

INPLASY

INPLASY2026100057

doi: 10.37766/inplasy2026.10.0057

Received: 12 October 2026

Published: 12 October 2026

Corresponding author:

Marco Ladino

mladino@med.miami.edu

Author Affiliation:

Katz Family Division of Nephrology,
University of Miami Miller School of
Medicine, and Miami Veterans
Affairs Healthcare System, Miami,
Florida, USA.

Patiromer or Sodium Zirconium Cyclosilicate to Enable Continuation and Up-Titration of Renin-Angiotensin-Aldosterone System Inhibitors and Mineralocorticoid Receptor Antagonists in Adults With Diabetic Kidney Disease: Protocol for a Systematic Review and Meta-Analysis

Ladino, MA; Asad, O; Alexander, B; Olivera, Y.

ADMINISTRATIVE INFORMATION**Support** - NA.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100057

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 October 2026 and was last updated on 12 October 2026.

INTRODUCTION

Review question / Objective In adults with diabetic kidney disease (DKD) and hyperkalemia, or at risk of hyperkalemia, who are receiving or eligible for guideline-directed renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, does treatment with patiromer or sodium zirconium cyclosilicate (SZC), compared with placebo, usual care, or no binder, increase the proportion of patients who continue, maintain, or up-titrate RAASi and/or mineralocorticoid receptor antagonist (MRA) therapy, and what are the effects on serum potassium, hyperkalemia recurrence, kidney function, albuminuria, blood pressure, safety, and clinical outcomes?

Population: adults with type 1 or type 2 diabetes and chronic kidney disease, not receiving dialysis, with hyperkalemia or at risk of hyperkalemia, receiving or eligible for RAASi or MRA therapy.

Intervention: patiromer or SZC.

Comparator: placebo, usual care, or no binder.

Outcomes: trial-defined RAASi/MRA enablement (persistence, up-titration, or attainment of the target dose); serum potassium; hyperkalemia; eGFR; urine albumin-to-creatinine ratio; blood pressure; adverse events; hospitalization, cardiovascular events, kidney failure, and death. Study designs: randomized controlled trials, including diabetes-subgroup reports, and comparative observational studies with a no-binder comparator.

Rationale Hyperkalemia is the most frequent reason for dose reduction or withdrawal of RAASi and MRA therapy in DKD. In observational cohorts, discontinuation of these agents after hyperkalemia is associated with higher mortality and more cardiovascular events, and current guidelines advise managing serum potassium rather than withdrawing RAASi or MRA therapy. Finerenone, recommended for people with type 2 diabetes and albuminuric CKD, should be initiated only when serum potassium is normal. Patiromer and SZC lower serum potassium in CKD, but previous meta-analyses pooled mixed CKD and heart failure

populations and did not restrict the population to DKD, did not treat MRA (including finerenone) enablement as a distinct question, and did not examine diabetes-specific subgroup data from broader trials. This review therefore evaluates whether these binders enable continuation and up-titration of RAASi and MRA therapy specifically in adults with DKD, and summarizes their effects on potassium, kidney function, safety, and clinical outcomes.

Condition being studied Diabetic kidney disease (DKD) is chronic kidney disease (eGFR <60 mL/min/1.73 m² and/or urine albumin-to-creatinine ratio ≥30 mg/g) in people with type 1 or type 2 diabetes. It is a leading cause of kidney failure and carries high cardiovascular risk. RAASi (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) and MRA (steroidal agents and the nonsteroidal MRA finerenone) slow kidney disease progression and reduce cardiovascular events in DKD, but they reduce renal potassium excretion. Hyperkalemia, or concern about it, frequently leads to under-dosing or discontinuation of these protective therapies. The condition studied is DKD with hyperkalemia, or at risk of hyperkalemia, in patients receiving or eligible for RAASi or MRA therapy.

METHODS

Search strategy All searches run October 11, 2026, from inception; no date, language, or study-design limits.

PubMed/MEDLINE (NCBI E-utilities; 530 records):
(patiomer[tiab] OR veltassa[tiab] OR RLY5016[tiab] OR "RLY 5016"[tiab] OR "zirconium cyclosilicate"[tiab] OR "ZS-9"[tiab] OR ZS9[tiab] OR lokelma[tiab] OR "potassium binder"[tiab] OR "potassium-binding"[tiab] OR "potassium binding"[tiab] OR "patiomer"[nm] OR "sodium zirconium cyclosilicate"[nm]) AND (diabet*[tiab] OR "Diabetes Mellitus"[mh] OR "Diabetic Nephropathies"[mh] OR "chronic kidney disease"[tiab] OR "Renal Insufficiency, Chronic"[mh] OR CKD[tiab] OR RAAS*[tiab] OR "renin-angiotensin"[tiab] OR "Renin-Angiotensin System"[mh] OR "Angiotensin-Converting Enzyme Inhibitors"[mh] OR "Angiotensin Receptor Antagonists"[mh] OR "Mineralocorticoid Receptor Antagonists"[mh] OR spironolactone[tiab] OR eplerenone[tiab] OR finerenone[tiab] OR mineralocorticoid[tiab] OR "heart failure"[tiab] OR "Heart Failure"[mh]) NOT (animals[mh] NOT humans[mh])

Embase (Embase.com; 1,366 records):

#1 'patiomer'/exp OR 'patiomer' OR 'sodium zirconium cyclosilicate'/exp OR 'sodium zirconium cyclosilicate' OR patiomer:ti,ab,kw OR veltassa:ti,ab,kw OR rly5016:ti,ab,kw OR 'rly 5016':ti,ab,kw OR 'zirconium cyclosilicate':ti,ab,kw OR 'zs 9':ti,ab,kw OR zs9:ti,ab,kw OR lokelma:ti,ab,kw OR 'potassium binder':ti,ab,kw OR 'potassium binders':ti,ab,kw OR 'potassium binding':ti,ab,kw (1,933)

#2 'diabetes mellitus'/exp OR 'diabetic nephropathy'/exp OR diabet*:ti,ab,kw OR 'chronic kidney failure'/exp OR 'chronic kidney disease':ti,ab,kw OR ckd:ti,ab,kw OR 'renin angiotensin aldosterone system'/exp OR 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'angiotensin receptor antagonist'/exp OR 'mineralocorticoid antagonist'/exp OR raas*:ti,ab,kw OR 'renin angiotensin':ti,ab,kw OR spironolactone:ti,ab,kw OR eplerenone:ti,ab,kw OR finerenone:ti,ab,kw OR mineralocorticoid:ti,ab,kw OR 'heart failure'/exp OR 'heart failure':ti,ab,kw (3,194,638)

#3 #1 AND #2 (1,374)

#4 #3 NOT ([animals]/lim NOT [humans]/lim) (1,366)

Cochrane CENTRAL (Title Abstract Keyword; Issue 10 of 12, October 2026; 252 trials):

(patiomer OR veltassa OR RLY5016 OR "RLY 5016" OR "zirconium cyclosilicate" OR "ZS 9" OR ZS9 OR lokelma OR "potassium binder" OR "potassium binders" OR "potassium binding") AND (diabet* OR "chronic kidney disease" OR "chronic renal insufficiency" OR CKD OR RAAS* OR "renin angiotensin" OR "angiotensin converting enzyme inhibitor" OR "angiotensin converting enzyme inhibitors" OR "angiotensin receptor antagonist" OR "angiotensin receptor antagonists" OR spironolactone OR eplerenone OR finerenone OR mineralocorticoid OR "heart failure")

Web of Science Core Collection (all editions; 721 records):

TS=(patiomer OR veltassa OR RLY5016 OR "RLY 5016" OR "zirconium cyclosilicate" OR "ZS-9" OR ZS9 OR lokelma OR "potassium binder*" OR "potassium-binding" OR "potassium binding") AND TS=(diabet* OR "chronic kidney disease" OR "chronic renal insufficiency" OR CKD OR RAAS* OR "renin-angiotensin*" OR "angiotensin-converting enzyme inhibitor*" OR "angiotensin receptor antagonist*" OR "angiotensin receptor blocker*" OR spironolactone OR eplerenone OR finerenone OR mineralocorticoid OR "heart failure")

ClinicalTrials.gov (API v2; 73 records):

patiomer OR "zirconium cyclosilicate" OR ZS-9 OR ZS9 OR Lokelma OR Veltassa OR RLY5016

Forward citation searching: PubMed 'cited by' links for included reports.

Participant or population Adults (≥ 18 years) with type 1 or type 2 diabetes and chronic kidney disease (eGFR < 60 mL/min/1.73 m² and/or albuminuria ≥ 30 mg/g), not receiving dialysis, with hyperkalemia or at risk of hyperkalemia, and receiving or eligible for angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor–neprilysin inhibitor, direct renin inhibitor, or steroidal or nonsteroidal MRA therapy. Trials enrolling broader CKD, heart failure, or resistant hypertension populations are eligible when outcomes are reported separately for participants with diabetes; diabetes subgroups of trials that did not require CKD are included with downgrading for indirectness.

Intervention Patiromer or sodium zirconium cyclosilicate at any dose and duration, used to enable continuation, maintenance, initiation, or up-titration of RAASi or MRA therapy.

Comparator Placebo, no binder, or usual care without a novel potassium binder (including dietary potassium restriction). Studies whose only comparator is an active binder (sodium or calcium polystyrene sulfonate, or the alternative novel binder) are excluded.

Study designs to be included Randomized controlled trials (parallel-group or randomized-withdrawal), including prespecified or post hoc diabetes-subgroup reports, and comparative observational studies with a no-binder comparator (including propensity-matched external controls), synthesized separately. Single-arm studies and trials randomizing only binder dose are excluded.

Eligibility criteria Inclusion: studies meeting the population, intervention, comparator, and design criteria above; full-text articles, conference abstracts, and results posted in trial registries; no date or language restrictions. Exclusion: dialysis-dependent or kidney transplant populations; children; treatment of acute (emergency) hyperkalemia only; studies without data reported separately for participants with diabetes; studies without a non-binder comparator; protocols or registry records without results (catalogued as ongoing or unreported studies).

Information sources PubMed/MEDLINE (NCBI E-utilities), Embase (Embase.com), the Cochrane Central Register of Controlled Trials (CENTRAL; which also indexes ClinicalTrials.gov and WHO International Clinical Trials Registry Platform

records), and Web of Science Core Collection, accessed through the University of Miami Calder Medical Library, and ClinicalTrials.gov (API version 2), each searched from inception to October 11, 2026. Forward citation searching of included reports using PubMed 'cited by' links. Conference abstracts and registry-posted results are eligible. Study investigators were not contacted.

Main outcome(s) Proportion of participants achieving trial-defined RAASi/MRA enablement, defined as persistence on, up-titration of, or attainment of the target dose of the RAASi or MRA under study, at each trial's prespecified time point (12 weeks in the trials identified). Effect measure: risk ratio with 95% confidence interval; absolute effects expressed per 1,000 patients by applying the pooled risk ratio to the observed control-group risk.

Additional outcome(s) Change in serum potassium (mean difference); hyperkalemia (≥ 5.5 and ≥ 6.0 mmol/L) and time to recurrence; change in eGFR and urine albumin-to-creatinine ratio; blood pressure; adverse events (including hypomagnesemia, hypokalemia, gastrointestinal events, and edema) and discontinuation for adverse events; hospitalization, cardiovascular events, kidney failure, and all-cause death.

Data management Records are exported from each source into a single record ledger and deduplicated programmatically (exact DOI match; normalized title with a publication-year tolerance of 1 year; prefix matching for truncated titles; registry identifiers), with manual verification of duplicate flags for all records assessed in full text. Titles and abstracts are screened against the eligibility criteria, and potentially eligible reports, including conference abstracts and registry records, are assessed in full; multiple reports of one study are linked and analyzed as one study. Data are extracted into a structured form (design, setting, eligibility, diabetes and CKD definitions, baseline eGFR and potassium, binder and dose, comparator, target RAASi or MRA, follow-up, outcome definitions, effect estimates, event counts, funding). Event counts not reported directly are back-calculated from reported percentages and arm sizes and accepted only when they reproduce the reported confidence interval or percentage exactly. A record-level screening log is maintained. Independent duplicate screening, extraction, and verification by two reviewers, with disagreements resolved by consensus, will be completed and documented before publication.

Quality assessment / Risk of bias analysis Risk of bias in randomized evidence is assessed for each outcome with the Cochrane RoB 2 tool. The credibility of subgroup-derived estimates is appraised with the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN). Non-randomized comparisons are assessed with ROBINS-I. Certainty of evidence for each outcome is rated with GRADE (risk of bias, inconsistency, indirectness, imprecision, and publication bias). Judgments will be confirmed by two independent reviewers, with disagreements resolved by consensus.

Strategy of data synthesis Dichotomous outcomes are expressed as risk ratios (RR) and continuous outcomes as mean differences, each with 95% confidence intervals. RRs are pooled with a random-effects model using restricted maximum likelihood (REML) estimation of between-study variance (τ^2) and Hartung–Knapp–Sidik–Jonkman (HKSJ) confidence intervals, with the HKSJ variance multiplier truncated at 1. A 95% prediction interval is calculated when at least 3 trials contribute, and heterogeneity is summarized with τ^2 , Cochran Q, and I^2 . Because trials operationalize enablement differently, the primary outcome is analyzed as a composite of trial-defined enablement, and the heterogeneity of definitions is carried into the certainty assessment. Continuous outcomes are pooled only when designs are comparable; randomized-withdrawal and parallel-group initiation designs are not combined. Observational evidence is synthesized separately and never combined with randomized data. Outcomes unsuitable for pooling are summarized narratively following the Synthesis Without Meta-analysis (SWiM) guideline. Small-study effects are assessed only when at least 10 studies contribute. Analyses are performed in Python (NumPy, SciPy).

Subgroup analysis By binder (patiomer vs sodium zirconium cyclosilicate) and by target drug (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker vs steroidal MRA vs finerenone). Subgroup results are reported descriptively when fewer than 3 trials contribute to a subgroup.

Sensitivity analysis DerSimonian–Laird random-effects and Mantel–Haenszel fixed-effect models; exclusion of open-label trials; exclusion of terminated or very small trials; available-case instead of intention-to-treat event counts.

Language restriction No language restrictions.

Country(ies) involved United States.

Other relevant information Retrospective registration. This protocol is registered retrospectively. The review question, eligibility criteria, and outcomes were specified on October 9, 2026, before the database searches of October 11, 2026. At the time of registration, searching, deduplication, title and abstract screening, full-text assessment, data extraction, risk-of-bias assessment, and the meta-analyses had been performed with artificial intelligence assistance (Claude, Anthropic); independent duplicate human verification of screening, data extraction, and risk-of-bias judgments will be completed and documented before publication. Decisions made after data collection, and reported as deviations in the final publication: change in serum potassium is not pooled because the contributing trials differ in design; subgroup analyses are descriptive because no subgroup contains more than 2 trials; small-study effects are not assessed because fewer than 10 studies contribute to any analysis. Reporting follows PRISMA 2020 and PRISMA-S.

Keywords diabetic kidney disease; hyperkalemia; patiomer; sodium zirconium cyclosilicate; mineralocorticoid receptor antagonists; renin-angiotensin system inhibitors; finerenone; meta-analysis.

Dissemination plans Publication in a peer-reviewed journal and presentation at scientific meetings. Search strategies, extracted data, analysis code, and the record-level screening log will be provided as supplementary material.

Contributions of each author

Author 1 - Marco A. Ladino - Conceived and designed the review; developed and ran the searches; screened records; extracted data; assessed risk of bias and certainty of evidence; performed the analyses; and drafted the protocol. Email: mladinoavellaneda@gmail.com

Author 2 - Omar Asad.

Author 3 - Brooke Alexander.

Author 4 - Yanetsy Olivera.