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SYSTEMATIC REVIEW

Renal Outcomes of GLP-1 Receptor Agonists and Tirzepatide Across CKD Stages and Metabolic Phenotypes (Type 2 Diabetes and/or Overweight/Obesity): A Scoping Review

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ABSTRACT

***Introduction*:** Diabetes mellitus is the leading global cause of chronic kidney disease (CKD) and end-stage renal disease. Although cardiovascular outcomes have improved substantially, renal risk remains high. Glucagon-like peptide 1 (GLP-1) receptor agonists and the dual GLP-1/GIP agonist tirzepatide have demonstrated potential cardiorenal benefits, but renal evidence has not been systematically mapped across CKD stages and metabolic phenotypes. This scoping review aimed to identify and describe clinical evidence on renal outcomes associated with GLP-1-based therapies in adults with type 2 diabetes and/or overweight/obesity, with or without CKD.

***Methods*:** Following the Joanna Briggs Institute framework and PRISMA-ScR guidelines (protocol: OSF.IO/SZ87J), we searched PubMed, Embase, and CENTRAL from inception to October 2025. Eligible studies included phase 2–4 randomized controlled trials (RCTs), post hoc RCT analyses, and comparative observational studies reporting kidney outcomes. Data were charted using a structured extraction form with AI-assisted screening and manual validation. Risk of bias and certainty were appraised using RoB 2, ROBINS-I, and GRADE frameworks.

***Results*:** Of 607 records identified, 35 studies met inclusion criteria. Randomized evidence supports renal benefits for semaglutide,

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dulaglutide, and liraglutide, including reductions in composite kidney outcomes and slower eGFR decline. Tirzepatide demonstrated consistent albuminuria reductions and attenuation of eGFR decline compared with insulin glargine. Efpeglenatide, cotadutide, exenatide, and lixisenatide showed class-consistent antiproteinuric effects. Observational data extended findings to real-world and advanced CKD populations. Across agents, renal benefits were partly independent of glycemic and weight effects.
Conclusion: GLP-1-based therapies demonstrate consistent renoprotective signals across CKD stages and metabolic phenotypes, particularly in type 2 diabetes. Evidence is strongest for semaglutide and dulaglutide, with emerging data for tirzepatide and other incretin-based agents. These findings provide a structured evidence map to inform future consensus and clinical decision-making.

Keywords: Chronic kidney disease; Renal outcomes; Albuminuria; eGFR slope; GLP-1 receptor agonist; Tirzepatide; Type 2 diabetes; Obesity; Scoping review; Evidence map

Key Summary Points

Why carry out this study?

Diabetes is a leading cause of CKD/ESRD, and despite cardiovascular improvements, renal outcomes remain suboptimal.

The renal evidence for GLP-1 receptor agonists and tirzepatide has expanded rapidly but had not been systematically mapped across CKD stages and metabolic phenotypes.

What was learned from the study?

Across 35 studies, GLP-1-based therapies consistently reduced albuminuria and attenuated eGFR decline, with the strongest RCT evidence for semaglutide, dulaglutide, and liraglutide.

Tirzepatide showed consistent albuminuria reductions and slower eGFR decline versus insulin glargine, with moderate-to-high certainty in available datasets.

Evidence gaps persist for advanced CKD (G4–G5) and for non-diabetic/non-obese populations, informing priorities for future trials and the forthcoming SLANH RAND/UCLA consensus.

INTRODUCTION

Diabetes affects approximately one in ten adults worldwide, predominantly type 2, and its prevalence continues to rise faster than earlier demographic forecasts [1]. Although incidences of major macrovascular complications have decreased by more than 50% in many settings over the past two decades, the decline in end-stage renal disease (ESRD) has been far more modest (approx. 29%). Consequently, a persistently high absolute number of people with diabetes—about 20 per 10,000 annually—initiate renal replacement therapy (RRT), and diabetes remains the leading cause of chronic kidney disease (CKD) and ESRD globally (approx. 33% of RRT initiations). These trends underscore the need for interventions capable of modifying kidney trajectories in adults with diabetes or overweight/obesity [2].

Beyond glycemic control, there is a strong biological rationale for investigating glucagon-like peptide 1 (GLP-1)-based therapies. GLP-1 is implicated in a putative gut–renal axis that rapidly regulates postprandial fluid and electrolyte homeostasis, supporting hypotheses of direct renal actions in addition to improvements in classical renal risk factors [1]. Experimental data also suggest anti-inflammatory effects relevant to diabetic kidney injury: GLP-1 signaling can suppress AGE–RAGE pathways, leading to downstream reductions in endothelial vascular cell adhesion molecule 1 (VCAM-1)

expression and mesangial monocyte chemoattractant protein 1 (MCP1) induction, alongside shifts toward an anti-inflammatory (M2-like) macrophage phenotype in the renal microenvironment [3].

Clinically, large randomized trials report kidney-related benefits with GLP-1 receptor agonists, most consistently reductions in albuminuria, with additional signals for slower estimated glomerular filtration rate (eGFR) decline in higher-risk subgroups [4, 5]. Given the rapid expansion of incretin-based trials and the emerging evidence of kidney benefit, a structured evidence map is essential to characterize the nature and scope of available data. A scoping review provides an appropriate framework for describing and categorizing this heterogeneous literature without aiming to quantitatively pool outcomes. The present review was commissioned by the Sociedad Latinoamericana de Nefrología e Hipertensión (SLANH) to support the development of a RAND/UCLA Appropriateness Method consensus statement on the positioning of incretin-based therapies within cardiorenal care.

The objective of this scoping review is to map and describe peer-reviewed clinical evidence on renal outcomes associated with GLP-1 receptor agonists and tirzepatide, using a framework structured primarily by CKD stage and metabolic phenotype (type 2 diabetes and overweight/obesity status). Within this population-based framework, agent-specific patterns are summarized to characterize the scope, strength, and gaps of available renal outcome evidence.

Specifically, the review aims to (i) summarize the range and characteristics of clinical studies—randomized controlled trials (RCTs), post hoc analyses, and comparative observational studies—reporting kidney-related outcomes; (ii) map renal outcome evidence across CKD stages and metabolic phenotypes, highlighting areas of convergence and limited or absent stratified data; and (iii) generate an evidence map to inform structured appropriateness statements for the forthcoming SLANH RAND/UCLA panel [6].

METHODS

Protocol and Registration

This scoping review was conducted following the methodological framework of the Joanna Briggs Institute (JBI) for scoping reviews [7] and is reported according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [8]. The protocol for this review was developed a priori and is publicly available (https://doi.org/10.17605/OSF.IO/SZ87J). The review was commissioned by the Sociedad Latinoamericana de Nefrología e Hipertensión (SLANH) to inform a forthcoming RAND/UCLA Appropriateness Method consensus process.

Eligibility Criteria

Eligibility criteria were established according to the Population–Concept–Context (PCC) framework recommended by the JBI, which is particularly appropriate for mapping broad evidence bases.

The population of interest comprised adults (≥ 18 years) with type 2 diabetes mellitus, mixed or unspecified diabetes populations (provided they were not exclusively composed of individuals with type 1 diabetes), or individuals with overweight or obesity, as defined by each included study. Participants could have or not have CKD at baseline, and studies reporting kidney outcomes in CKD subgroups were also considered eligible.

The concept focused on interventions involving any glucagon-like peptide 1 receptor agonist (GLP-1RA)—such as liraglutide, semaglutide, dulaglutide, exenatide, or lixisenatide—or the dual GLP-1/ GIP receptor agonist tirzepatide, irrespective of dose or route of administration, whether approved or investigational. Eligible comparators included placebo or active treatments such as standard care, sodium–glucose cotransporter 2 (SGLT2) inhibitors, finerenone,

renin–angiotensin–aldosterone system (RAAS) inhibitors, or other glucose-lowering agents. Outcomes of interest encompassed kidney and cardiorenal endpoints, including measures of kidney function (e.g., eGFR slope, eGFR decline, or kidney failure events), changes in albuminuria, composite renal endpoints, and cardiorenal outcomes reported within CKD subgroups. For contextual completeness, safety data and adverse renal events were also charted.

Regarding context, studies conducted in any healthcare or research setting involving adults with diabetes, overweight, or obesity were eligible. No geographic or economic restrictions were applied. All publication years were considered, and studies published in any language were eligible, provided that an English abstract was available.

Finally, the types of evidence included phase 2–4 RCTs, prespecified or post hoc analyses of randomized trials, and extensive comparative observational studies reporting kidney-relevant outcomes. Excluded sources comprised case reports or case series with fewer than 10 participants, editorials, narrative reviews, single-arm studies without a comparator group, and preclinical or animal research.

Information Sources and Search Strategy

A comprehensive search strategy was designed in collaboration with an experienced medical librarian, following the three-step approach recommended by JBI. First, a preliminary search was performed in PubMed to identify key terms and indexing related to incretin-based therapies and kidney outcomes. Second, the strategy was adapted and expanded for Embase (Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL) using both controlled vocabulary (e.g., Emtree and MeSH terms) and free-text keywords. Third, reference lists of included studies and relevant systematic reviews were screened to identify additional eligible sources.

Searches were run from database inception to the final search date (October 2025) with no initial language or date restrictions. Given the purpose of this review—to provide a transparent evidence map of peer-reviewed literature for RAND/UCLA consensus—gray literature sources were not searched.

The final search strategy for each database, including all Boolean operators, proximity terms, and field tags, is provided in Supplementary Table 1. The search strategy combined three main concept blocks:

1. *Incretin-based therapies* (e.g., GLP-1 receptor agonists, tirzepatide, incretin, glucagon-like peptide 1, GIP agonist).
2. *Kidney-related terms* (e.g., renal, kidney, nephropathy, albuminuria, eGFR, chronic kidney disease).
3. *Population terms* for diabetes, overweight, or obesity. These blocks were combined using the Boolean operator AND, and within each block, synonyms and related terms were connected with OR. Truncation and proximity operators (e.g., adj3 or NEAR/3) were applied as appropriate.

All records were exported from each database, de-duplicated in EndNote 21, and then transferred to Rayyan (Qatar Computing Research Institute) for screening [9]. A record of search dates, yield, and de-duplication results was maintained for reproducibility.

Selection of Sources of Evidence

The selection process followed JBI recommendations for transparency and reproducibility. After removal of duplicates, titles and abstracts were independently screened by two reviewers using the inclusion and exclusion criteria defined in the protocol. Potentially relevant records were retrieved in full text and assessed for eligibility by the same reviewers.

Discrepancies were resolved through discussion; consultation with a third reviewer was not necessary. Reasons for exclusion at the full-text stage were recorded and reported in accordance with the PRISMA-ScR flow diagram (Supplementary Fig. 1).

Screening was conducted at Rayyan (Qatar Computing Research Institute), enabling blinded decisions and tagging of exclusion reasons, before formal screening. The overall selection

process is illustrated in a PRISMA-ScR flowchart detailing the number of records identified, screened, excluded (with reasons), and included in the review.

Data Charting, Appraisal, and AI-Assisted Processes

Data were extracted (charted) by one reviewer using a structured and pilot-tested data extraction form. The extraction form was piloted on a small subset of studies to ensure clarity and internal consistency before complete data collection. To improve efficiency and consistency, a supervised artificial intelligence (AI) tool was used during data extraction and evidence appraisal. The AI system automatically identified and organized key study attributes (e.g., design, sample size, outcomes) and flagged sections relevant to renal endpoints and risk-of-bias domains. All AI outputs were manually verified, corrected, and approved by the reviewer, ensuring complete human oversight and accountability in accordance with current reporting transparency principles.

Data Items Collected

The following variables were charted for each included source of evidence:

- *Bibliographic information:* author, year, country, funding
- *Study characteristics:* design, phase, sample size, duration, setting
- *Population:* diabetes type, overweight/obesity definitions, CKD stage, albuminuria status, baseline eGFR, concomitant therapies
- *Intervention(s) or exposure:* GLP-1 receptor agonist or tirzepatide (dose, route, duration)
- *Comparator(s):* placebo or active comparator
- *Outcomes:* kidney and cardiorenal measures (eGFR slope, composite renal endpoints, albuminuria, safety)
- *Main findings:* direction and magnitude of renal effect
- *Appraisal and evidence rating:* methodological quality, certainty, and relevance
- *Notes:* contextual remarks, analytic subgroups, and comments on applicability

Appraisal and Evidence Rating

Because this review was conducted to inform the RAND/UCLA Appropriateness Method for SLANH, each included study underwent a structured critical appraisal using the appropriate validated tool for its design:

- *Randomized controlled trials:* Cochrane Risk of Bias 2 (RoB 2) [10]
- *Post hoc or secondary RCT analyses:* adapted Cochrane or NIH tool
- *Observational comparative studies:* ROBINS-I [11]

The AI tool was programmed to assist in preclassifying bias domains (e.g., randomization, blinding, confounding) and to highlight textual evidence for reviewer judgment. Final classifications were made and approved by the human reviewer, ensuring methodological rigor.

Appraisal results were summarized as low, moderate, or high risk of bias, and a global level of evidence was assigned using an adapted GRADE framework [12].

Data Analysis and Synthesis of Results

Data analysis followed the JBI methodological framework for scoping reviews, emphasizing descriptive mapping and transparent presentation of evidence rather than statistical pooling or effect estimation. Extracted data were organized in Microsoft Excel and analyzed using a combination of quantitative descriptive analysis (frequencies and cross-tabulations) and qualitative content analysis for thematic synthesis. The analytical approach was adapted to accommodate the dual purpose of the review: (1) to provide a comprehensive evidence map and (2) to support the RAND/UCLA Appropriateness Method (RAM) consensus process.

Quantitative (Descriptive) Synthesis

Studies were categorized and summarized according to key dimensions:

- *Study design* (RCT, post hoc RCT analysis, observational comparative study)
- *Population characteristics* (diabetes type, CKD stage, overweight/obesity criteria)
- *Intervention or exposure and comparator* (drug, dose, route, active vs. placebo)
- *Outcome domain* (eGFR slope, albuminuria, kidney failure composite, cardiorenal composite, safety)

Frequency counts were used to describe the number and proportion of studies per category. Cross-tabulations (e.g., *drug vs. CKD stage*, *outcome vs. study design*) were generated to visualize the distribution of evidence and identify gaps.

Qualitative and Thematic Synthesis

In parallel, a fundamental qualitative content analysis was conducted to identify recurring themes and contextual patterns across studies. Text segments describing renal outcomes, mechanisms, or subgroup effects were coded and clustered into thematic categories (e.g., "early intervention and kidney protection", "CKD progression attenuation", "cardiorenal benefit beyond glycemia").

AI-assisted text analysis helped identify frequently co-occurring concepts and outcome terms across abstracts and results sections. All AI-generated coding suggestions were reviewed and validated by the human reviewer to ensure contextual accuracy and interpretive coherence.

Evidence Mapping and Visualization

Extracted data were summarized descriptively and organized into structured summary tables. These tables captured key study characteristics, population features, interventions or exposure, comparators, and renal outcomes, enabling comparisons across drug classes, CKD stages, and clinical scenarios (early versus add-on therapy).

Quantitative synthesis included frequency counts and cross-tabulations to describe the number and type of studies per outcome domain (eGFR slope, albuminuria, composite kidney outcomes, safety). Qualitative synthesis identified recurring patterns and contextual themes, such as consistency of renal benefit across CKD strata or alignment with renal outcomes.

Integration with RAND/UCLA Appropriateness Method

The synthesized evidence from this scoping review is intended to inform a subsequent RAM consensus process, to be conducted under the auspices of SLANH. While this consensus exercise will use the current review as its primary evidence base, the RAND/UCLA process itself is not included in this publication.

Ethics

Ethics approval was not required for this review because it is based exclusively on previously conducted, publicly available studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

The search identified 607 records from electronic databases. After removal of 51 duplicates, 556 unique records were screened by title and abstract. Of these, 520 records were excluded for failing to meet the inclusion criteria. A total of 36 reports were sought for full-text retrieval, and one could not be obtained. The remaining 35 full-text articles were assessed for eligibility. Following full-text review, three reports were excluded for the following reasons: no relevant outcomes ($n=1$), conference poster ($n=1$), and secondary analysis of already included studies ($n=1$). In addition, three eligible reports were identified through other sources (reference list screening/citation searching) and were included. Ultimately, 35 studies met the inclusion criteria

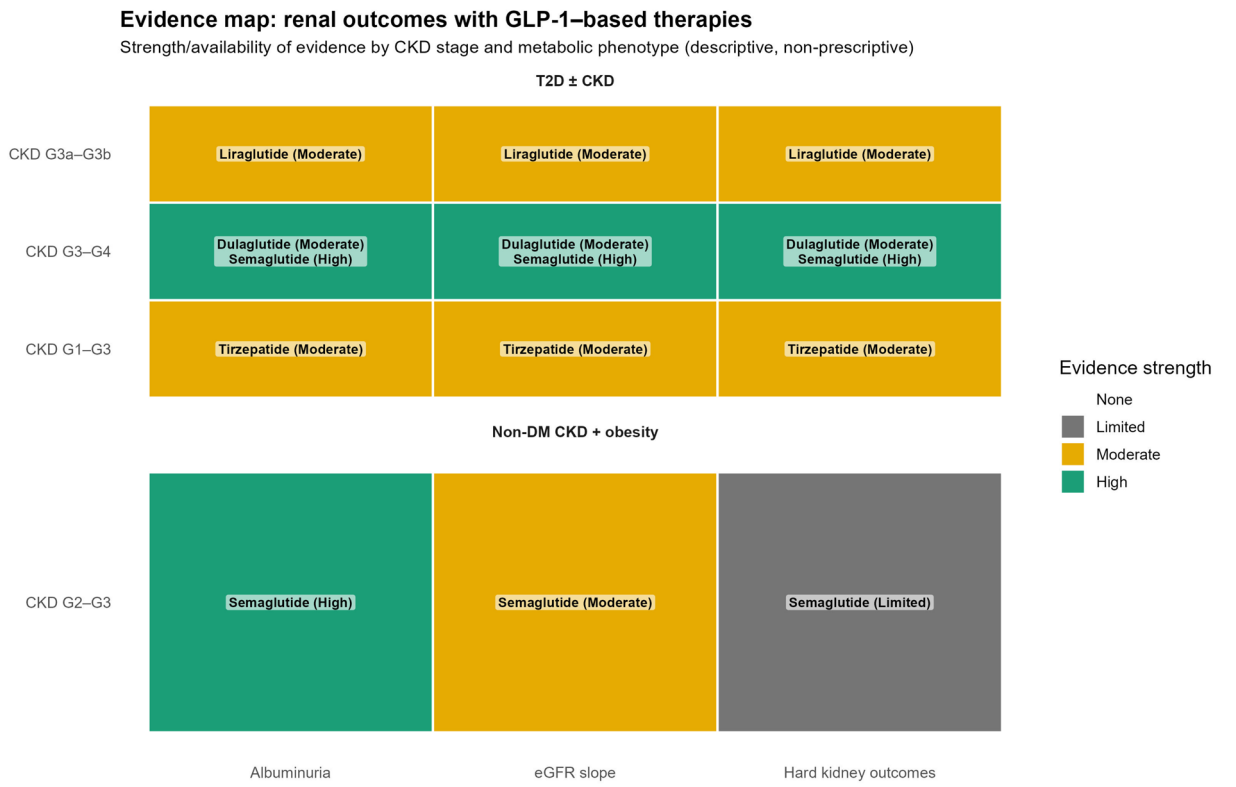

Fig. 1 Evidence map of renal outcomes with GLP-1-based therapies across CKD stages and metabolic phenotypes. The figure summarizes the strength and availability of evidence for renal outcomes stratified by chronic kidney disease (CKD) stage and metabolic phenotype (type 2 diabetes and overweight/obesity status). Colors represent the strength/availability of evidence by renal outcome domain and endpoint hierarchy (GRADE-informed), not effect size. High indicates high-certainty randomized evidence (including trials with adjudicated kidney outcomes and/or dedicated kidney-endpoint trials); Moderate indicates moderate-certainty evidence, typically derived from secondary or post hoc renal endpoints; Limited indicates evidence from shorter-duration, indirect, or exploratory datasets. When multiple agents contribute evidence within the same CKD–phenotype stratum, drug names are grouped within the corresponding cell, and the color reflects the highest level of evidence available for that outcome in that stratum. Cells with limited or absent evidence primarily reflect lack of stratified reporting rather than absence of effect. This figure is descriptive and non-prescriptive and does not imply comparative effectiveness

and were included in the scoping review. The study selection process and report counts are summarized in Supplementary Fig. S1 (PRISMA-ScR flow diagram). The synthesis of individual studies findings is presented in Supplementary Table 2, while the main characteristics and renal outcomes of included studies are summarized in Table 1.

Renal outcome evidence was first mapped by CKD stage and metabolic phenotype (Fig. 1), after which agent-specific findings were summarized within this framework. This figure integrates medications with the population phenotype (type 2 diabetes with or without CKD, and non-diabetic CKD with obesity), CKD stage, and renal outcome domains (albuminuria, eGFR slope, and hard kidney outcomes), using a GRADE-informed approach. The evidence map is intended to support rapid appraisal of where evidence is most robust or remains limited and does not imply effect size or clinical recommendation. In addition to Fig. 1, we summarized the availability of renal outcome reporting using a CKD stage × metabolic phenotype matrix (Supplementary Table 3), which highlights strata where evidence is limited or not reported.

Table 1 Summary of renal outcome evidence for GLP-1 receptor agonists and tirzepatide (synthesis by study design and outcome hierarchy)

Drug	Study design and renal outcome hierarchy	Population and context (n range)	Renal outcomes assessed	Summary of findings (direction/magnitude)	Overall risk of bias	Certainty (GRADE)
Semaglutide	Multiple double-blind RCTs with renal endpoints: FLOW (dedicated renal outcomes trial, primary composite ≥ 50% eGFR decline / ESKD / eGFR < 15 / renal–CV death); SUSTAIN-6 (CVOT with prespecified secondary renal endpoint "new or worsening nephropathy"); SOUL (broad CV population, renal composite secondary endpoint); SEMPA (mechanistic MRI study of renal volume); *Nature Medicine* 2025 CKD RCT (24-week placebo-controlled trial in overweight/obesity and CKD without diabetes; primary endpoint UACR change). Also observational real-world cohorts including CKD G4–G5	Adults with T2D ± CKD, eGFR 25–90 mL/min/1.73 m^2, frequent albuminuria; > 10,000 participants across major RCTs and several hundred in real-world studies. Additional populations: adults ≥ 45 y ears of age with overweight/obesity and established CVD without diabetes (SELECT) and adults with overweight/obesity and CKD without diabetes (*Nature Medicine* 2025; eGFR ≥ 25; UACR 30–3500 mg/g), plus advanced CKD (G4–G5) in observational cohorts	Composite kidney endpoint (ESKD, sustained eGFR < 15, ≥ 50% eGFR decline, renal–CV death, new or worsening nephropathy); eGFR slope; UACR; renal structural metrics (MRI); short-term albuminuria response in non-diabetic CKD	Consistent renoprotective effect across RCTs and settings: SUSTAIN-6: 36% relative risk reduction in new/worsening nephropathy vs placebo (HR 0.64, 95% CI 0.46–0.88). FLOW: primary composite HR 0.76 (95% CI 0.66–0.88), slower eGFR decline (+ 1.16 mL/min/1.73 m^2/year) and approx. 32% UACR reduction. SOUL/SELECT: concordant benefit (renal HR ≈ 0.78–0.91), eGFR stabilization of about + 1 mL/min/1.73 m^2/year and UACR ↓approx. 30%, including non-diabetic overweight/obese high-CV-risk populations. *Nature Medicine* 2025 non-diabetic CKD trial: approx. 52% placebo-corrected reduction in UACR at 24 weeks ($p < 0.0001$) on top of RAS blockade (± SGLT2i) with stable eGFR and no excess renal adverse events. Mechanistic data: renal volume ↓ approx. 3% without functional deterioration. Observational cohorts: eGFR stability even in CKD G4–G5, albuminuria reduction and improvement in KDIGO risk category	Low for RCTs (robust design, blinding, adequate follow-up, consistent effects across T2D, CV and non-diabetic CKD populations); serious for observational studies (residual confounding, non-random allocation)	High for composite kidney outcomes and eGFR slope; high for albuminuria reduction (multiple RCTs including a dedicated non-diabetic CKD trial, some limitation in duration); low for observational evidence

Table 1 continued

Drug	Study design and renal outcome hierarchy	Population and context (n range)	Renal outcomes assessed	Summary of findings (direction/magnitude)	Overall risk of bias	Certainty (GRADE)
Tirzepatide	Active-controlled RCT vs insulin with secondary/post hoc renal endpoints (eGFR slope, composite) Pooled IPD post hoc analysis (UACR main outcome) Double-blind RCT in HFpEF/obesity with secondary renal endpoints (creatinine- and cystatin-based eGFR, UACR) Prospective cohort (switch from prior GLP-1RA)	Adults with T2D ± CKD, high CV risk; CKD-enriched HFpEF populations. (> 5000 in RCTs; approx. 50 in cohort)	eGFR slope; UACR (dose–response); expanded composite renal outcome; eGFR–cystatin trajectories	Favorable effect: slower eGFR decline vs insulin ($\Delta \approx +2.2$ mL/min/1.73 m^2/year); UACR ↓20–45% (dose–response); less albuminuria progression; improved cystatin C eGFR	Low–moderate (RCT; post hoc concerns); serious (observational)	Moderate (eGFR/composite, downgraded for indirectness); moderate (UACR); low (observational)

Table 1 continued

Drug	Study design and renal outcome hierarchy	Population and context (n range)	Renal outcomes assessed	Summary of findings (direction/magnitude)	Overall risk of bias	Certainty (GRADE)
Dulaglutide	Double-blind CVOT RCT with pre-specified secondary composite renal endpoint (macroalbuminuria, ≥ 30–50% eGFR decline, RRT) Open-label active-controlled RCT in CKD G3–G4 with secondary renal outcomes (eGFR creat/cystatin; ≥ 40% eGFR decline / ESKD) Pooled phase II/III meta-analyses (secondary renal) Observational cohort (IPW-adjusted)	T2D with CKD G1–G4; macroalbuminuric subgroups; follow-up up to 5.4 years in CVOT	Composite renal outcome; eGFR slope; UACR; ESKD incidence	Consistent reductions: composite renal risk approx. 15% (HR ≈ 0.85); higher eGFR vs insulin (+ 2.7–2.9 mL/min/1.73 m^2 at 52 weeks); UACR ↓18–40% (largest in A3)	Low (RCTs); moderate–serious (observational)	Moderate (composite/eGFR, downgraded for indirectness); moderate (UACR)

Table 1 continued

Drug	Study design and renal outcome hierarchy	Population and context (n range)	Renal outcomes assessed	Summary of findings (direction/magnitude)	Overall risk of bias	Certainty (GRADE)
Liraglutide	LEADER: double-blind CVOT RCT with prespecified secondary renal composite (persistent macroalbuminuria, sustained eGFR decline, initiation of RRT) LIRA-RENAL: double-blind 26-week RCT in moderate CKD (eGFR 30–59) Double-blind 12-week crossover RCT with UACR as primary outcome Mechanistic before–after studies (hemodynamics, volume) and observational cohorts	Adults with T2D ± CKD; persistent albuminuria under RAS blockade; eGFR ≥ 30 mL/min/1.73 m^2 (LIRA-RENAL: CKD G3a–G3b; $n = 279$)	Composite kidney endpoint; UACR (primary in crossover study); measured GFR (^{51}Cr-EDTA); eGFR slope; 24-h BP	Consistent renoprotective signal focused on albuminuria reduction and kidney function preservation: LEADER: ↓ renal composite (HR ≈ 0.78), mainly driven by ↓ macroalbuminuria LIRA-RENAL: stable eGFR (week 26/baseline ratio approx. 0.99 vs 1.01; ETR 0.98; $P = 0.36$) and numerically lower UACR (ratio 0.87 vs 1.05; ETR 0.83; $P = 0.19$); no renal safety signal or increased hypoglycemia; GI intolerance most frequent AE Mechanistic/crossover studies: approx. 30–35% UACR reduction without measured GFR change; effect correlated with ↓ systolic BP > HbA1c or weight ⇒ predominantly hemodynamic antiproteinuric mechanism; replicated in before–after trial showing ↓ extracellular volume and biphasic BP response Real-world cohorts: proteinuria reduction and improved annual eGFR slope, consistent with RCT findings	Low (RCTs: robust design, blinding, adjudication); moderate (mechanistic/observational: small sample, confounding)	Moderate (composite, downgraded for indirectness); moderate (UACR, downgraded for imprecision); moderate (eGFR slope)

Table 1 continued

Drug	Study design and renal outcome hierarchy	Population and context (n range)	Renal outcomes assessed	Summary of findings (direction/magnitude)	Overall risk of bias	Certainty (GRADE)
Other GLP-1RAs / duals (efpeglenatide, exenatide, lixisenatide, cotadutide GLP-1/glucagon)	Double-blind CVOT RCT with secondary renal endpoint (efpeglenatide) Phase 2 randomized trials with UACR as primary endpoint (cotadutide, 26 weeks & 32 days) Post hoc CVOT analyses (exenatide, lixisenatide) and open RCT in DKD with macroalbuminuria (exenatide)	T2D ± CKD G2–G4 or high CV risk; albuminuric subgroups	Composite renal; UACR; eGFR slope	Class effect: efpeglenatide ↓renal composite (HR ≈ 0.68); cotadutide ↓UACR 44–50% (primary); exenatide/lixisenatide ↓UACR 20–35% and improved eGFR slope in albuminuric subgroups	Low–moderate (RCTs); moderate (post hoc/open)	High (efpeglenatide); moderate (cotadutide, primary but short duration); moderate (exenatide/lixisenatide, post hoc)

This table summarizes renal outcome evidence from randomized and observational studies of GLP-1 receptor agonists and tirzepatide, organized by study design and outcome hierarchy (primary, secondary, exploratory/post hoc). Certainty was rated using the GRADE framework, with downgrades for indirectness when renal outcomes were not primary

Hazard ratios and percentage changes represent integrated synthesis across studies; individual estimates are reported in Supplementary Tables. "Composite renal endpoint" includes, per study, combinations of ≥ 40–50% sustained eGFR decline, ESKD, eGFR < 15 mL/min/1.73 m^2, and renal/cardiovascular death. When both creatinine- and cystatin C-based eGFR were reported, concordance between biomarkers was prioritized; early eGFR "dip" was interpreted as a transient hemodynamic adjustment. Certainty was downgraded for indirectness when renal outcomes were not primary or derived from post hoc analyses

Abbreviations: *A3* severely increased albuminuria, *BP* blood pressure, *CKD* chronic kidney disease, *CV* cardiovascular, *CVOT* cardiovascular outcomes trial, *DKD* diabetic kidney disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *GRADE* Grading of Recommendations Assessment, Development and Evaluation, *HFpEF* heart failure with preserved ejection fraction, *HR* hazard ratio, *IPD* individual participant data, *IPW* inverse probability weighting, *MRI* magnetic resonance imaging, *RAS* renin–angiotensin system, *RCT* randomized controlled trial, *RRT* renal replacement therapy, *T2D* type 2 diabetes, *UACR* urinary albumin-to-creatinine ratio

Semaglutide

Renal Outcomes

Across the included studies, semaglutide consistently demonstrated favorable effects on renal endpoints in patients with type 2 diabetes (T2D) with and without CKD.

In the SUSTAIN-6 trial [4], one of the earliest extensive cardiovascular outcome studies, semaglutide significantly reduced the risk of new or worsening nephropathy, defined as persistent macroalbuminuria, doubling of serum creatinine, need for RRT, or death from renal causes, compared with placebo (3.8% vs 6.1%; HR 0.64, 95% CI 0.46–0.88; $p=0.005$). This 36% relative risk reduction in nephropathy progression represented the first robust evidence of semaglutide's kidney-protective potential in a high cardiovascular risk T2D population, preceding and complementing later dedicated renal trials.

In the pivotal FLOW trial [13], once-weekly semaglutide 1.0 mg significantly reduced the primary composite kidney outcome—comprising end-stage kidney disease, sustained eGFR < 15 mL/min/1.73 m^2, ≥ 50% sustained eGFR decline, or renal/cardiovascular death—compared with placebo (HR 0.76, 95% CI 0.66–0.88; $p=0.0003$). The benefit was consistent across renal subcomponents and accompanied by a slower decline in eGFR (+1.16 mL/min/1.73 m^2/year; $p<0.001$) and an approximate 32% reduction in albuminuria compared to placebo.

The SOUL trial [14], conducted in a broader cardiovascular population, also showed a numerically lower rate of renal composite events (HR 0.91, 95% CI 0.80–1.05) and stable kidney function over a mean follow-up of nearly 4 years, complementing the findings from FLOW.

In the smaller SEMPA substudy [15], semaglutide was associated with modest decreases in total kidney volume (−3%) and stability of measured GFR and albuminuria over 32 weeks, consistent with early renal structural modulation but without detectable clinical deterioration.

Observational data supported the trial findings. In a Spanish multicenter real-world cohort ($n=486$) [16], 12-month treatment with subcutaneously administered semaglutide maintained eGFR stability and significantly reduced albuminuria, particularly among participants with KDIGO high or very-high risk, with one-third improving their risk category. In a retrospective cohort of advanced CKD (G4–G5) [17], renal function remained stable (ΔeGFR ≈ 0 mL/min/1.73 m^2) with no excess of renal adverse events.

The SELECT prespecified renal analysis [18] demonstrated that once-weekly subcutaneously administered semaglutide 2.4 mg significantly reduced the incidence of major kidney events (HR 0.78, 95% CI 0.63–0.96; $p=0.02$) in adults with overweight or obesity and established cardiovascular disease without diabetes. These renal benefits were consistent across baseline kidney function and albuminuria subgroups, including individuals with eGFR < 60 mL/min/1.73 m^2, in whom the mean eGFR improved by +2.19 mL/min/1.73 m^2 at 104 weeks. The treatment effect was independent of glycemic status, supporting a kidney-protective mechanism of semaglutide in non-diabetic populations.

The recently published RCT in overweight/obesity and CKD without diabetes [19] provides the most direct evidence to date in a non-diabetic CKD population. In this study, semaglutide 2.4 mg weekly achieved a −52.1% reduction in albuminuria versus placebo at 24 weeks (95% CI −65.5 to −33.4; $p<0.0001$), with progressive decreases observed throughout dose escalation. This clinically meaningful reduction was achieved despite high background renin–angiotensin system (RAS) activity. Safety findings were consistent with the known gastrointestinal (GI) profile of GLP-1 receptor agonists.

Risk of Bias

Methodological appraisal revealed a low risk of bias for all RCTs (SUSTAIN-6, FLOW, SOUL, and SEMPA), as assessed using the RoB 2 tool. Randomization and allocation concealment were centrally managed; investigators, participants, and outcome assessors were blinded; and independent blinded committees adjudicated renal endpoints. Follow-up completeness exceeded 97% in all trials. The risk of selective reporting

was low, as all trials were prospectively registered and reported prespecified kidney outcomes.

In contrast, the observational studies exhibited a serious risk of bias, primarily due to confounding by indication, non-randomized treatment allocation, and the absence of concurrent control groups. Measurement and reporting biases were moderate but mitigated by the standardized definitions of eGFR and UACR (urine albumin-to-creatinine ratio). Consequently, causal inference relies primarily on randomized evidence, whereas observational data contribute to external validity and contextual interpretation.

Certainty of Evidence (GRADE Assessment)

The overall certainty of evidence was rated as high for the composite kidney outcome and eGFR slope, based on large, low-bias RCTs (FLOW and SUSTAIN-6). Certainty was graded as moderate for albuminuria outcomes due to population heterogeneity and variable measurement across studies, and low for observational cohorts due to residual confounding and imprecision. Mechanistic data from imaging and structural studies were downgraded due to indirectness and small sample sizes.

Safety data achieved high certainty, as adverse event patterns were consistent across randomized and observational studies, with no signal of nephrotoxicity or deterioration in renal function. Collectively, the GRADE assessment supports high confidence in the evidence for semaglutide's renoprotective efficacy and safety across CKD stages and populations, including non-diabetic individuals.

Adverse Events

Across all studies, semaglutide displayed a favorable safety profile. Gastrointestinal events—nausea, vomiting, and abdominal discomfort—were the most frequent, occurring in 10–12% of participants and leading to discontinuation. Serious adverse events were less common in participants treated with semaglutide than in those treated with placebo in the pivotal FLOW trial (49.6% vs 53.8%). Hypoglycemia was rare (<3%) and occurred mainly in patients receiving insulin.

Pancreatitis and gallbladder events were infrequent (<0.5%), and no increase in adjudicated diabetic retinopathy events was observed. In advanced CKD cohorts, adverse events were similar to those in patients without CKD, though GI intolerance prompted higher discontinuation rates (up to 35%). No study reported drug-related decline in eGFR or worsening renal function.

Taken together, evidence from randomized and real-world studies provides a coherent picture of semaglutide's renoprotective efficacy and favorable safety across the T2D–CKD spectrum and extending to individuals without diabetes. Large-scale trials demonstrate robust reductions in primary kidney outcomes, slower decline in eGFR, and improvements in albuminuria, independent of glycemic effects and concomitant therapies such as SGLT2 inhibitors or RAS blockade. In particular, the SELECT trial demonstrated a significant 22% relative reduction in a prespecified composite kidney endpoint (HR 0.78, 95% CI 0.63–0.96; $p = 0.02$) in adults with overweight or obesity and established cardiovascular disease without diabetes, with consistent benefits across subgroups and a mean eGFR improvement of +2.19 mL/min/1.73 m^2 in participants with baseline eGFR < 60 mL/min/1.73 m^2. These findings indicate that semaglutide's kidney-protective effect is not contingent on glycemic modulation, supporting its role in reducing non-diabetic CKD risk.

Observational data further extend these benefits to advanced CKD and heterogeneous real-world populations, supporting generalizability. The consistent direction and magnitude of effects across study designs, together with low risk of bias and high GRADE certainty, reinforce the causal nature of semaglutide's renal benefit. Mechanistically, the observed reduction in kidney volume and structural diffusion metrics suggests early modulation of intrarenal hemodynamics that may underpin the long-term preservation of renal function. Overall, the integrated findings substantiate semaglutide as an evidence-based therapeutic option

for cardiorenal protection in T2D and potentially in non-diabetic CKD associated with obesity or cardiovascular disease, complementary to SGLT2 inhibitors and RAS blockade, with high-quality evidence for efficacy and safety across CKD stages.

Tirzepatide

Renal Outcomes

Across randomized and observational studies, tirzepatide consistently demonstrated favorable effects on renal parameters among adults with T2D, with or without CKD.

In a post hoc analysis of the SURPASS-4 clinical trial [20, 21], which enrolled participants with T2D and high cardiovascular risk, tirzepatide significantly slowed kidney function decline compared with insulin glargine. The annual eGFR slope was − 1.4 versus − 3.6 mL/min/1.73 m^2, yielding an adjusted between-group difference of + 2.2 mL/min/1.73 m^2 (95% CI 1.6–2.8). The renal benefit was more pronounced among participants with baseline eGFR < 60 mL/min/1.73 m^2 (difference + 3.7, 95% CI 2.4–5.1). Albuminuria remained stable with tirzepatide but increased with glargine, resulting in a − 31.9% between-group difference that persisted through 52 and 104 weeks. Progression to higher albuminuria categories was reduced (HR 0.43), while regression among participants with UACR ≥ 30 mg/g was more frequent (HR 1.97). A broad composite renal endpoint occurred less often with tirzepatide (HR 0.58, 95% CI 0.43–0.80). Adjustment for changes in HbA1c and body weight did not materially affect these findings, suggesting kidney-specific effects beyond glycemic or weight-mediated mechanisms.

A pooled individual participant-level analysis of the SURPASS 1–5 trials [22] further supported these findings. Tirzepatide reduced UACR in a dose-dependent manner over approximately 40–42 weeks (− 19.3%, − 22.0%, and − 26.3% with 5, 10, and 15 mg, respectively). Among participants with baseline UACR ≥ 30 mg/g, the reductions were larger at higher doses (− 31.3%, − 42.2%, and − 47.3%). Overall, eGFR remained stable during follow-up (< 1 year). Mediation analysis indicated that approximately 46% of the reduction in albuminuria could be explained by improvements in HbA1c and weight, while about 54% appeared independent, consistent with direct renal mechanisms.

Although primarily designed for heart failure outcomes, the SUMMIT trial [23], which included a CKD-enriched population, also demonstrated renal benefits with tirzepatide. Creatinine-based eGFR exhibited a slight early dip at 12 weeks, followed by improvement relative to placebo by week 52 (+ 1.9 mL/min/1.73 m^2). Cystatin C-based eGFR improved steadily without an initial dip (+ 2.9 mL/min/1.73 m^2 at 52 weeks). Albuminuria decreased by approximately 25% at 24 weeks and 15% at 52 weeks (borderline statistical significance), with consistent effects across CKD classifications based on creatinine or cystatin C.

In a prospective observational cohort of individuals with CKD G3a–G3b (A2–A3) [24] previously treated with another GLP-1 receptor agonist (dulaglutide), switching to tirzepatide improved HbA1c and body weight, maintained eGFR stability, and prevented the increase in UACR observed in participants who continued dulaglutide therapy over 6 months. Despite its non-randomized design and limited sample size, this study provides real-world evidence of renal stability during tirzepatide treatment.

Finally, a systematic review and three-level meta-analysis [25] including eight RCTs and 9533 participants synthesized the renal evidence for tirzepatide. All trials were judged at low risk of bias (RoB2). Pooled estimates showed a mean reduction in UACR of − 26.9% (95% CI − 34.8 to − 19.0; $p < 0.001$), with more potent effects among participants with baseline UACR ≥ 30 mg/g (− 41.4%, 95% CI − 54.4 to − 28.5). This antiproteinuric benefit persisted across all doses (5, 10, and 15 mg), confirming a dose–response relationship. Comparative subgroup analyses found tirzepatide superior to placebo and insulin regimens, with no significant difference versus semaglutide. The pooled effect on eGFR

was neutral [mean difference + 0.39 mL/min/1.73 m^2 (95% CI − 0.64 to + 1.42); $p = 0.46$], indicating that the renal benefit is primarily mediated through albuminuria reduction rather than filtration improvement. The overall level of evidence was rated moderate, limited by trial duration and the absence of hard kidney endpoints.

Risk of Bias

The overall methodological quality of the randomized evidence was high, with only minor concerns related to the post hoc nature of some renal analyses.

In the SURPASS-4 trial, randomization procedures and centralized laboratory assessments reduced the risk of selection and measurement bias. However, the open-label design introduced some potential for deviations from intended interventions and selective reporting, particularly for exploratory renal endpoints. Consequently, the overall risk of bias for kidney outcomes was rated as low to moderate.

The pooled SURPASS 1–5 individual participant-level analysis demonstrated a low risk of bias across most domains, including randomization, adherence, completeness of follow-up, and outcome measurement. Nevertheless, the post hoc analytical approach and multiple comparisons raised some concerns regarding selective reporting, resulting in an overall low-to-moderate risk of bias.

In the SUMMIT trial, which incorporated prespecified endpoints and blinded adjudication for cardiovascular and heart failure outcomes, the renal biomarker assessments followed predefined schedules and consistent analytical methods across CKD subgroups. These features, together with its double-masked design, supported a low overall risk of bias.

For the observational evidence, assessed using the ROBINS-I framework, the prospective switch cohort was judged to have a serious overall risk of bias. This rating was driven by potential confounding by indication, single-center recruitment, absence of randomization, and short follow-up duration. Outcome measurement and reporting were adequate, but the lack of blinding and the limited comparators limit the internal validity of the findings, rendering them primarily hypothesis-generating.

Certainty of Evidence (GRADE Assessment)

The overall certainty of the renal evidence for tirzepatide was rated as moderate to high, primarily supported by large randomized datasets demonstrating consistent benefits on kidney outcomes.

For composite kidney outcomes and eGFR slope, the certainty was judged as moderate to high. This rating reflects robust evidence from randomized comparisons showing a slower rate of eGFR decline and reduced incidence of renal composite endpoints compared with active control (insulin glargine). The effects were consistent across predefined subgroups and remained significant after adjustment for changes in HbA1c and weight, indicating partial independence from metabolic improvements. Certainty was downgraded by one level in some judgments due to the post hoc nature of the analyses and the open-label design of SURPASS-4.

For albuminuria (UACR) outcomes, the certainty of evidence was graded as moderate. Pooled analyses from SURPASS 1–5 demonstrated clear, dose-dependent reductions in UACR, with directionally similar findings observed in the SUMMIT trial. However, the evidence was downgraded due to reliance on post hoc analyses and relatively short follow-up durations (< 1 year) in most studies, which limit precision regarding long-term renal trajectories.

The evidence from observational CKD cohorts was rated as low certainty. Although findings were consistent with the direction of effect observed in randomized trials—showing stability of eGFR and reduced progression of albuminuria—these studies were downgraded for residual confounding, lack of randomization, and limited sample sizes, which restrict causal inference.

In summary, the GRADE assessment supports moderate-to-high certainty for tirzepatide's renoprotective effects on composite kidney outcomes and eGFR decline, moderate certainty for

albuminuria improvement, and low certainty for observational evidence.

Adverse Effects

Across trials and observational data, GI events were more frequent with tirzepatide than with comparators, typically mild to moderate and dose-related; no new renal safety signals emerged. In SUMMIT, GI events were more common with tirzepatide and were not modified by CKD status. Hypoglycemia risk was low overall but higher in insulin-treated participants; in the switch cohort, two hypoglycemic events occurred in insulin users. No sustained acute kidney injury signal or CKD adverse SMQ imbalance was observed in SURPASS-4 analyses.

Taken together, randomized and real-world data indicate that tirzepatide provides cardiorenal risk modification in T2D, with slower eGFR decline and lower albuminuria, and effects that are consistent across CKD strata and not fully explained by glycemic/weight changes. The highest-certainty evidence arises from SURPASS-4 comparisons with insulin glargine, corroborated by pooled SURPASS analyses (UACR) and by CKD-enriched findings in SUMMIT showing favorable mid-term renal biomarker trajectories. Observational data in CKD G3a–G3b align with these trends but are limited by confounding and short duration. Overall, the profile supports tirzepatide as a reasonable add-on within comprehensive T2D-CKD care alongside RAS blockade and, when indicated, SGLT2 inhibitors/mineralocorticoid antagonists, with ongoing monitoring of albuminuria, eGFR, and tolerability.

Dulaglutide

Renal Outcomes

Across randomized and observational studies, dulaglutide demonstrated consistent renoprotective effects in adults with T2D, with evidence spanning a broad range of baseline kidney function—from normal to stage 4 CKD—and follow-up extending up to 5.4 years.

In the REWIND RCT [26], once-weekly dulaglutide 1.5 mg significantly reduced the composite kidney outcome—new macroalbuminuria, sustained ≥ 30% eGFR decline, or chronic RRT—compared with placebo (HR 0.85, 95% CI 0.77–0.93; $p = 0.0004$) over a median follow-up of 5.4 years. The benefit was driven mainly by a reduction in new macroalbuminuria (HR 0.77; 0.68–0.87), with supportive trends for ≥ 40% (HR 0.70) and ≥ 50% (HR 0.56) eGFR decline. Mean eGFR was preserved, and albuminuria decreased by approximately 18% relative to placebo. Mediation analyses suggested that improvements in HbA1c and systolic blood pressure accounted for only a minor proportion of the renal benefit (approx. 25–30%), suggesting possible kidney-specific mechanisms.

The AWARD-7 trial [5] compared dulaglutide (0.75 mg or 1.5 mg weekly) with insulin glargine in participants with T2D and CKD G3–G4 receiving background RAS blockade. After 52 weeks, eGFR (both creatinine- and cystatin C-based) declined significantly less with dulaglutide than with glargine, with between-group differences of +2.7 to +2.9 mL/min/1.73 m^2 ($p < 0.01$). The effect was most pronounced in participants with macroalbuminuria (A3), who exhibited a 43% reduction in UACR at 26 weeks and a 29% reduction at 52 weeks compared with glargine. Rates of end-stage kidney disease (ESKD) were numerically lower with dulaglutide (4–5%) than with glargine (8%), though the difference was not statistically significant given the sample size. The incidence of hypoglycemia was roughly half with dulaglutide, and GI events were more common but generally mild.

An exploratory analysis of AWARD-7 [27] evaluated outcomes by baseline albuminuria and in participants with macroalbuminuria, dulaglutide 1.5 mg reduced the risk of ≥ 40% eGFR decline or ESKD versus insulin glargine (HR 0.25, 95% CI 0.10–0.68; events 7% vs 22%), while the overall population showed a 55% risk reduction (HR 0.45; 0.20–0.97). No renal deaths occurred, and results were consistent whether eGFR was calculated by creatinine or cystatin C, indicating robustness independent of muscle mass.

In an individual-patient meta-analysis of nine phase II/III AWARD trials [28], dulaglutide showed stable eGFR trajectories over

26–104 weeks compared with placebo and active comparators (metformin, sitagliptin, exenatide, insulin glargine). UACR decreased modestly but significantly at 26 weeks ($p < 0.05$ across all comparators). The incidence of ≥ 40% eGFR decline within 1 year was lower with dulaglutide (0.26%) than with glargine (1.25%; $p = 0.012$). No increase in acute kidney injury events was observed, and overall renal safety was favorable.

Complementing trial data, the JDDM67 observational study [29] evaluated Japanese adults with T2D and CKD G3–G4 treated with dulaglutide 0.75 mg versus non-GLP-1RA therapy for ≥ 6 months using propensity-weighted analyses. Over 3 years, the annual eGFR slope was significantly less negative with dulaglutide (+0.11 vs − 1.29 mL/min/1.73 m^2 per year; difference + 1.40, 95% CI 0.83–1.97). The benefit was most significant in participants with macroalbuminuria (A3) and in those using concomitant SGLT2 inhibitors, suggesting additive or complementary mechanisms. UACR remained essentially unchanged between groups. Despite residual confounding, these findings support the real-world preservation of kidney function with dulaglutide.

Collectively, randomized and observational evidence indicate that dulaglutide slows eGFR decline and reduces albuminuria, with benefits most pronounced in individuals with higher baseline albuminuria or advanced CKD. The consistency of effects across creatinine and cystatin C measures, along with mediation analyses showing independence from glycemic control, supports a direct renal effect beyond glucose lowering.

Risk of Bias

The overall methodological quality of the dulaglutide evidence base was high, with a consistently low risk of bias across the principal RCTs and only minor limitations that did not compromise internal validity. All major studies employed rigorous randomization procedures, centralized laboratory measurements, and prespecified renal outcomes, while attrition rates were minimal and baseline characteristics were well balanced between groups.

In the REWIND trial, randomization and allocation concealment were implemented through a centralized system, ensuring comparability between treatment arms. Renal outcomes were predefined and adjudicated by blinded expert committees using standardized definitions, effectively minimizing measurement and reporting bias. The large sample size and extended median follow-up of 5.4 years strengthened the internal validity and statistical precision of the findings. The only limitation identified was the relatively low proportion of participants with advanced CKD at baseline, which may restrict generalizability to late-stage disease but does not affect the credibility of the primary results.

The AWARD-7 trial, which specifically targeted patients with moderate-to-severe CKD, also demonstrated a low risk of bias across domains. Its double-blind, double-dummy design and use of an active comparator (insulin glargine) reduced the likelihood of performance and detection bias. Centralized assessment of serum creatinine, cystatin C, and UACR further enhanced reliability. The relatively modest sample size and 1-year duration were potential sources of imprecision for long-term outcomes. Yet, the direction and consistency of the effects across renal endpoints minimize concerns about systematic bias.

The AWARD phase II/III pooled meta-analysis maintained a similar standard of methodological rigor. All trials included in the analysis were prospectively registered, conducted under uniform protocols, and reported renal parameters using harmonized definitions. Although industry sponsorship was present, the transparency of reporting and consistency of results across trials make selective reporting bias unlikely.

In contrast, the observational evidence was subject to the inherent limitations of non-randomized designs. The risk of bias was rated as moderate to severe according to the ROBINS-I framework, mainly due to potential residual confounding, single-country data, and absence of blinding. Nevertheless, methodological strengths included the use of propensity score weighting and standardized definitions of CKD outcomes, which enhance comparability with randomized data and mitigate, though not eliminate, bias.

Certainty of Evidence (GRADE Assessment)

The certainty of the evidence for dulaglutide's renal effects was rated as high for randomized comparisons and moderate for observational data.

For composite kidney outcomes, the certainty was high, supported by robust results from the large-scale REWIND trial demonstrating consistent risk reduction for new macroalbuminuria and sustained eGFR decline, with a clear dose–response pattern and long-term follow-up of over 5 years.

For eGFR slope and renal function preservation, evidence from AWARD-7 and supporting meta-analyses provided high certainty. Both doses of dulaglutide attenuated eGFR decline relative to insulin glargine and maintained renal stability across CKD stages G3–G4. Findings were consistent across creatinine- and cystatin C-based estimations, reinforcing reliability and generalizability.

Evidence for albuminuria outcomes was graded as moderate to high certainty. Trials consistently showed significant reductions in UACR, especially in macroalbuminuric participants. Minor downgrading applied due to variability in timing and methods of UACR measurement, and modest sample sizes in subgroup analyses.

Evidence from observational studies was graded as moderate certainty, given consistency with RCT directionality but downgraded for confounding and limited duration.

Overall, the GRADE assessment supports high certainty for dulaglutide's ability to slow renal function decline and reduce albuminuria in T2D, with moderate certainty for observational data extending these benefits to real-world settings.

Adverse Events

The safety profile of dulaglutide was consistent across all studies and aligned with the known class effects of GLP-1 receptor agonists.

In REWIND, GI adverse events (nausea, vomiting, diarrhea) occurred more frequently with dulaglutide than placebo (47% vs 34%) but were primarily mild or moderate and rarely led to discontinuation (< 3%). Hypoglycemia rates were low and similar to placebo in participants not receiving insulin or sulfonylureas. No increase in acute kidney injury or renal adverse events was observed.

In AWARD-7, GI events were reported in 13–20% of participants, leading to discontinuation in 3–5%. Hypoglycemia incidence was significantly lower than with insulin glargine, while other serious adverse events occurred at similar rates. No signal of pancreatitis, gallbladder disease, or worsening kidney function was identified.

Observational data reported comparable tolerability, with GI symptoms as the leading cause of withdrawal, but no evidence of renal toxicity. Across all trials, dulaglutide maintained a favorable safety profile in CKD populations, including stages G3–G4, with no dose adjustment required for reduced eGFR.

The totality of evidence supports dulaglutide as an effective and safe renoprotective therapy in individuals with T2D across a broad spectrum of CKD. Randomized data demonstrate consistent attenuation of eGFR decline, reductions in albuminuria, and lower incidence of renal composite outcomes, with benefits observed independently of glycemic control or weight reduction.

Long-term results from REWIND provide compelling evidence of renal protection extending beyond glucose lowering, while AWARD-7 establishes efficacy and safety in patients with moderate-to-severe CKD. Mechanistic plausibility is reinforced by findings that renal improvements parallel but are not fully explained by metabolic changes, suggesting direct effects on intrarenal hemodynamics and inflammation.

Observational data complement these findings, confirming kidney function stability and favorable tolerability in the real world. Taken together, the consistency, magnitude, and duration of benefit provide high-certainty evidence supporting the integration of dulaglutide into comprehensive renal risk management for T2D, either as monotherapy or in combination with other evidence-based agents, such as SGLT2 inhibitors or RAS blockade.

Liraglutide

Renal Outcomes

Across randomized and observational studies, liraglutide demonstrates a consistent pattern of albuminuria reduction and preservation of kidney function in adults with T2D, including those with established CKD.

In the long-term LEADER cardiovascular outcomes trial [30], once-daily liraglutide significantly reduced the prespecified renal composite outcome—new persistent macroalbuminuria, sustained eGFR decline, or initiation of chronic RRT—compared with placebo (HR ≈ 0.78) over a median follow-up of 3.8 years. A lower incidence of new macroalbuminuria primarily drove the benefit, while effects on eGFR decline were directionally favorable and consistent across baseline renal function strata. The renal findings paralleled the reductions in major adverse cardiovascular events and all-cause mortality, supporting a broad cardiorenal protective profile that extends beyond glycemic control.

The dedicated LIRA-RENAL trial [31] further evaluated liraglutide in patients with T2D and moderate renal impairment (eGFR 30–59 mL/min/1.73 m^2). In this 26-week, randomized, double-masked study ($n = 279$), liraglutide 1.8 mg achieved better glycemic control and weight reduction without affecting renal function (eGFR ratio to baseline 0.99 vs 1.01; estimated treatment ratio 0.98; $p = 0.36$) or increasing albuminuria (UACR 0.87 vs 1.05; $p = 0.19$). The absence of eGFR decline, coupled with a nonsignificant 17% reduction in albuminuria, supports renal safety and potential early benefit, even in stage 3 CKD.

Complementary evidence from the Steno Diabetes Center [32] provides insight into the underlying renal physiology. In a 12-week randomized crossover trial among individuals with T2D and persistent albuminuria receiving stable RAS blockade, liraglutide reduced 24-h urinary albumin excretion by approximately 32% relative to placebo, without affecting measured GFR (^{51}Cr-EDTA clearance). The change in albuminuria correlated more strongly with reductions in 24-h systolic blood pressure than with changes in HbA1c or weight, suggesting a predominantly hemodynamic antiproteinuric effect rather than a metabolic mechanism. A subsequent before–after study [33] from the same group confirmed these findings, showing a reversible biphasic blood pressure response, initially rising and then falling, together with a transient, nonprogressive reduction in measured GFR, a 30% fall in albumin excretion, and reductions in extracellular volume and MR-proANP concentrations. These findings point to intrarenal hemodynamic and volume-mediated mechanisms as key contributors to liraglutide's renal effects.

Real-world evidence complements these controlled trials. In a Japanese cohort [34] with overt diabetic nephropathy despite optimized renin–angiotensin therapy, 1 year of liraglutide treatment led to a marked reduction in proteinuria (from approximately 2.5 to 1.5 g/gCr) and an improvement in annual eGFR slope from −6.6 to −0.3 mL/min/1.73 m^2 per year. Although uncontrolled, the magnitude and temporal pattern of improvement closely mirror those observed in the mechanistic trials, reinforcing the biological plausibility of a renal hemodynamic effect.

Risk of Bias

The overall methodological quality of the liraglutide evidence base is high, with the randomized trials demonstrating robust design, careful outcome ascertainment, and low risk of bias across domains. Both LEADER and LIRA-RENAL employed centralized randomization, double-blinding, and independent adjudication of renal outcomes, thereby minimizing selection and detection bias. Attrition was low, and prespecified renal endpoints were consistently reported.

The short-term randomized crossover study evaluating albuminuria and hemodynamic responses also maintained high methodological rigor. It employed standardized measurements of urinary albumin excretion, directly measured GFR, and 24-h blood pressure monitoring, all assessed under blinded conditions. These methodological strengths minimize measurement bias and enhance confidence in the findings, despite the short 12-week duration and relatively small sample size. The main limitations

include potential attrition bias due to GI intolerance and the restricted observation period, which limit inference about long-term kidney outcomes.

By contrast, the open before–after mechanistic study and the uncontrolled 1-year observational cohort are more susceptible to confounding, regression to the mean, and temporal effects. Their lack of control groups and short follow-up preclude causal inference. However, the consistent direction and magnitude of renal effects across these studies reinforce the physiologic plausibility of the findings. Both studies used standardized renal endpoints and careful follow-up procedures, which lend credibility to their mechanistic conclusions despite inherent design limitations.

Taken together, the randomized evidence provides high internal validity and low risk of bias for liraglutide's effects on albuminuria reduction and composite renal outcomes. At the same time, the smaller mechanistic and observational studies serve as complementary, hypothesis-generating evidence.

Certainty of Evidence (GRADE Assessment)

According to the GRADE framework, the certainty of evidence for liraglutide's renal effects is generally high. For composite kidney outcomes, the evidence from LEADER was rated as high certainty, supported by consistent benefit across subgroups, rigorous blinding, and extended follow-up, with no downgrading warranted. Evidence for albuminuria reduction was graded as moderate to high certainty, based on the concordant results of the short-term randomized trial and LEADER, which showed a consistent direction of effect and a clinically meaningful magnitude. A minor downgrading was applied to account for the small sample size and limited duration of the mechanistic studies.

For eGFR slope and measured GFR outcomes, the certainty rating was moderate. Randomized evidence shows stability or reversible hemodynamic changes in measured GFR and fewer large eGFR declines over long-term follow-up; however, downgrading was applied for indirectness and the short time frame of mechanistic studies. The observational and mechanistic evidence, while coherent with RCT results, was rated as low certainty due to confounding, non-randomized design, and small sample sizes.

Overall, the GRADE assessment supports high-certainty evidence for liraglutide's beneficial effect on composite renal outcomes, moderate-to-high certainty for albuminuria reduction, and moderate certainty for eGFR stabilization. Mechanistic and real-world studies strengthen biological plausibility but remain supplementary in the hierarchy of evidence.

Adverse Events

Across studies, liraglutide's safety profile was consistent with that of other GLP-1 receptor agonists. Gastrointestinal events (nausea, vomiting, diarrhea) were more frequent than with the comparator or placebo and accounted for most discontinuations in short-term studies; events were usually mild to moderate. In LEADER, severe hypoglycemia was less frequent than placebo in the overall cohort (driven by background therapy patterns), while gallbladder events were slightly increased; pancreatitis incidence was not significantly different. Heart rate rose modestly (approx. 3–5 bpm) in mechanistic trials, without a renal safety signal.

Taken together, these data indicate that liraglutide reliably lowers albuminuria and stabilizes kidney function over the short- to intermediate-term, with long-term renal protection supported by the LEADER trial. The consistency of findings across diverse populations, trial designs, and outcome measures supports a genuine renoprotective effect, likely mediated through direct renal and hemodynamic pathways that complement improvements in glycemia and cardiovascular risk factors. Although small mechanistic and before–after studies limit causal inference about hard kidney endpoints, the concordance across designs, endpoints, and time horizons supports incorporating liraglutide as a cardiorenal protective option in T2D, particularly in patients with persistent albuminuria despite RAS blockade.

Integration with SGLT2 inhibitors and standard CKD therapy is biologically and clinically plausible, with ongoing monitoring of UACR, eGFR, BP, and tolerability.

Other GLP-1 Receptor Agonists and Dual GLP-1/Glucagon Receptor Agonists

Evidence from randomized and mechanistic trials of GLP-1 receptor agonists, including efpeglenatide, exenatide (short- and long-acting formulations), lixisenatide, and the dual GLP-1/glucagon receptor agonist cotadutide, consistently demonstrates reductions in albuminuria and attenuation of kidney function decline in adults with T2D and CKD, with varying degrees of certainty depending on study design and duration.

In the AMPLITUDE-O trial [35], which enrolled more than 4000 adults with T2D and established cardiovascular disease or CKD (eGFR 25–59.9 mL/min/1.73 m^2), weekly efpeglenatide significantly reduced the composite renal outcome—including new macroalbuminuria, sustained ≥ 40% eGFR decline, or RRT—compared with placebo (HR 0.68, 95% CI 0.57–0.79). The mean change in eGFR slope favored efpeglenatide (+0.9 mL/min/1.73 m^2), and mean UACR fell by approximately 21%, with consistent benefit across subgroups defined by eGFR and concurrent SGLT2 inhibitor use. These findings, observed alongside robust cardiovascular protection (MACE HR 0.73), support efpeglenatide's dual cardiorenal efficacy. The trial's double-masked design, centralized adjudication, and minimal attrition underpin a low overall risk of bias, with slight downgrading for relatively short follow-up (median 1.8 years) and early termination, which limit precision for long-term renal events.

Two phase 2 studies of cotadutide [36, 37], a dual GLP-1/glucagon receptor agonist, extend these findings to patients with T2D and CKD stages 2–3. In the larger phase 2b trial ($n = 248$, 26 weeks), cotadutide 300–600 µg daily achieved dose-dependent reductions in UACR (– 44% to – 50%) and a favorable trend in eGFR slope at the highest dose ($P = 0.016$) compared with placebo. These effects persisted after adjustment for HbA1c, body weight, and systolic blood pressure, suggesting mechanisms partly independent of glycemic control. Similar antiproteinuric effects (– 51% UACR reduction) were observed in an earlier 32-day phase 2a study in CKD stage 3, without eGFR decline and with good tolerability. Both trials were double-masked, used centralized laboratory assessments, and achieved high completion rates, supporting a low-to-moderate risk of bias. However, they were limited by small sample sizes and short durations typical of early-phase studies.

Exenatide, both in its twice-daily (short-acting) and once-weekly (extended-release) formulations, has shown consistent renal signals. In a 24-week randomized open-label trial in T2D with macroalbuminuric diabetic kidney disease [38], exenatide + basal insulin reduced albuminuria by approximately 30%. It preserved eGFR compared with basal-bolus insulin intensification, with fewer hypoglycemic episodes and modest weight loss. The EXSCEL post hoc analysis [39, 40] corroborated these findings: exenatide QW improved annual eGFR slope in participants with higher baseline albuminuria (UACR > 100–200 mg/g; +0.8 to +1.3 mL/min/1.73 m^2 per year vs placebo) and reduced UACR by 28–35% in albuminuric subgroups. The benefits were concentrated in patients at greater renal risk, indicating a possible effect modification by baseline albuminuria. Although exploratory, the analyses were methodologically sound, with consistent results across renal risk categories and objective outcome ascertainment, leading to an overall moderate risk of bias and moderate-certainty evidence.

In the ELIXA exploratory analysis [41], lixisenatide (10–20 µg daily) reduced UACR by approximately 21% in microalbuminuric and 39% in macroalbuminuric participants after 108 weeks, without changes in eGFR trajectory. The study maintained rigorous blinding and centralized measurements, resulting in a low risk of bias in most domains. However, downgrading applies due to the post hoc nature of renal endpoints and lack of adjustment for multiplicity. The findings suggest albuminuria reduction independent of HbA1c change, consistent with hemodynamic and anti-inflammatory

mechanisms seen with other GLP-1 receptor agonists.

Across this collective evidence, the risk of bias was generally low to moderate for the RCTs and higher for exploratory or early-phase designs. Blinded allocation, centralized measurement of renal endpoints, and high retention rates support confidence in directionality of effect, while limitations arise primarily from study duration, sample size, and surrogate endpoints (albuminuria, eGFR slope).

From a GRADE perspective, the certainty of evidence was rated as high for efpeglenatide's renal composite benefit (large, blinded CVOT with consistent effects); moderate to high for cotadutide's antiproteinuric efficacy (consistent across doses, mechanistic plausibility, but limited by duration); moderate for exenatide's renal protection in albuminuric subgroups (post hoc and open-label data); and moderate for lixisenatide's reduction in albuminuria. Collectively, these agents demonstrate a class-consistent renal benefit, primarily mediated through reductions in albuminuria and slower eGFR decline, appearing additive to background renin–angiotensin blockade and SGLT2 inhibition.

Comparative and Combined Therapeutic Evidence

Across real-world and post hoc clinical data, comparative analyses of liraglutide, dulaglutide, and exenatide, alone or in combination with SGLT2 inhibitors, provide converging evidence of similar renal effectiveness, while highlighting clinically relevant nuances related to treatment sequence, phenotypic response, and kidney disease stage.

In the RECAP post hoc cohort [42], adults with T2D treated with combined SGLT2i + GLP-1RA (liraglutide or dulaglutide) were evaluated to determine whether treatment sequence or molecule choice influenced renal outcomes. After extensive adjustment with inverse-probability weighting and propensity matching, the initiation order (SGLT2i → GLP-1RA vs GLP-1RA → SGLT2i) did not alter renal risk. However, within-class differences emerged: liraglutide was associated with a greater albuminuria reduction (OR 0.44, 95% CI 0.04–0.85) but a higher frequency of ≥ 30% eGFR decline (OR 2.63, 95% CI 1.07–6.45) compared with dulaglutide. Overall composite renal events were similar between drugs (approx. 25–28%). These findings suggest distinct renal phenotypes of response—liraglutide favoring albuminuria improvement and dulaglutide showing more stable filtration rates—underscoring the potential for individualized selection based on predominant renal trajectory (proteinuria-dominant vs eGFR-decline phenotype). The study had moderate risk of bias (ROBINS-I) but robust control of confounding.

Complementing this, the large multicenter new-user cohort from Taiwan [43] confirmed equivalent renal and cardiovascular effectiveness between liraglutide and dulaglutide over a mean 2.4 years. Renal composite outcomes—including incident macroalbuminuria, ≥ 50% eGFR decline, and dialysis—did not differ (SHR 1.07, 95% CI 0.99–1.16). MACE risk was comparable (HR 0.99), though non-fatal myocardial infarction occurred less frequently with liraglutide (SHR 0.69). Metabolic profiles were complementary, with greater weight loss under liraglutide and superior HbA1c reduction with dulaglutide. These results reinforce class homogeneity for cardiorenal endpoints, while supporting drug selection tailored to patient goals. Quality appraisal indicated moderate overall risk of bias, limited primarily by residual confounding and incomplete albuminuria data.

Evidence from randomized settings aligns with these real-world observations. The EXSCEL post hoc analysis [44] compared participants exposed to exenatide once weekly (EQW) ± SGLT2i. Combination therapy improved eGFR slope (+ 1.94 mL/min/1.73 m^2 per year vs placebo; + 2.38 vs EQW alone) and showed numerically lower rates of all-cause and cardiovascular mortality (aHR 0.38–0.41 vs comparators), without increased hypoglycemia or renal adverse events. Although renal composite reductions were not statistically significant due to limited events, the consistent direction supports

synergistic cardiorenal benefit of combining SGLT2 inhibitors with GLP-1 receptor agonists.

Further insight into kidney-stage heterogeneity arises from the [45] analysis of 1572 patients across CKD stages 1–5. While overall MACE risk was similar for both agents, risk gradients by eGFR differed: liraglutide's cardiovascular risk increased as kidney function declined (p for trend = 0.0079), whereas dulaglutide maintained a stable risk profile across CKD stages ($p = 0.19$). Dulaglutide also exhibited a slower eGFR decline over time ($p < 0.05$), though absolute renal function and "hard" endpoints were comparable. These findings suggest greater cardiovascular stability with dulaglutide in advanced CKD, whereas liraglutide's risk profile may be more sensitive to renal deterioration. Both agents had similar safety profiles, with no differences in infection, pancreatitis, amputation, or malignancy.

From a methodological standpoint, most analyses demonstrated moderate risk of bias with sound statistical adjustment (IPW, matching, multiple imputation) but limited causal inference due to observational design. Despite this, the consistency of direction and magnitude across independent cohorts and trial extensions supports the reliability of these findings.

DISCUSSION

This scoping review provides a structured map of the available evidence on renal and cardiorenal outcomes associated with GLP-1 receptor agonists and the dual GLP-1/GIP agonist tirzepatide, organized primarily by CKD stage and metabolic phenotype, and complemented by agent-specific synthesis. Rather than issuing clinical recommendations, this approach delineates where renal evidence is most robust, where it is heterogeneous, and where important gaps persist, thereby supporting interpretation and future appropriateness deliberations.

Evidence Across CKD Stages and Metabolic Phenotypes

Across CKD stages G1–G4, GLP-1-based therapies consistently reduced albuminuria and attenuated the rate of eGFR decline across study designs. These effects were observed in individuals with preserved kidney function as well as in those with established CKD, and were frequently independent of glycemic or weight changes. Such consistency across renal risk strata supports kidney-specific mechanisms, including intrarenal hemodynamic modulation, anti-inflammatory signaling, endothelial restoration, and reductions in renal fat depots.

Importantly, recent randomized evidence extends renal benefit beyond traditional diabetic populations. In adults with overweight or obesity and CKD without diabetes, semaglutide produced a marked reduction in albuminuria with stable eGFR and no renal safety signal [19], addressing a population historically underrepresented in GLP-1 receptor agonist trials. Together with findings from SELECT [18], these data suggest that GLP-1-based therapies may exert renoprotective effects that are not contingent on glycemic modulation, expanding their potential relevance across metabolic phenotypes.

When evidence is examined through the lens of CKD stage and metabolic phenotype, however, substantial gaps become apparent. Data remain sparse for advanced CKD (G4–G5), particularly for hard kidney endpoints, and are exceedingly limited for non-diabetic, non-obese populations across all CKD stages. In many trials, stratified reporting by CKD stage or phenotype was absent, precluding more granular inference. Identification of these gaps represents a central output of this scoping review.

Agent-Specific Patterns Within the CKD Framework

Within this CKD- and phenotype-based framework, differences in the strength and certainty

of evidence across individual agents emerge. Semaglutide provides the most comprehensive and highest-certainty renal evidence. The FLOW trial [13], one of the few large-scale RCTs powered for a primary kidney endpoint, demonstrated significant reductions in major renal outcomes and slower eGFR decline in patients with T2D and CKD. These findings were complemented by SELECT [18], which demonstrated kidney benefit in non-diabetic individuals with overweight or obesity and established cardiovascular disease, positioning semaglutide as a benchmark GLP-1 receptor agonist for kidney protection across metabolic phenotypes.

Mechanistic studies further reinforce biological plausibility. Integrative imaging and tissue analyses demonstrated reductions in albuminuria, improvements in renal hemodynamics and diffusion metrics, and downregulation of inflammatory and fibrotic pathways, linking clinical benefits to structural and molecular kidney changes [46]. These observations align closely with the antiproteinuric and eGFR-stabilizing effects observed in FLOW and SELECT [13, 18].

For tirzepatide, evidence of renal benefit derives primarily from post hoc analyses of the SURPASS program and meta-analyses [20–22], demonstrating dose-dependent reductions in albuminuria and slower eGFR decline compared with insulin glargine. Although these effects appear partly independent of metabolic improvements, the absence of dedicated kidney-outcome trials limits certainty regarding long-term renal protection. Ongoing studies specifically designed to assess kidney endpoints will be critical to define tirzepatide's role within the cardiorenal therapeutic landscape.

Dulaglutide is supported by randomized evidence from REWIND [26] and AWARD-7 [5], demonstrating reductions in composite kidney outcomes and sustained preservation of kidney function, including in patients with moderate-to-severe CKD. The long duration of follow-up and consistent effects across renal measures substantiate high-certainty evidence for renoprotection independent of glycemic control.

Liraglutide demonstrated significant renal benefit in the LEADER trial [30], primarily through reductions in macroalbuminuria, with mechanistic studies supporting reversible hemodynamic and antiproteinuric effects. However, renal outcomes were largely secondary, limiting direct inference on hard kidney endpoints.

Other GLP-1 receptor agonists—including efpeglenatide in AMPLITUDE-O [35], as well as exenatide, lixisenatide, and cotadutide—show class-consistent reductions in albuminuria and favorable eGFR trajectories. For several of these agents, evidence is derived from secondary or shorter-duration analyses, supporting biological plausibility but limiting certainty regarding long-term renal outcomes.

As summarized in the evidence map (Fig. 1), the certainty of evidence varies by renal outcome domain and population phenotype.

Heterogeneity of Renal Endpoints and Implications

A major source of heterogeneity across the evidence base relates to the definition and reporting of renal outcomes. Albuminuria reduction is the most consistently reported endpoint, whereas eGFR slope and hard kidney outcomes are less uniformly captured and often reported as secondary or post hoc outcomes. This heterogeneity constrains quantitative synthesis and complicates direct comparisons across agents or CKD stages, reinforcing the value of an evidence-mapping approach rather than effect-size pooling.

Strengths, Limitations, and Implications for Future Research

Key strengths of this review include a comprehensive and transparent search strategy, adherence to JBI and PRISMA-ScR standards, and structured appraisal using validated risk-of-bias tools (RoB 2 and ROBINS-I). By organizing evidence primarily by CKD stage and metabolic phenotype, this review provides a clinically intuitive map of where renal evidence is concentrated and where it is lacking.

Nevertheless, important limitations must be acknowledged. Few trials were designed with kidney outcomes as primary endpoints; definitions of renal outcomes varied; data in advanced CKD (G4–G5) remain scarce; and for several agents, renal evidence relies heavily on post hoc analyses. Future research should prioritize dedicated kidney-outcome trials in advanced CKD, expand inclusion of non-diabetic kidney disease populations, and standardize renal endpoint definitions. Such efforts will be essential to clarify class versus molecule-specific effects and to support phenotype-guided use of GLP-1-based therapies in kidney disease.

CONCLUSION

In summary, the current evidence demonstrates that GLP-1-based therapies exert consistent and clinically meaningful renoprotective effects across the spectrum of T2D and CKD. Among these agents, semaglutide and dulaglutide provide the most robust and high-certainty data, supported by large, well-designed RCTs showing significant reductions in major kidney outcomes and sustained preservation of kidney function. Liraglutide and efpeglenatide offer additional evidence of benefit through reductions in albuminuria and attenuation of eGFR decline, while tirzepatide shows promising, dose-dependent renal effects that remain to be confirmed in dedicated kidney-outcome trials.

Renal benefits appear partly independent of glycemic and weight effects, suggesting mechanisms that include intrarenal hemodynamic modulation and anti-inflammatory pathways. Collectively, these findings support the integration of GLP-1 receptor agonists as a cornerstone of comprehensive cardiorenal risk management in T2D, complementary to RAS blockade and SGLT2 inhibition.

Future research should focus on defining the magnitude of benefit in advanced CKD, elucidating additive or synergistic effects with other nephroprotective agents, and assessing long-term outcomes beyond traditional renal endpoints. As the evidence base continues to expand, GLP-1-based therapies are poised to play an increasingly central role in the prevention and management of diabetic kidney disease.

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Declarations

Conflicts of Interest. The authors declare the following conflicts of interest. Rodrigo Daza-Arnedo has received speaker honoraria from Novo Nordisk, AstraZeneca, Bayer, and Boehringer Ingelheim. Alicia Elbert has been a member of the speaker boards of AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi, Servier, Raffo, Baliarda, and Adium, and has served as an investigator in studies sponsored by Novo Nordisk, Boehringer Ingelheim, AstraZeneca, and Merck. Ricardo Correa-Rotter has served as a member of the Global Research Committee of FLOW and as national lead for the FLOW and TRIUMPH programs. Eliana Dina-Batlle declares no conflicts of interest. Eduardo Lorca-Herrera has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, Axon Pharma, and Fresenius Medical Care; has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Axon Pharma; and has received travel or conference support from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Thyago Proença de Moraes has received speaker or consulting fees from AstraZeneca, Bayer, Baxter/Vantive, Boehringer Ingelheim, CSL Vifor, Libbs, Lilly, Merck, Novo Nordisk, Servier, and Takeda. Vicente Sánchez-Poli has received speaker honoraria from Bayer, Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Novartis, and Janssen. Jorge Rico-Fontalvo has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lilly, Sanofi, Eurofarma, Adium, GSK, MSD, Merck, and Bayer. He has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, Adium, Lilly, Bayer, and Novo Nordisk. Carlos E. Builes-Montaño has received consulting and speaking fees from Sanofi, Novo Nordisk, Novartis, Recordati Rare Diseases, Janssen, Chiesi, Abbott, and Boehringer Ingelheim, and is a shareholder of Festina Lente. These disclosures are not necessarily related to the submitted work.

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