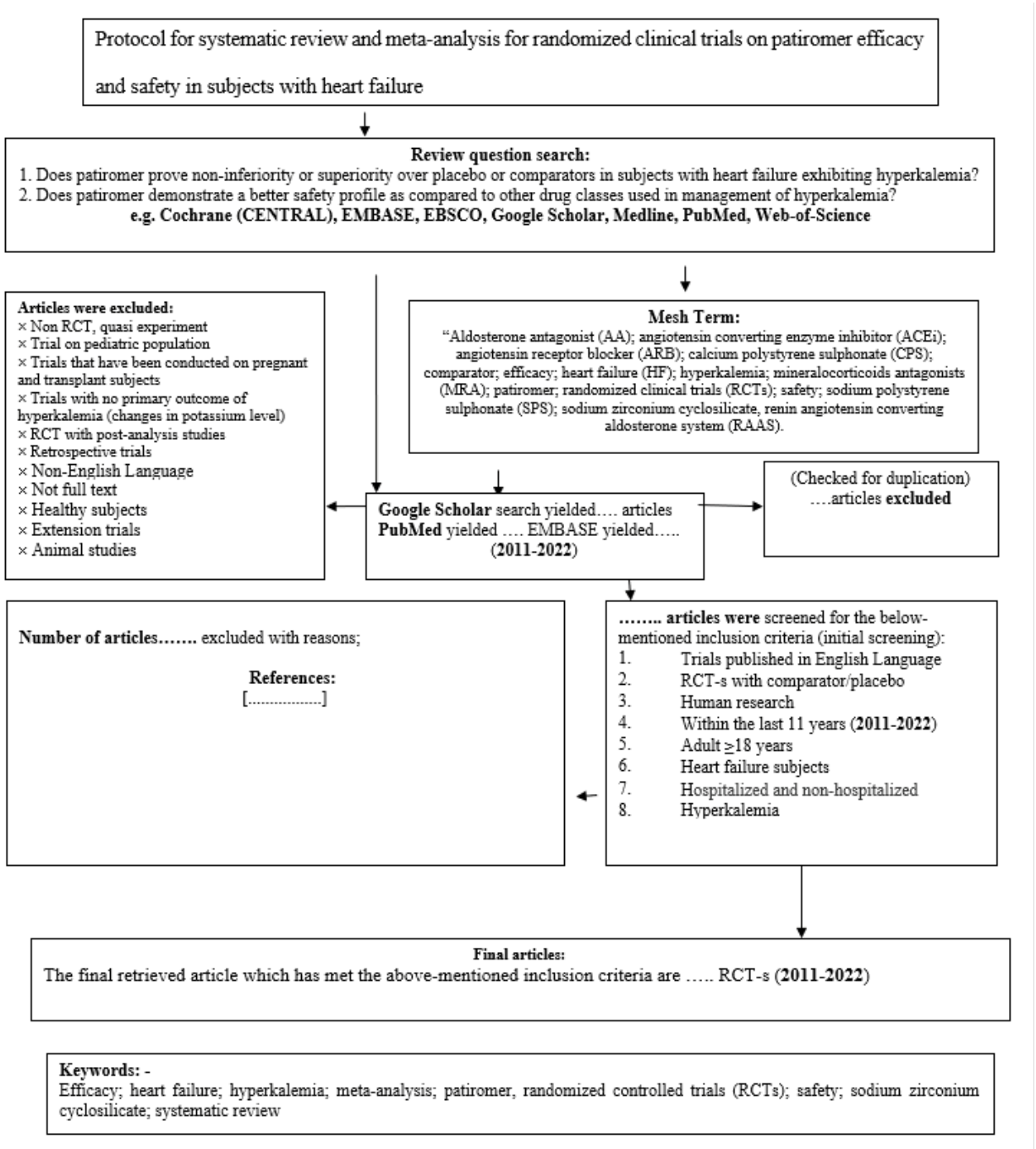

Figure 1. Flow diagram of included and excluded articles in the current systematic review

Method: Randomized controlled trial with placebo and/or active-comparator

Participants: Subjects with heart failure; population size and the number of randomized subjects in each arm of the trial; age range (mean ± SD); BMI (mean ± SD); and relevant baseline clinical characteristics of subjects recruited.

Interventions Patiromer (different doing) versus the comparator (doses of other comparators.

Comparators placebo or sodium zirconium cyclosilicate.

Outcomes:

1. The primary outcome measure will be the clinical improvement in hyperkalemia at the end of treatment in the ITT population (changes in serum potassium from baseline).

2. The differences in treatment (effect size) between the intervention drug (patiromer) and placebo/comparators (sodium zirconium cyclosilicate) as non-inferiority or superiority will be reported.

- **The magnitude of difference between patiromer and the placebo or the comparator will be of high priority.**

3. Secondary outcomes: treatment emergent adverse events like (**mild-to-moderate hypomagnesemia**) due to which some patients have discontinued the treatment and/or withdrawn from the trial.

Key words:
efficacy; heart failure; hyperkalemia; meta-analysis; patiromer, randomized controlled trials (RCTs); safety; sodium zirconium cyclosilicate; systematic review

Figure 2. Characteristics of included articles (PICO)

"Aldosterone antagonist (AA); angiotensin converting enzyme inhibitor (ACEi); angiotensin receptor blockers (ARBs); calcium polystyrene sulphonate (CPS); comparator; efficacy; heart failure (HF); hyperkalemia; mineralocorticoids antagonists (MRA); patiromer; randomized clinical trials (RCTs); safety; sodium polystyrene sulphonate (SPS); sodium zirconium cyclosilicate (SZC), renin angiotensin converting aldosterone system (RAAS), [Figure 3].

The selection criteria are going to be patiromer alone or together with any other cardiovascular medications. The chosen trials citations are going to be imported into systematic review managers/software (COVIDENCE https://www.covidence.org/ or RAYYAN https://rayyan.qcri.org/welcome). Additionally, we will use manual searched citations with the identical MeSH terms and conditions.

The search method for identification of RCTs is conducted on known data-bases by using the predefined Cochrane library-approved structured modified forms. The relevant data-sets are collated using the predefined Cochrane library-approved structured modified forms. The draft of the search strategy used for one electronic information service including planned limits was shown in [diagram flow chart, Figure 1].

The trials, information sources (data) and study records: the gathering of information and therefore the data analysis are via the access of full articles, screened and reviewed content with predefined checklist (Cochrane templates) developed and modified specifically to align with the strict inclusion criteria. We will follow the checklist that has been adapted to be used with protocol submissions to Systematic Reviews from Moher.[17]

The selection process for the trials will be conducted by all the authors based on the inclusion and exclusion criteria. The methods used for identifying published trials on the official websites are going to be structured, predefined, and specific MeSH terms for identifying eligible trials for inclusion within

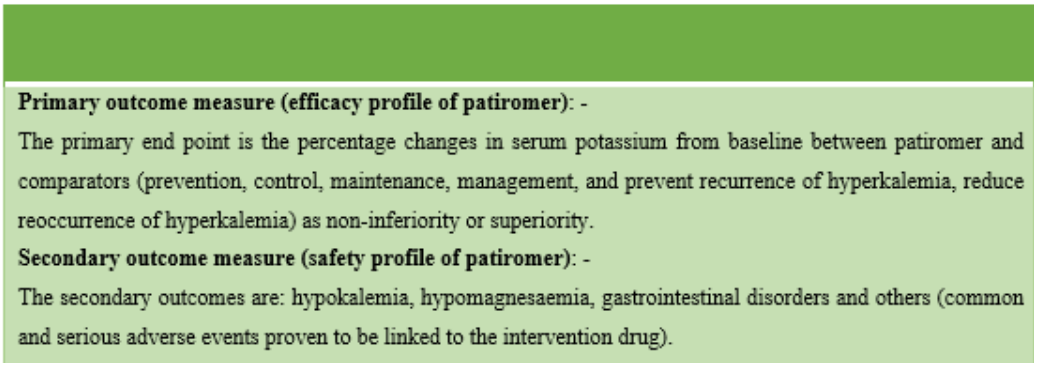

Figure 3. The protocol summary of outcomes measures

the current systematic review and meta-analysis. We will follow a strict checklist with pre-specified inclusion and exclusion criteria to make sure that the identified trials are as per the present systematic review and meta-analysis methodology. The authors (A Elnour, and A. Shehab) will countercheck the method and repeat the search terms individually and can compare the attempts, whereby, discrepancies are resolved with discussions in reporting. The chosen trials are further reviewed by all authors, are double-checked by other different authors, and can be verified by repeating the method mentioned above.

The final double checking and verification will make sure that the chosen trials precisely met the ultimate relevant information and primary outcome needed for this systematic review and meta-analysis. The kind of HF, trial duration, follow-up duration and primary end point (outcomes measures) are going to be shown within the supplementary material. The trials registration, DOI, author details, and results of the end result of the respective included RCT are going to be presented. The safety outcomes (AEs) for the trials included within the current systematic review are going to be presented in tables.

Data extraction and synthesis will strictly follow the well-liked Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, which can be accustomed abstract data and assess quality and validity from original RCTs and supplementary materials. Data extraction (selection and coding) are performed on the relevant variables from the initial RCT and supplementary materials. the info extraction will contain trial registration, study country, number of involved countries (trial centers), class of HF, category of hyperkalemia, mean dose of patiromer, history of hyperkalemia, recurrent hyperkalemia, trial duration, follow-up duration, withdrawal, the efficacy data, primary endpoint (outcomes measures), the safety outcomes (AEs) for the included trials. The above data are collated with structured forms, verified, reviewed, double-checked, and recorded in final format (Cochrane templates) and can be transferred into the RevMan 5.4 data-base.

Data items are defined for all variables that data are sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications. PICO items: we are going to conduct a systematic review and meta-analysis (participants, interventions, comparisons and outcomes [PICO]) of phase II and III RCT-s for subjects with cardiovascular diseases including HF who have received patiromer. Subjects both gender with any sort of HF (participants) and receiving patiromer (intervention) for management of HF randomized versus comparator (comparison). The primary efficacy endpoints are going to be the prevention, control, and management of hyperkalemia (outcomes) [Figure 2].

Outcome measures

The primary outcome measures are clinical responses and treatment improvement of hyperkalemia measured using the potassium level at the top of ITT population (change in potassium serum level). The differences in treatment between the intervention drug (patiromer) and comparators (placebo/SZC) as non-inferiority or superiority are going to be reported. The secondary outcome measures defined as safety (development of AEs) are assessed by the amount (affected individuals) and level of hyperkalemia, other AEs and serious adverse events (SAE), withdrawals due to lack of efficacy or AEs, overall withdrawals, and death [Figure 3]. The measure of effect is going to be expressed as relative risks, odds ratios, risk difference, and/or number needed to treat (NNT). The magnitude of difference between patiromer and the comparator are going to be of high priority.

Methods for quality assessment of studies: assessment of risk of bias (quality)

The risk of bias in individual studies (quality of RCT-s and assessment of risk of bias)

The quality of the RCT-s (both at study level and outcome) are assessed with a five-point scale to attenuate and avoid bias within the inclusion of relevant RCT-s.[18] The tactic that may be followed as per the risk of bias tool, version 2.0 (Cochrane) are used for the chance risk bias assessment.

Meta-bias: Publication bias is defined as the failure to publish the results of a study on the

bases of the direction or strength of the study findings. Within the current systematic review and meta-analysis we'll use a funnel plot to test for the existence of publication bias or systematic heterogeneity within the studies taken for analysis. We will use Egger's regression for quantifying funnel plot

asymmetry or Rosenthal's fail-safe number or "fail-safe N method". We will ensure to avoid selective reporting within trials by not excluding non-significant study outcomes and by describing structured search criteria supported published methodologies.

Data synthesis

The purpose of this systematic review and meta-analysis is to assess, compare, and explore the efficacy and safety of patiromer; versus other comparators in terms of the prevention, control, maintenance, and management of hyperkalemia. Data synthesis (quantitative, qualitative, descriptive, inferential statistics and meta-analysis) are going to be performed. The quantitative synthesis for the variation in effects (clinical heterogeneity) within the included RCTs are in any respect levels of trials (relevant population level, the intervention level, outcomes level (ITT: clinical success of control of hyperkalemia, superiority/inferiority, and statistical magnitude of difference) and planned summary measure.

RevMan version 5.4 (or comprehensive meta-analysis [CMA] are used for meta-analyses with consistency) to combine and explore data from respective trials. The clinical outcomes are going to be assessed with the random effects model (e.g. I2 index, tau squared, and also the Q-test P value, meta-regression for heterogeneity) with the Mantel-Haenszel (MH) method (pooled estimates of odds ratio (OR) with 95% confidence interval [CI]), independent pooling of information to scale back the chance of bias, and funnel plots and Egger's regression test of funnel plot. Other measures which will be used, like sensitivity analysis to reveal inconsistency and forest plots to point out the relative effect size of the intervening drug/comparator for every clinical endpoint (pre-specified and expected outcomes freed from selective reporting).

The variations of effects (heterogeneity) within the RCTs included within the current systematic review and meta-analysis comprised a group of clinical covariates (clinical heterogeneity) from the relevant population level (matched groups of HF), the intervention level (intervention-patiromer vs. comparator-SZC/placebo), outcomes level (ITT: clinical success of management in hyperkalemia). Appropriate data for quantitative synthesis, are reported as planned summary measures (handling and mixing data from studies), including exploration of consistency (e.g., I2, Kendall's tau).

Analysis of subgroups or subsets

The proposed additional analyses: we will conduct meta-analysis within the current systematic review and report the sensitivity analysis. We also plan a structured synthesis of data and comparison between the inferences within the respective trials (e.g., sensitivity and/or subgroup analyses and/or meta-regression). The proposed additional analyses are structured synthesis of data and comparison between the inferences within the respective trials (e.g., sensitivity and/or subgroup analyses [those with history of hyperkalemia] and/or meta-regression). Data are going to be pooled using random-effects models.

Confidence in cumulative evidence: we are going to assess the strength of evidence within the final ends up in a GRADE Evidence Profile (GEP). This GEP will contain the PICO question; the sort and number of trials included; the amount of participants within the trials; the effect sizes and their confidence intervals, and the grading of the standard quality of the evidence and its starting level and reasons for upgrading or downgrading the standard quality. The standard quality of evidence for all outcomes for the included trials are judged using an adaptation of the GRADE methodology assessment.[19-21] This can be assessed crosswise within the domains of risk of bias (consistency, directness, precision and publication bias). The treatment estimates are going to be summarized by random effects meta-analysis and expressed as relative risk (RR) or mean difference (MD), with 95% CI. Evidence certainty assessed using GRADE processes.

The full electronic search strategy within the database, limits of search used, check of duplication as per the PRISMA guidelines, are going to be shown in; [Figure-diagram 2]. The PRISMA chart [Figure 1] and therefore the complete PRISMA-P form are provided within the supplementary material, [Appendix I].

Literature overview

The versatile remedies available for the management of hyperkalemia weren't supported by any superior evident treatment over the other. The literature evident regarding fluid hyper-alimentation, intravenous calcium chloride/gluconate, sodium bicarbonate, and loop diuretics are either weak or lacking. The insulin-glucose infusion is the most effective management in lowering serum potassium, while beta-agonists (salbutamol/terbutaline) is also effective in some cases. Potassium-exchange resins (SPS/CPS) are often used, but their efficacy within the short-term is insufficient due to sluggish onset of action.

This protocol is meant to present the systematic review results and therefore the meta-analysis regarding the employment of patiromer in management of hyperkalemia in subjects with HF (based on PICO comparison between the included trials). The results will contain a scientific systematic critical evaluation of the included RCT-s conducted on patiromer in terms of the amount of the population (characteristics) those with/without history of hyperkalemia, degree of severity, the dosing of intervention (patiromer), duration of treatment, the comparators, andthe main outcome measures (changes in hyperkalemia). The necessary elements of PRISMA are strictly followed to report the systematic review. The meta-analysis are reported per the Cochrane guidelines for synthesis of RCT-s and all forms will be based on the quality measures as per the validated Cochrane templates.

The PEARL-HF (2011) is a placebo double blind phase III RCT enrolled 105 subjects with HF with or without CKD initiating spironolactone [25] receiving patiromer 25.2 g (fixed dose) to halt hyperkalemia. Patiromer 15 g twice every day for 28 days reduced mean serum potassium (primary end point), by 0.22 mEq/L while increased by 0.23 mEq/L with placebo on day 28 ($P < 0.001$). In subgroup analysis, those with hyperkalemia

history didn't show changes in serum potassium (P =0.058). Patiromer effectively maintained serum potassium at 0.45 to 0.72 mmol/L lower than placebo while allowing spironolactone dose titration in additional patients (91% versus 74%, P =0.019).

The incidence of hyperkalemia (potassium > 5.5 mEq/L) was less common with patiromer than placebo (7% versus 25%; P =0.015), whereas hypokalemia incidence (6% versus 0%; P =0.094) was similar. Hypomagnesaemia (Mg <1.8 mg/dL) occurred more frequently with patiromer than placebo (24.0% versus 2%; P =0.001). The foremost common AEs were GIT disorders, which occurred in 21.0% versus 6.0% with patiromer and placebo, respectively. Events were noted as mild to moderate and didn't cause a major difference in drug discontinuation rate: 7.0% patiromer versus 6.0% placebo. Four severe AEs, including worsening coronary artery disease (CAD), atrial fibrillation (AF), and non–ST-elevated myocardial infarction (STEMI), were noted within the patiromer group. Further, two SAE, gout and sudden cardiac arrest, occurred within the placebo group. However, no SAE were identified as secondary to patiromer.[22]

OPAL-HK (2015) pre-specified analysis was a single-blind, placebo-controlled, parallel group, (compared subgroup of subjects with CKD and with HF compared those results with CKD without HF). The sub-analysis involved 243 subjects with CKD with moderate to severe hyperkalemia (102 [42.0%] with HF and 141 [58%] without HF). Within the initial trial phase (no placebo) 76.0% of subjects with HF achieved a serum potassium within the target range (≥3.8 mEq/L to <5.1 mEq/L) (95% CI 69–84). Within the randomized withdrawal phase median change in serum potassium from baseline to week 4 was 0.74 mEq/L for subjects with HF taking placebo and 0.10 mEq/L for those taking patiromer, for a between-group difference of 0.64 mEq/L (95% CI 0.29–0.99; P < 0.001). The authors concluded that in subjects with CKD and HF, patiromer may have a very important role in initiating and maintaining RAASi and also the potential for subsequent minimization of cardiovascular death.[23]

In the original OPAL-HK placebo controlled trial (2015) for subjects with CKD (receiving RAASi) with hyperkalemia, patiromer decreases serum potassium levels and, reduces the recurrence of hyperkalemia.[24] In 2018, an open-label 8-week study enrolled 63 subjects with HF and CKD, serum potassium 4.3-5.1 mEq/L, and having chronic HF, investigated the effectiveness of a lower starting dose of patiromer (16.8 g/day) followed by individualized titration to stop hyperkalemia and hypokalemia when commencing spironolactone. Serum potassium was maintained within the target range (57, 90.5%) even during up-titrated spironolactone 50 mg/day, with a low incidence of hyperkalemia, hypokalemia, and hypomagnesaemia.[25]

DIAMOND (2021) may be a phase IIIb multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study. It assessed the results of patiromer compared with placebo on serum potassium levels in subjects with HF receiving RAASi medications. The results of the trial remain to be published (outcome is mean change from baseline in serum potassium levels).[26]

The AMETHYST-DN (2015) was a phase II clinical trial on patiromer (8.4, 12.6, or 16.8 g twice daily). It included 324 subjects with type 2 DM and CKD and who were on a minimum of one RAASi (4-week run-in period [79 subjects]; an 8-week treatment phase, and a 44-week maintenance phase). The normokalemia at each scheduled visit was achieved in 77.4% to 95.1% of subjects. All subjects remained on a RAASi throughout 52 weeks. Patiromer discontinuation due to AEs occurred in 9.2% of subjects.[27]

DISCUSSIONS

The efficacy and safety of patiromer and SZC (ZS-9) were compared in meta-analysis (phase II [2 trials] and III [four trials]) clinical trials for the treatment of hyperkalemia. Patiromer reduced potassium levels significantly −0.70 mEq/L (95% [CI] −0.48 to −0.91 mEq/L) at 4 weeks. On day 3 after patiromer potassium change was −0.36 mEq/L (range of ordinary deviation 0.07–0.30). For ZCS the change in potassium was −0.67 mEq/L (95% CI −0.45 to −0.89 mEq/L). By one hour after SZC, change in potassium was −0.17 mEq/L (95% CI −0.05 to −0.30). The adverse effects reported for patiromer were more GIT (7.6% constipation; 4.5% diarrhea) and (7.1% hypomagnesaemia), whereas for SZC AEs reported were urinary tract infections (1.1%) and edema (0.9%). The meta-analysis concluded that considering time-dependent effects, ZS-9 may provide a stronger option in treating acute hyperkalemia.[28]

A Cochrane data-base systematic review and meta-analysis investigated the evidence of effectiveness and tolerability of potassium exchange resins among people with CKD to assess the advantages and harms of potassium binders for treating chronic hyperkalemia among adults and children with CKD. A total of 1849 adult subjects were included in 15 trials (12 trials included subjects not requiring dialysis and three trials where subjects were treated with hemodialysis-HD), of which three were cross-over designs. The potassium binders included calcium polystyrene sulfonate, sodium polystyrene sulfonate (SPS), patiromer, and SZC. The study duration varied from 12 hours to 52 weeks (median 4 weeks). The mean study age ranged from 53.1 years to 73 years. No studies evaluated treatment in children. Ten studies (1367 randomized participants) compared a potassium binder to a placebo.

Patiromer or SZC may make little or no difference to death (any cause) (4 studies, 688 participants: RR 0.69; 95% CI 0.11, 4.32; I2 = 0%; low certainty evidence) in CKD. Potassium binders had uncertain effects on nausea (3 studies, 229 participants: RR 2.10, 95% CI 0.65, 6.78; I2 = 0%; low certainty evidence), diarrhea (5 studies, 720 participants: RR 0.84, 95% CI 0.47, 1.48; I2 = 0%; low certainty evidence), and vomiting (2 studies, 122 participants: RR 1.72, 95% CI 0.35 to 8.51; I2 = 0%; low certainty evidence) in CKD. Potassium binders may lower serum potassium levels (at the end of treatment) (3 studies; 277 participants: MD -0.62 mEq/L, 95% CI -0.97, -0.27; I2 = 92%; low certainty evidence) in CKD and HD. Potassium binders had uncertain effects on constipation (4 studies, 425

participants: RR 1.58, 95% CI 0.71, 3.52; I2 = 0%; low certainty evidence) in CKD. Potassium binders may decrease systolic vital sign (BP) (2 studies, 369 participants: MD -3.73 mmHg; 95%CI -6.64 to -0.83; I2 = 79%; low certainty evidence) and diastolic BP (one study) at the tip of the treatment. CPS may make little or no difference to serum potassium levels at end of treatment, compared to SPS (2 studies; 117 participants: MD 0.38 mEq/L, 95% CI -0.03 to 0.79; I2 = 42%, low certainty evidence) [29]. The summary of findings for this Cochrane systematic review and meta-analysis was summarized in.[29] (Appendix II).

The role of patiromer has evolved within the previous couple of years with successful control of hyperkalemia, improved clinical outcomes (changes in potassium levels). Hence, our current systematic review and meta-analysis will provide highly relevant findings of evidence for the role of patiromer within the management of HF. Patiromer may provide new approaches to the gap knowledge and limitations in management of hyperkalemia in subjects with HF.

This will permit practitioners and prescribers to form informed decisions about the foremost efficacious and safest regimen for the management of hyperkalemia in subjects with HF and co-existing CKD/diabetes. The findings of this systematic review and meta-analysis will contribute to inform evidence-based clinical practices and boost the gained knowledge of patiromer therapy. Furthermore, the findings will help to inform researcher and expand future subsequent research, and evaluation of additional population interventions; for example use of patiromer in subjects with HF and diabetes.

The work will provide evidence by synthesis of well-designed and robust RCT-s conducted on one among the efficacious and safest potassium binders. We shall minimize the publication bias and reporting bias with the utilization of published technical methods as mentioned previously within the protocol. We will share our findings with academia and cardiology societies worldwide.

Patiromer may provide better efficacy than former potassium binders in lowering elevated potassium. Patiromer is also superior to placebo in maintaining normal potassium levels in subjects with HF and CKD receiving RAASi (lasting up to 52 weeks). It seems that patiromer offers better control of hyperkalemia that allows up-titration of RAASi therapy. However, recently, new trials are specializing in clinically-relevant cardiac complications or death as tangible endpoints.

The main findings within the systematic review regarding the clinical utility of patiromer within the prevention, control, maintenance, and management of hyperkalemia may depend on four

main subpopulations with HF of interest: -

1. Subjects with HF and diabetes on RAASi therapy (ACEi/ARB or AA or both).

2. Subjects with HF with reduced ejection fraction (HFrEF) and CKD on RAASi therapy (ACEi/ARB plus AA).

3. Subjects with decompensated HF on dual RAASi therapy.

4. Subjects with HF who require up-titration of RAASi therapy.

Key messages

The following are clinical features of patiromer within the management of hyperkalemia: -

Patiromer efficacy profile

Patiromer reduces serum potassium levels and therefore the hazard of recurrent hyperkalemia in subjects with CKD and/or diabetic nephropathy with or without HF.[23,24,27] It allows continued and up titration of RAASi use in most subjects with CKD, or diabetes and/or HF [25]. It maintains normokalemia in subjects with HF and a propensity for hyperkalemia. It enables concomitant administration and up titration of aldosterone antagonist (spironolactone/eplerenone).

Patiromer safety profile

Patiromer is usually well tolerated; low hazard of hypokalemia (in comparison to other remedies e.g. SZC). Patiromer has better gastrointestinal tract (GIT) adverse effects. Mild-to-moderate hypomagnesaemia (Mg < 1.8 mg/dL) occurred more frequently with patiromer (PEARL-HF trial). Patiromer may decrease the GI absorption of other drugs. Therefore, concomitant oral medications should be taken a minimum of 6 hours before or after patiromer administration. The evidence on safety of patiromer in CKD continues to be limited according to a recent Cochrane systematic review.[29]

CONCLUSION

We will present the systematic review and the meta-analysis results supported by the PICO comparison between the included RCTs. The results will contain a scientific systematic critical evaluation in terms of the quantity of the population (characteristics of subjects with HF), the dosing of intervention (patiromer-potassium binder), the comparators (SZC), and the main outcome measures (prevention, control, maintenance, and management of hyperkalemia) with resultant change in potassium serum level.

This protocol will report the aligned differences within the efficacy and safety of patiromer (intervention) as compared to the comparators (SZC) in subjects with HF exhibiting hyperkalemia with or without CKD or diabetes.

ABBREVIATIONS

AA: aldosterone antagonist

AEs: adverse events

ACEi: angiotensin-converting enzyme inhibitor

AKI: acute kidney injury

ARB: angiotensin receptor blocker

CI: Confidence interval

CPS: calcium polystyrene sulfonate

CENTRAL: Cochrane Central Register of Controlled Trials

CI: confidence interval

CKD: chronic kidney disease

CMA: comprehensive meta-analysis

FDA: The Food and Drug Administration

ECG: electrocardiogram

eGFR: estimated glomerular filtration rate

FDA: Food and Drug Administration

GEP: GRADE Evidence Profile

GIT: gastrointestinal tract

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HF: heart failure

HFrEF: heart failure with reduced ejection fraction

ITT: intent-to-treat

MACE: major cardiovascular events

MD: mean difference

MeSH: Medical Subject Headings

MH: Mantel-Haenszel

MRA: Mineralocorticoids receptor antagonist

NCBI: National Center of Biotechnology Information

NLM: National Library of medicine

OR: Odds ratio

PICO: population, intervention, comparators, and outcome

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

RAASi: renin angiotensin aldosterone system inhibitor

RCTs: Randomized controlled trials

RR: relative risk

SAEs: Serious adverse events

SPS: sodium/calcium polystyrene sulfonate

UAE: United Arab Emirates

SZC: sodium zirconium cyclosilicate (ZS-9)

References

1. Rosano GMC, Tamargo J, Kjeldsen KP, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J. 2018;4(3):180-8. https://doi.org/10.1093/ehjcvp/pvy015
2. Kumar R, Kanev L, Woods SD, et al. Managing hyperkalemia in high-risk patients in long-term care. Am J Manag Care. 2017;23(2 Suppl):S27-36.
3. Long B, Warix JR, Koyfman A. Controversies in management of hyperkalemia. J Emerg Med. 2018;55(2):192-205. https://doi.org/10.1016/j.jemer med.2018.04.004
4. Nunez J, Bayes-Genis A, Zannad F, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. Circulation. 2018;137(13):1320-30. https://doi.org/10.1161/circulationaha.117.030576
5. Collins AJ, Pitt B, Reaven N, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46(3):213-21. https://doi.org/10.1159/000479802
6. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nat Rev Nephrol. 2014;10(11):653-62. https://doi.org/10.1038/nrneph.2014.168
7. Seliger SL. Hyperkalemia in patients with chronic renal failure. Nephrol Dial Transplant. 2019 Dec 1;34(Suppl 3):iii12-8. https://doi.org/10.1093/ndt/gfz231
8. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009 Jun 22;169(12):1156-62. https://doi.org/10.1001/archinternmed.2009.132
9. Georgianos PI, Agarwal R. Revisiting RAAS blockade in CKD with newer potassium-binding drugs. Kidney Int. 2018;93(2):325-34. https://doi.org/10.1016/j.kint.2017.08.038
10. Tzamaloukas AH, Glew RH. Efficacy and safety of patiromer in prevention and treatment of hyperkalemia. J Sympt Signs. 2013;2(6):475-484.
11. Veltassa® (patiromer) for oral suspension [package insert]. Redwood City, CA: Relypsa, Inc. 2018. https://www.veltassa.com/pi.pdf
12. European Medicines Agency. Veltassa (patiromer). https://www.ema.europa.eu/en/medicines/human/EPAR/veltassa. Updated 19 June 2019. Accessed 30 April 2022
13. Sterns RH, Rojas M, Bernstein P, et al. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol. 2010;21:733-5. https://doi.org/10.1681/asn.2010010079
14. Agarwal R, Rossignol P, Garza D, et al. Patiromer to Enable Spironolactone Use in the Treatment of Patients with Resistant Hypertension and Chronic Kidney Disease: Rationale and Design of the AMBER Study. Am J Nephrol. 2018;48(3):172-180. https://doi.org/10.1159/000492622

15. Rajiv Agarwal, Patrick Rossignol, Jeffrey Budden, et al. Patiromer and Spironolactone in Resistant Hypertension and Advanced CKD: Analysis of the Randomized AMBER Trial. White Kidney360. 2021;2 (3):425-34; https://doi.org/10.34067/KID.0006782020
16. Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349(jan02 1):g7647.
17. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1. https://doi.org/10.1186/2046-4053-4-1
18. Jadad AR, Moore RA, Carroll D,et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. https://doi.org/10.1016/0197-2456(95)00134-4
19. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6. https://doi.org/10.1016/j.jclinepi.2010.07.015
20. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94. https://doi.org/10.1016/j.jclinepi.2010.04.026
21. Morgan RL, Thayer KA, Bero L, et al. GRADE: Assessing the quality of evidence in environmental and occupational health. Environ Int. 2016;92-93:611-616. https://doi.org/10.1016/j.envint.2016.01.004
22. Pitt B, Anker SD, Bushinsky DA,et al . PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011;32:820-8. https://doi.org/10.1093/eurheartj/ehq502
23. Pitt B, Bakris GL, Bushinsky DA, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. Eur J Heart Fail. 2015;17(10):1057-5. https://doi.org/10.1002/ejhf.402
24. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211-21. https://doi.org/10.1056/NEJMoa1410853
25. Pitt B, Bushinsky DA, Kitzman DW, et al. Evaluation of an individualized dose titration regimen of patiromer to prevent hyperkalaemia in patients with heart failure and chronic kidney disease. ESC Heart Fail. 2018;5(3):257-66. https://doi.org/10.1002/ehf2.12265
26. Bolaños JA, Seliger SL. Recurrent Hyperkalemia in Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Treatment: Stuck between a Rock and a Hard Place. Clin J Am Soc Nephrol. 2021;16(3):345-7. https://doi.org/10.2215/CJN.00950121
27. Bakris GL, Pitt B, Weir MR, et al. AMETHYST-DA Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA. 2015;314:151-161. https://doi.org/10.1001/ jama.2015.7446
28. Meaney CJ, Beccari MV, Yang Y, et al. Systematic review and meta-analysis of patiromer and sodium zirconium cyclosilicate: a new armamentarium for the treatment of hyperkalemia. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2017;37(4):401-1. https://doi.org/10.1002/phar.1906. 10.1002/phar.1906
29. Natale P, Palmer SC, Ruospo M, et al. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. Cochrane Database Syst Rev. 2020;6(6):CD013165. https://doi.org/10.1002/14651858.CD013165.pub2

APPENDIX 1

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review			3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			-
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			50,179
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author			11-60
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review			33-39
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			182
Support					
Sources	5a	Indicate sources of financial or other support for the review			42-47
Sponsor	5b	Provide name for the review funder and/or sponsor			42-47
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			42-47
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known			143-164
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)			165-171, 203-207
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review			183-207
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage			208-229
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated			224-228
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review			230-264
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)			230-264
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators			230-264
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications			265-273
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale			274-284

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis			285-296
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized			297-344
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)			297-344
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)			297-344
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned			297-344
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)			297-344
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)			344-397

APPENDIX II

The summary for the Cochrane systematic review and meta-analysis [29]: -

Cardiovascular evidence: -

There was no difference between high-dose and low-dose patiromer for death (sudden death) (one study), stroke (one study), myocardial infarction (one study), or constipation (one study).

One cardiovascular death was reported with potassium binder in one study, showing that there was no difference between patiromer or sodium zirconium cyclosilicate and placebo for cardiovascular death in CKD and HD.

The treatment effect of older potassium binders on death (any cause) was unknown.

No study reported outcome data for cardiac arrhythmias

Health-related quality of life (HRQoL) evidence: -

There was no evidence of a difference between patiromer or sodium zirconium cyclosilicate and placebo for (HRQoL at the end of treatment (one study) in CKD or HD.

Efficacy evidence: -

Evidence supporting clinical decision-making for different potassium binders to treat chronic hyperkalaemia in adults with CKD is of low certainty; no studies were identified in children.

Safety evidence: -

No study reported outcome data for major GI events.

There was no evidence of a difference in systolic BP (one study), diastolic BP (one study), or constipation (one study) between calcium polystyrene sulfonate and sodium polystyrene sulfonate.

The comparative effects whether potassium binders were administered with or without food, laxatives, or sorbitol, were very uncertain with insufficient data to perform meta-analysis.

Lack of definitive studies despite the clinical importance of potassium binders for chronic hyperkalaemia in people with CKD.

The certainty of the evidence was low for all outcomes.

Available studies have not been designed to measure treatment effects on clinical outcomes such as cardiac arrhythmias or major GI symptoms.

The Cochrane review suggests the need for a large, adequately powered study of potassium binders versus placebo that assesses clinical outcomes of relevance to patients, clinicians and policy-makers.

Some studies had methodological domains that were at high or unclear risks of bias, leading to low certainty in the results.