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Albuminuria as a surrogate and hyperkalaemia as a safety signal in combined mineralocorticoid receptor antagonist and SGLT2 inhibitor therapy for chronic kidney disease: a protocol for a systematic review with surrogate-threshold and meta-epidemiological analysis

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ADMINISTRATIVE INFORMATION**Support** - No support.**Review Stage at time of this submission** - Data extraction.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100042

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 October 2026 and was last updated on 9 October 2026.

INTRODUCTION

Review question / Objective Two prespecified objectives.

First, to establish what the observed incremental albuminuria effect of adding a mineralocorticoid receptor antagonist (MRA) or an aldosterone synthase inhibitor to an SGLT2 inhibitor licenses as a quantitative claim about hard kidney outcomes. This is addressed by pooling the incremental effect on the urinary albumin-to-creatinine ratio (UACR), converting it to a predicted clinical-endpoint hazard ratio using published trial-level surrogacy parameters, and reporting the resulting prediction interval together with the composition of the trials from which those parameters were derived.

Second, to establish whether the apparent attenuation of MRA-associated hyperkalaemia by SGLT2 inhibition reflects pharmacology or trial design. This is addressed by decomposing the MRA-attributable effect on both the ratio and the difference scale within strata of SGLT2 inhibitor

use, and by relating trial-level hyperkalaemia incidence to each trial's serum potassium eligibility ceiling and exposure duration.

Rationale Randomised trials show that adding an MRA or an aldosterone synthase inhibitor to an SGLT2 inhibitor lowers albuminuria further than either agent alone. No trial of the combination is powered for kidney failure, and none is planned; an event-driven trial against active monotherapy comparators would require roughly 41,000 participants. The field has therefore settled on albuminuria as the endpoint and on the inference that an additive surrogate effect implies an additive clinical one. That inference rests on trial-level meta-regressions estimated from trials of single interventions against control, and whether their parameters transfer to a regimen combining two mechanistically distinct agents has not been examined.

A second claim attached to the combination concerns safety. Subgroup analyses showing lower hyperkalaemia incidence among MRA-treated

patients on background SGLT2 inhibitors are read as evidence that one agent protects against the other, and are used to argue that combination therapy can be offered to patients otherwise considered too hyperkalaemia-prone for an MRA. Crude incidence cannot support that reading, because it conflates a shift in baseline risk with attenuation of the drug effect, and because every contributing trial excluded patients above a screening potassium threshold.

Several systematic reviews have pooled the same small set of trials and reported the same incremental UACR effect and the same elevated hyperkalaemia risk. None addressed either question above, because neither is answerable by pooling effect estimates. Surrogate validity is a property of the relationship between two endpoints, not of an effect size; confounding by eligibility criteria is a property of who was enrolled, not of who had an event.

Condition being studied Chronic kidney disease in adults, diabetic and non-diabetic, including chronic kidney disease within heart failure and type 2 diabetes trial populations.

METHODS

Search strategy Three concept blocks combined with AND, each block combining controlled vocabulary with free-text synonyms using OR.

Block 1, mineralocorticoid receptor antagonist or aldosterone synthase inhibitor: the pharmacological action and subject heading for mineralocorticoid receptor antagonists, plus finerenone, esaxerenone, apararenone, balcinrenone, ocedurenone, spironolactone, eplerenone, canrenone, baxdrostat, lorundrostat, vicastrostat, and the phrases “mineralocorticoid receptor antagonist” and “aldosterone synthase inhibitor”.

Block 2, SGLT2 inhibitor: the pharmacological action and subject heading for sodium-glucose transporter 2 inhibitors, plus the abbreviations SGLT2 and SGLT-2 inhibitor, the phrases “sodium glucose cotransporter 2” and “sodium-glucose cotransporter 2”, the stem gliflozin, and dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin, bexagliflozin, sotagliflozin and henagliflozin.

Block 3, chronic kidney disease: subject headings for chronic renal insufficiency, diabetic nephropathies and albuminuria, plus “chronic kidney disease”, CKD, “diabetic kidney disease”, “diabetic nephropathy”, DKD, albuminuria, proteinuria, UACR, “albumin-to-creatinine”, nephropathy and “renal insufficiency”.

A fourth block applied the sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy for randomised trials, with animal-only records removed. No date limit was applied. Full strings for each database interface, with field tags and record yields, are reported verbatim as a supplementary file of the review.

Participant or population Adults aged 18 years or older with chronic kidney disease, with or without diabetes, with or without albuminuria.

Intervention A steroidal or nonsteroidal mineralocorticoid receptor antagonist (finerenone, esaxerenone, apararenone, balcinrenone, ocedurenone, spironolactone, eplerenone, canrenone), or an aldosterone synthase inhibitor (vicastrostat, baxdrostat, lorundrostat), combined with an SGLT2 inhibitor.

Comparator Either component given as monotherapy, or placebo on a background of the other agent.

Study designs to be included Two streams. Stream A comprises randomised controlled trials, whether parallel, crossover or factorial, comparing the combination against either monotherapy. Stream B comprises prespecified or post hoc analyses of randomised trials reporting outcomes stratified by baseline or concomitant SGLT2 inhibitor use among MRA-treated patients, or stratified by MRA use among SGLT2 inhibitor-treated patients. Observational studies, single-arm studies, protocols without results, narrative reviews, and modelling or cost-effectiveness studies are excluded.

Eligibility criteria Population, intervention, comparator and design as specified in Items 12 to 15. Reports had to provide at least one outcome of interest. The unit of analysis is the trial rather than the publication, so companion and secondary reports are linked to their parent trial and not counted as separate studies. Analyses in which SGLT2 inhibitor use entered only as a covariate in a model, without stratum-specific estimates, were excluded. Records available only as conference abstracts, with no corresponding full report, were excluded.

Information sources MEDLINE via PubMed (NCBI E-utilities), Embase (embase.com), Scopus, and Web of Science Core Collection, each searched from inception to 9 October 2026 through the University of Miami Calder Medical Library. Supplemented by reference-list screening of all included trial reports and of fourteen prior

syntheses on this topic, forward citation chasing in Scopus and Web of Science, and ClinicalTrials.gov for trial eligibility criteria and ongoing trials.

Main outcome(s) For the first objective, the relative change in urinary albumin-to-creatinine ratio, expressed as a geometric-mean ratio against the SGLT2 inhibitor comparator, and the clinical-endpoint hazard ratio predicted from it using published trial-level surrogacy parameters, reported with its prediction interval.

For the second objective, hyperkalaemia, defined as investigator-reported events, serum potassium above 5.5 mmol/L, and serum potassium above 6.0 mmol/L, expressed as risk ratios and as risk differences within strata of SGLT2 inhibitor use.

Additional outcome(s) Estimated glomerular filtration rate and eGFR slope; acute eGFR decline; kidney and cardiovascular composite outcomes; hyperkalaemia leading to treatment discontinuation; hospitalisation for hyperkalaemia. Five trial design variables are extracted as outcomes in their own right for the second objective: the serum potassium eligibility ceiling, exclusion of potassium binders, the potassium monitoring schedule, dose titration and dose-hold rules keyed to serum potassium, and the presence and nature of any run-in period.

Data management Records from all four databases are combined and de-duplicated on normalised digital object identifier, then on normalised title, with the normalisation rules recorded in the analysis code. Screening proceeds at title and abstract and then at full text, with a reason recorded for every full-text exclusion and a screening decision file retained for all records. Data are extracted into a structured evidence table capturing design, population, eligibility thresholds, outcomes with effect estimates and confidence intervals exactly as reported, and funding source. Where a trial registry record and a publication disagree, the registry record is used for eligibility criteria. Values not reported are recorded as such and never estimated.

Quality assessment / Risk of bias analysis RoB 2 for the randomised trials in Stream A. Stream B analyses are appraised against standard credibility criteria for subgroup effects: whether the comparison is within-trial and randomised, whether the subgroup variable was measured at baseline, whether the analysis was prespecified, how many subgroup hypotheses were tested, and whether a formal interaction test was reported. Certainty of evidence is rated per outcome using GRADE.

Strategy of data synthesis Incremental UACR effects are pooled on the log scale using DerSimonian-Laird random effects, with a Hartung-Knapp sensitivity analysis. Heterogeneity is reported as I-squared, tau-squared and Cochran's Q with its p value. One arm per trial enters the primary analysis to avoid unit-of-analysis error in multi-arm trials.

The pooled ratio is converted to a predicted clinical-endpoint hazard ratio by proportional scaling on the log scale, calibrated to the published anchor of the trial-level surrogacy meta-analysis because that analysis does not report its regression intercept. The prediction interval is scaled by the same factor, and the arithmetic is reported in full so that it can be checked. Both the 2019 and the 2025 published parameter sets are applied to the same pooled effect. The composition of the trials contributing to those parameter sets is reported, so that the extent to which they represent combination regimens is visible to the reader.

For the second objective, two-by-two tables are reconstructed from published counts and the MRA-attributable effect is expressed both as a risk ratio and as a risk difference within each stratum. Interaction is tested on both scales, because an effect that is constant on one scale is necessarily non-constant on the other. Trial-level hyperkalaemia incidence in combination arms is regressed on the potassium eligibility ceiling and on exposure duration in a binomial model, reported as descriptive rather than confirmatory given the small number of trials.

Where pooling is inappropriate, synthesis follows SWiM guidance and the reason is stated.

Subgroup analysis By drug class, comparing nonsteroidal MRA, steroidal MRA and aldosterone synthase inhibitor. By population, comparing chronic kidney disease with heart failure accompanied by chronic kidney disease. By diabetes status.

Sensitivity analysis One arm per trial at the highest dose in the primary analysis, with all randomised dose arms in sensitivity. Hartung-Knapp confidence intervals alongside DerSimonian-Laird. Inclusion and exclusion of any trial without an albuminuria entry criterion, since the trial-level surrogacy relationship was estimated in albuminuric populations. Application of both published surrogacy parameter sets to the same pooled effect.

Country(ies) involved United States.

Keywords hyperkalaemia; mineralocorticoid receptor antagonists; aldosterone synthase inhibitors.

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