INPLASY

INPLASY202690081

doi: 10.37766/inplasy2026.9.0081

Received: 19 September 2026

Published: 19 September 2026

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SGLT2 inhibitors, GLP-1 receptor agonists, mineralocorticoid receptor antagonists and endothelin receptor antagonists in active and chronic lupus nephritis: a scoping review with exploratory meta-analysis

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ADMINISTRATIVE INFORMATION

Support - NA.

Review stage at the time of initial registration - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202690081

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 September 2026 and was last updated on 1 November 2026.

INTRODUCTION

Review question / Objective Immunosuppression controls immune activity in lupus nephritis (LN) but does not treat the non-immune mechanisms of nephron loss that carry patients to kidney failure. Four drug classes changed outcomes in other proteinuric kidney diseases. This review maps the evidence for each in LN and turns it into practice points clinicians can apply.
Amended 27 October 2026. The review addresses three clinical questions: (Q1) whether SGLT2 inhibitors, GLP-1 receptor agonists (including dual GIP/GLP-1 agonists), steroidal or non-steroidal mineralocorticoid receptor antagonists and endothelin receptor antagonists are effective in active lupus nephritis; (Q2) whether, added to induction therapy, they improve renal response; and (Q3) whether, in established lupus nephritis in the maintenance phase or with chronic kidney disease, they reduce residual proteinuria or preserve kidney function over time. Secondary, post hoc and exploratory: to pool comparable adjusted or matched ratio estimates for incident lupus nephritis, kidney failure and all-cause mortality with SGLT2 inhibitors in SLE. PCC: population, people with SLE or lupus nephritis and animal models of lupus; concept, exposure to one of the four drug classes; context, unrestricted.

Background Immunosuppression controls immune activity in lupus nephritis (LN) but does not treat the non-immune mechanisms of nephron loss that carry patients to kidney failure. Four drug classes changed outcomes in other proteinuric kidney diseases. This review maps the evidence for each in LN and turns it into practice points clinicians can apply.

Rationale The population, adults with LN or SLE with kidney involvement; for indirect evidence, adults with proteinuric CKD of non-diabetic or glomerular cause; and for animal evidence, murine models of lupus or immune-complex glomerulonephritis. The concept, adjunctive nephroprotective drug therapy of four classes:

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SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), steroidal or non-steroidal mineralocorticoid receptor antagonists, and selective or dual endothelin receptor antagonists (ERAs). Immunosuppression controls immune activity in lupus nephritis (LN) but does not treat the non-immune mechanisms of nephron loss that carry patients to kidney failure. Four drug classes changed outcomes in other proteinuric kidney diseases. This review will map the evidence for each in LN and turns it into practice points clinicians can apply.
Amended 27 October 2026. The evidence required differs at three points in the course of lupus nephritis: an effect on immune-mediated injury in active disease, an additive effect on renal response during induction, and reduction of residual proteinuria or preservation of kidney function in established disease. Earlier syntheses merged these questions; the amended review classifies each study by disease phase at entry so that each question is answered from the evidence that bears on it.

METHODS

Strategy of data synthesis PubMed, OVID, SCOPUS. Charted variables were first author, year, country, design, sample size, population, drug and dose, comparator, follow-up, and outcomes with effect estimates. For the clinical sections, eligibility thresholds, starting doses, titration, monitoring intervals and adverse event rates will be charted separately. Each source placed in one of four tiers by directness: A, drug given to patients with SLE or LN with lupus-specific outcomes; B, animal study in a lupus or immune-complex model; C, large human trial in proteinuric CKD outside lupus; D, guideline, review, commentary or registration.
Amended 27 October 2026. Narrative synthesis organized by clinical question (Q1-Q3) and drug class. Two independent reviewers, with consensus, classify each human study by disease phase at entry (active or relapsing lupus nephritis/induction; established lupus nephritis in maintenance or with residual proteinuria; lupus nephritis with CKD and long-term outcomes, activity unspecified; SLE without lupus nephritis; mixed or unclear; safety reports) and by relevance to each question. Post hoc exploratory meta-analysis (added after charting): random-effects pooling (restricted maximum likelihood, Wald and Hartung-Knapp confidence intervals, I-squared and prediction intervals) of adjusted or matched ratio estimates for SGLT2 inhibitors versus non-users or DPP-4 inhibitors in SLE for incident lupus nephritis, kidney failure and all-cause mortality; primary analyses restricted to peer-reviewed full-text cohorts, secondary analyses add conference abstracts. Risk of bias with ROBINS-I V2 (pooled cohorts) and RoB 2 (randomized trials in lupus nephritis), certainty with GRADE.

Eligibility criteria Patient with CKD and LN.
Amended 27 October 2026. Eligible evidence is restricted to primary data on exposure to an SGLT2 inhibitor, a GLP-1 receptor agonist (including dual GIP/GLP-1 agonists), a steroidal or non-steroidal mineralocorticoid receptor antagonist, or an endothelin receptor antagonist in SLE, lupus nephritis or lupus animal models, and to interventional registrations in SLE or lupus nephritis. Human studies are eligible when they report kidney outcomes, lupus activity or safety in SLE or lupus nephritis, or attribute a lupus-like reaction to one of the drugs; mixed cohorts qualify only with SLE- or lupus nephritis-specific data. Conference abstracts and letters with original data are eligible. Reviews, guidelines and large trials in non-lupus CKD are excluded from the evidence map and cited as context only. Reports in which the drug appears only in a medication list without an outcome, and reports of an endothelin receptor antagonist given solely for pulmonary arterial hypertension, digital ulcers or skin disease without a kidney, lupus-activity or lupus-specific safety outcome, are excluded. No date or language limits. Categories: A1 treatment studies in lupus nephritis; A2 SLE populations with outcomes by exposure, including incident lupus nephritis; A3 safety reports and drug-induced lupus; B animal studies; C interventional registrations.

Source of evidence screening and selection Stage 1, identification and deduplication. Records returned by each prespecified search string are exported with PMID, title, journal and year, and deduplicated across strings on PMID. Records appearing in more than one string are screened once, with all source strings recorded.

Stage 2, title and abstract screening in duplicate. Two reviewers independently screen every deduplicated record against the eligibility criteria fixed before screening, recording INCLUDE, EXCLUDE or UNCLEAR and, for exclusions, one of five prespecified reason codes. Reviewers are blinded to each other's decisions until both sets are complete. Records marked UNCLEAR are carried forward to full-text assessment on the same footing as INCLUDE, so that uncertainty is resolved by reading the paper rather than by a forced call on an abstract. Before full screening, both reviewers screen the first 20 records and compare decisions to calibrate application of the criteria; any criterion found to be ambiguous is

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clarified in writing before screening resumes, and the 20 calibration records are then rescreened.

Stage 3, full-text assessment in duplicate. Records carried forward are retrieved in full and assessed independently by the same two reviewers against the same criteria. Reasons for exclusion at this stage are recorded individually in the retrieval log.

Stage 4, charting. Each included source is assigned a directness tier and charted on the prespecified form. Charting is performed by one reviewer and verified against the source by the second.

Resolution of disagreements. Disagreements at stages 2 and 3 are resolved by discussion between the two reviewers, working through each flagged record against the written criteria. Any disagreement not resolved by discussion is referred to the third author, whose decision is final. The number of disagreements, the number resolved by discussion, and the number requiring adjudication are recorded and reported. Inter-reviewer agreement at stage 2 is reported as raw percentage agreement and Cohen's kappa.

Scope of duplicate screening. Duplicate independent screening applies to records retrieved by the four searches that identify direct evidence in lupus. Indirect-evidence sources (large randomised trials in non-lupus proteinuric chronic kidney disease, clinical practice guidelines and background reviews) are identified purposively rather than by systematic screening, and are charted as context. This distinction is reported in the Methods.
Amended 27 October 2026. Searches: MEDLINE (PubMed), Ovid MEDLINE(R) ALL, Embase, Scopus, Web of Science Core Collection, Cochrane CENTRAL, Europe PMC preprints, ClinicalTrials.gov and WHO ICTRP, searched on 27 October 2026 with one strategy combining a lupus block with four drug-class blocks, without date, language or publication-type limits; reference lists of recent reviews and forward citations of included studies (Scopus) were screened. Google Scholar could not be searched (automated access blocked). Every retrieved record is screened. Title-abstract screening, full-text assessment and charting are performed by two independent reviewers blinded to each other using written instruction packets, with a consensus assessment that re-reads the source for every disagreement and records a verbatim quotation; one primary exclusion reason is assigned from a fixed hierarchy, and reports of one study are linked. The reviewers and the consensus assessment are separate instances of a large language model (Anthropic Claude Opus 5.5 and Claude Sonnet 5.5) run under author supervision; the authors verified decisions at prespecified gates (calibration set of 100 records, all escalations and a random sample of exclusions, every full-text decision, every charted value, phase classification, risk-of-bias and GRADE judgment). Agreement is reported as percentage agreement, Cohen's kappa and Gwet's AC1. Addition of 31 October 2026: one study published before the search date but not yet indexed, and the published protocol of an included registration, were assessed by the same process.

Data management Records and formats. All retrieved records are held in a single reference ledger keyed on PMID, with DOI, full citation, and the search string that retrieved each record. Search output is exported from PubMed in CSV; the ledger is maintained in JSON and rendered to the numbered reference list used in the manuscript, so that citation numbering is generated from the ledger rather than entered by hand. Screening decisions are held in two reviewer workbooks and a reconciliation workbook (XLSX). Charted data are held in a single charting table (XLSX), one row per source, with the fields fixed before screening.

Verification. Every included record is verified against PubMed by PMID or DOI before charting. Every effect estimate entered in the charting table is checked against the source abstract or, where the abstract is unavailable or incomplete, the full text obtained from PubMed Central. Figures are transcribed exactly as reported, including confidence intervals and P values, with no rounding or recalculation. Where a study reports a value only in full text, the charting table records that fact.

Version control and provenance. Each search is logged with its string as run, the date run, the interface used, and the number of records returned (Online Resource 2). Supplementary records identified outside the prespecified searches are logged separately with their source and the verification performed. Successive drafts of the manuscript and the ledger are retained, so that any figure in the final text can be traced to the record it came from.

Confidentiality and data protection. The review uses published aggregate data and trial registrations only. No individual participant data, identifiable information or unpublished data were obtained, so no data protection approval, data sharing agreement or de-identification procedure

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applies. Reviewer screening decisions are held by the reviewing authors during screening and are not personal.
Amended 27 October 2026. Screening, full-text and charting decisions of each reviewer and the consensus records, with verbatim source quotations and locators, are held in structured files. References are kept in a single ledger verified against PubMed or Crossref by PMID or DOI, and the numbered reference list is generated from the ledger. All decisions (screening, full-text, phase classification) and the charting table are published as supplementary material; analysis code and charted data are available from the corresponding author.

Reporting results / Analysis of the evidence Amended 27 October 2026. Reporting follows PRISMA-ScR for the scoping component, PRISMA 2020 for the quantitative synthesis and PRISMA-S for the search. Randomized trials in lupus nephritis reported proteinuria on incompatible scales and are synthesized narratively; cohort ratio estimates are pooled only when at least two cohorts report the same outcome and exposure contrast.

Presentation of the results Amended 27 October 2026. PRISMA 2020 flow diagram; evidence map of human studies by clinical question, drug class and design; table of human studies in lupus nephritis grouped by question; GRADE summary table and forest plots for the exploratory meta-analysis; supplementary tables of registrations, charting, risk of bias, screening decisions, SLE cohorts and phase classification. Provisional clinical considerations replace the original practice points and are presented separately from the evidence, each statement labeled as guideline, labeling or trial eligibility, extrapolation, or authors' opinion.

Language restriction Only English.

Country(ies) involved United States.

Keywords Lupus Nephritis; Sodium-Glucose Transporter 2 Inhibitors; Glucagon-Like Peptide-1 Receptor Agonists; Mineralocorticoid Receptor Antagonists; Endothelin Receptor Antagonists; Proteinuria.

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Reason for amendment Peer review of an earlier version identified screening of relevance-ranked subsets, single-reviewer screening and charting, and omission of Embase, Scopus/Web of Science and CENTRAL. The amendment was made on 27 October 2026, before the searches were rerun. The meta-analysis, risk-of-bias assessment and certainty rating were added after charting and are reported as post hoc and exploratory. Large language model use (Anthropic Claude) for searching, screening, charting, classification, risk-of-bias assessment, analysis code and drafting assistance is disclosed in the manuscript; the authors verified all outputs and take full responsibility.

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