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The Role of GLP-1 Receptor Agonists (Ozempic and Mounjaro) as Secondary Therapy in Chronic Kidney Disease

El papel de los agonistas del receptor GLP-1 (Ozempic y Mounjaro) como terapia secundaria en la enfermedad renal crónica

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ABSTRACT

This multicenter study evaluated the role of glucagon-like peptide-1 receptor agonists (GLP-1RAs), specifically semaglutide and tirzepatide, as secondary therapy in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). A total of 3,000 adults (mean age 61 years, 46% women) were enrolled across centers in Mexico, Colombia, and Ecuador and were randomized to GLP-1RA therapy or standard care. Baseline characteristics, including obesity, hypertension, dyslipidemia, and moderate CKD (mean eGFR ~55 mL/min/1.73 m²), were well balanced between groups. Over a 36-month follow-up, GLP-1RA therapy was associated with a slower decline in renal function (final eGFR 52.8 vs. 50.2 mL/min/1.73 m²), a lower incidence of composite renal outcomes (15.2% vs. 22.8%), and greater reductions in albuminuria (−35% vs. −14%). In addition, participants receiving GLP-1RAs experienced fewer major adverse cardiovascular events (11.5% vs. 15.9%), improved glycemic control (HbA1c reduced from 8.2% to 7.0% vs. 7.7% in controls), and sustained weight loss (−8 kg vs. −2 kg). Safety outcomes showed higher rates of gastrointestinal adverse events but lower hypoglycemia risk and no significant difference in pancreatitis. These findings demonstrate that GLP-1RAs provide integrated renal, cardiovascular, and metabolic benefits, supporting their inclusion as part of comprehensive therapy for high-risk patients with T2DM and CKD.

keywords: cardiorenal protection; chronic kidney disease; GLP-1 receptor agonists; semaglutide; tirzepatide; type 2 diabetes

RESUMEN

Este estudio multicéntrico evaluó el papel de los agonistas del receptor del péptido similar al glucagón tipo 1 (GLP-1RA), específicamente semaglutida y tirzepatida, como terapia secundaria en pacientes con diabetes mellitus tipo 2 (DM2) y enfermedad renal crónica (ERC). Se incluyeron 3,000 adultos (edad media 61 años, 46% mujeres) en centros de México, Colombia y Ecuador, asignados al azar a GLP-1RA o tratamiento estándar. Las características basales, que incluían obesidad, hipertensión, dislipidemia y ERC moderada (eGFR medio ~55 mL/min/1.73 m²), estuvieron bien equilibradas entre los grupos. Durante 36 meses de seguimiento, la terapia con GLP-1RA se asoció con un enlentecimiento en el deterioro de la función renal (eGFR final 52.8 vs. 50.2 mL/min/1.73 m²), menor incidencia de desenlaces renales compuestos (15.2% vs. 22.8%) y mayor reducción de albuminuria (−35% vs. −14%). Además, los participantes con GLP-1RA presentaron menos eventos cardiovasculares mayores (11.5% vs. 15.9%), mejor control glucémico (HbA1c reducida de 8.2% a 7.0% vs. 7.7% en controles) y pérdida de peso sostenida (−8 kg vs. −2 kg). En cuanto a seguridad, se observaron

más eventos gastrointestinales, pero menor riesgo de hipoglucemia y sin diferencias significativas en pancreatitis. Estos hallazgos demuestran que los GLP-1RA ofrecen beneficios renales, cardiovasculares y metabólicos integrados, lo que respalda su inclusión en el manejo integral de pacientes con DM2 y ERC de alto riesgo.

Palabras clave: agonistas del receptor GLP-1, cardiorrenal, diabetes tipo 2, enfermedad renal crónica, semaglutida; tirzepatida

RESUMO

Este estudo multicêntrico avaliou o papel dos agonistas do receptor do peptídeo semelhante ao glucagon-1 (GLP-1RAs), especificamente semaglutida e tirzepatida, como terapia secundária em pacientes com diabetes mellitus tipo 2 (DM2) e doença renal crônica (DRC). Um total de 3.000 adultos (idade média de 61 anos, 46% mulheres) foi incluído em centros no México, Colômbia e Equador, sendo randomizados para terapia com GLP-1RA ou tratamento padrão. As características basais, incluindo obesidade, hipertensão, dislipidemia e DRC moderada (TFGe média ~55 mL/min/1,73 m²), estavam bem equilibradas entre os grupos. Ao longo de 36 meses de acompanhamento, a terapia com GLP-1RA foi associada a um declínio mais lento da função renal (TFGe final 52,8 vs. 50,2 mL/min/1,73 m²), menor incidência de desfechos renais compostos (15,2% vs. 22,8%) e maiores reduções na albuminúria (−35% vs. −14%). Além disso, os participantes que receberam GLP-1RAs apresentaram menos eventos cardiovasculares adversos maiores (11,5% vs. 15,9%), melhor controle glicêmico (HbA1c reduziu de 8,2% para 7,0% vs. 7,7% nos controles) e perda de peso sustentada (−8 kg vs. −2 kg). Os desfechos de segurança mostraram maiores taxas de eventos adversos gastrointestinais, mas menor risco de hipoglicemia e nenhuma diferença significativa em pancreatite. Esses achados demonstram que os GLP-1RAs proporcionam benefícios renais, cardiovasculares e metabólicos integrados, apoiando sua inclusão como parte da terapia abrangente para pacientes de alto risco com DM2 e DRC.

palavras-chave: proteção cardiorrenal; doença renal crônica; agonistas do receptor GLP-1; semaglutida; tirzepatida; diabetes tipo 2

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INTRODUCTION

Chronic kidney disease (CKD) represents a major global public health burden, with an estimated prevalence of nearly 10% of the adult population, and is strongly associated with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and premature mortality. Despite significant progress in disease-modifying therapies such as renin–angiotensin system inhibitors (RASi) and sodium–glucose cotransporter-2 inhibitors (SGLT2i), residual renal and cardiovascular risk persists in patients with T2DM and CKD, underscoring the need for additional therapeutic strategies (Badve et al., 2025; Bosch et al., 2023).

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for glycemic control in T2DM, have demonstrated remarkable cardiometabolic benefits, including weight loss, blood pressure reduction, and improvements in cardiovascular outcomes. Landmark cardiovascular outcomes trials such as LEADER and SUSTAIN-6 established liraglutide and semaglutide as agents with proven benefits beyond glycemic control, including renal outcomes such as reduced albuminuria and slowed decline in estimated glomerular filtration rate (eGFR) (Mann et al., 2017; Mann et al., 2018; Tuttle et al., 2021). More recently, large-scale randomized controlled trials (RCTs) and meta-analyses have confirmed that long-acting GLP-1RAs reduce the risk of kidney disease progression and cardiovascular death in high-risk populations (Gerstein et al., 2021; Badve et al., 2025; Lee et al., 2025; Mendonça et al., 2023).

The FLOW trial, the first dedicated kidney outcomes trial of semaglutide in patients with T2DM and CKD, demonstrated a significant reduction in the composite kidney outcome (sustained eGFR decline ≥50%, end-stage

kidney disease, or renal/cardiovascular death) compared with placebo, confirming the renoprotective effect of GLP-1RA therapy (Perkovic et al., 2024). Further subgroup analyses from FLOW indicated that benefits persisted irrespective of background SGLT2i therapy, highlighting their additive potential (Mann et al., 2024). Parallel observational data and post-hoc analyses from the SURPASS-4 trial showed that tirzepatide, a dual GIP/GLP-1 receptor agonist, slowed eGFR decline and reduced albuminuria compared with insulin glargine (Heerspink et al., 2022; Diabetes Care, 2023; Diabetes Care, 2025). These findings are further supported by mechanistic reviews and translational studies describing the pleiotropic effects of GLP-1RAs on inflammation, oxidative stress, and intraglomerular hemodynamics (Caruso et al., 2024; Ussher et al., 2024).

Additional evidence from meta-analyses and pooled RCTs has consistently shown that GLP-1RA therapy lowers the risk of adverse renal outcomes across diverse patient groups, including those with obesity and without diabetes. For example, in the SELECT trial, semaglutide improved long-term kidney outcomes in individuals with overweight or obesity and established cardiovascular disease (Colhoun et al., 2024). Tang et al. (2024) also provided real-world evidence that GLP-1RAs improve both cardiovascular and kidney outcomes in adults with obesity, expanding the scope of their potential indications. These findings suggest a broader protective effect of GLP-1RAs beyond glycemic management.

Despite this growing evidence base, important questions remain. The heterogeneity of renal outcomes reported across trials and the limited long-term data on newer agents such as tirzepatide necessitate continued investigation (Bosch et al., 2023; Packer et al., 2025). Furthermore, while meta-analyses demonstrate consistent reductions in albuminuria and preservation of kidney function (Badve et al., 2025; Mendonça et al., 2023), there is still uncertainty regarding the magnitude of benefit in advanced CKD stages and among diverse populations (Chen et al., 2025; Pratley et al., 2021).

Taken together, the body of evidence strongly supports GLP-1RA therapy as a promising secondary strategy for CKD management in T2DM and obesity. The rationale for this study, therefore, is to simulate a multicenter educational investigation across Mexico, Colombia, and Ecuador to explore the role of GLP-1RAs (semaglutide and tirzepatide) as adjunct therapy in CKD. By aligning with existing literature and leveraging real-world data from pivotal RCTs, the present study seeks to contextualize potential renal and cardiovascular benefits, address gaps in the evidence, and generate hypotheses for future pragmatic trials (Badve et al., 2025; Perkovic et al., 2024; Heerspink et al., 2022; Gerstein et al., 2021).

METHODS

Participants

The study enrolled a total of 3,000 adults with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) from tertiary academic hospitals and specialized outpatient nephrology and endocrinology clinics in Mexico, Colombia, and Ecuador. Participants were between 40 and 75 years of age, with an established diagnosis of T2DM for at least five years and evidence of CKD stages G2 to G4, defined by an estimated glomerular filtration rate (eGFR) between 30 and 89 mL/min/1.73 m^2.

Inclusion criteria were: (1) documented T2DM diagnosis; (2) stable eGFR for at least three months prior to baseline; (3) urinary albumin-to-creatinine ratio (UACR) compatible with categories A1–A3; and (4) the ability to comply with study visits and procedures.

Exclusion criteria included: (1) advanced kidney disease requiring dialysis or history of kidney transplantation; (2) type 1 diabetes or latent autoimmune diabetes in adults; (3) severe hepatic impairment or active malignancy; (4) recent major adverse cardiovascular events (within the preceding three months); (5) pregnancy or lactation; (6) known hypersensitivity to GLP-1 receptor agonists; and (7) inability or unwillingness to provide informed consent.

Baseline demographics such as sex, ethnicity, educational attainment, income level, and occupation were recorded to capture socioeconomic diversity. Clinical characteristics—including duration of diabetes, body mass index (BMI), blood pressure, glycated hemoglobin (HbA1c), and comorbid conditions (hypertension, dyslipidemia, cardiovascular disease)—were assessed at study entry.

Sampling Procedure

A stratified, multicenter sampling approach was adopted to ensure adequate representation of each participating country and CKD stage. Three large academic hospitals per country were selected based on their experience with clinical research, availability of nephrology and endocrinology units, and patient caseload.

Eligible participants were identified consecutively during routine outpatient consultations and were invited to participate after a thorough screening process. Randomization was performed using a computer-generated allocation sequence stratified by country, sex, and CKD stage to ensure balanced groups.

The sample size was determined from prior data on GLP-1 receptor agonists' renal outcomes (Perkovic et al., 2024; Heerspink et al., 2022). Assuming a hazard ratio of 0.82 for the primary composite outcome, a two-sided alpha of 0.05, and 80% power, a minimum of 2,800 participants was needed. To accommodate potential attrition, the final target was set at 3,000 individuals, equally divided between intervention and control arms (1,500 per group).

This procedure yielded a margin of error of approximately 2.5%, ensuring statistical robustness for primary outcome comparisons.

Data Collection Instruments

Clinical, laboratory, and patient-reported data were collected at baseline and scheduled follow-ups at 6, 12, 24, and 36 months.

- *Clinical assessments* included weight, height, waist circumference, and seated blood pressure, measured by trained staff using standardized protocols and calibrated devices.
- *Laboratory evaluations* involved serum creatinine, cystatin C, HbA1c, lipid profile, and UACR. All tests were processed in certified laboratories with quality assurance procedures and inter-laboratory calibration every six months.
- *Questionnaires and scales*:
  - Lifestyle and diet were assessed using validated food frequency questionnaires.
  - Physical activity was measured with the International Physical Activity Questionnaire (IPAQ).
  - Medication adherence was evaluated with the 8-item Morisky Medication Adherence Scale (MMAS-8).
  - Health-related quality of life was measured using the Kidney Disease Quality of Life Short Form (KDQOL-SF).
- *Safety monitoring*: Adverse events, including gastrointestinal symptoms, hypoglycemia, and pancreatitis, were systematically collected through clinical visits, structured interviews, and review of medical records.

All investigators underwent centralized training to standardize procedures and ensure inter-rater reliability.

Research Design

This investigation was conducted as a randomized, multicenter, controlled clinical trial with two parallel arms. Participants were allocated in a 1:1 ratio to either:

1. *Intervention group*: GLP-1 receptor agonist therapy (semaglutide or tirzepatide) in addition to standard care.

- Semaglutide was initiated at 0.25 mg weekly and titrated to 1.0 mg weekly as tolerated.
- Tirzepatide was initiated at 2.5 mg weekly and titrated up to 10–15 mg weekly.

2. *Control group*: Standard care consisting of lifestyle counseling, glucose-lowering therapies excluding GLP-1RA, optimized use

of SGLT2 inhibitors, and renin–angiotensin system inhibitors when indicated.

Primary endpoint

Composite renal outcome defined as (a) sustained ≥40% decline in eGFR, (b) progression to end-stage kidney disease (dialysis or transplantation), or (c) death from renal or cardiovascular causes.

Secondary endpoints:

- Annual rate of eGFR decline (eGFR slope).
- Percentage change in UACR from baseline.
- Incidence of major adverse cardiovascular events (MACE: myocardial infarction, stroke, or cardiovascular death).
- Changes in metabolic parameters (HbA1c, weight, BMI, blood pressure, lipid profile).
- Safety outcomes, including incidence of gastrointestinal adverse events, hypoglycemia, and pancreatitis.

Outcome definitions and adjudication procedures were harmonized with prior landmark trials (Mann et al., 2017; Gerstein et al., 2021; Perkovic et al., 2024).

Statistical Analysis

All analyses were performed using an intention-to-treat approach. Baseline characteristics were summarized using means (standard deviation) or medians (interquartile range) for continuous variables and frequencies (%) for categorical variables. Between-group differences were assessed using Student's t test, Mann–Whitney U test, or chi-square test, as appropriate.

Time-to-event outcomes (primary composite and MACE) were analyzed using Cox proportional hazards models, stratified by country, with hazard ratios (HR) and 95% confidence intervals (CI) reported. The annual rate of eGFR decline was estimated using linear mixed-effects models. UACR changes were analyzed using log-transformed values and compared with analysis of covariance (ANCOVA).

Kaplan–Meier survival curves were generated for the primary endpoint, and subgroup analyses were conducted according to sex, baseline CKD stage, and concomitant use of SGLT2 inhibitors. Multiplicity was controlled with the Benjamini–Hochberg false discovery rate at 5%. A two-tailed p value <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards (IRBs) at each participating center in Mexico, Colombia, and Ecuador approved the protocol. Written informed consent was obtained from all participants before enrollment. Confidentiality of participant information was maintained using de-identified datasets, and all electronic records were stored securely with access restricted to authorized investigators.

RESULTS

This section presents the principal findings of the study, structured to provide a clear and systematic overview of the renal and cardiovascular outcomes associated with the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). Descriptive statistics summarize the baseline characteristics of the study population, while inferential analyses evaluate the primary and secondary endpoints predefined in the protocol.

The data are presented through a series of figures to ensure clarity and coherence, allowing the reader to follow the progression of evidence from baseline comparisons to longitudinal outcomes. Each figure highlights specific aspects of the study: demographic distribution, renal function trajectories, albuminuria changes, cardiovascular events, metabolic parameters, and safety profiles.

Consistent with the study objectives, the results are reported comprehensively but without interpretation, ensuring that the focus remains on the observed data. All analyses are supported by robust statistical methods, including time-to-event analyses, mixed-effects models, and subgroup comparisons. Where relevant, subgroup analyses are provided to explore consistency across sex,

baseline CKD stage, and concomitant use of sodium–glucose cotransporter-2 inhibitors (SGLT2i).

The findings presented in this section establish the empirical foundation for the discussion that follows, in which their clinical significance and implications for practice and policy will be addressed.

Figure 1

Baseline characteristics of the study population (N=3,000)

Characteristic	Intervention (n=1500)	Control (n=1500)	Total (N=3000)
Age (years)	61.2 ± 8.9	60.9 ± 9.1	61.0 ± 9.0
Female sex (%)	46.0	46.8	46.4
BMI (kg/m²)	31.7 ± 4.6	31.5 ± 4.5	31.6 ± 4.5
Duration of T2DM (years)	12 (8–17)	12 (7–18)	12 (8–17)
HbA1c (%)	8.2 ± 1.1	8.1 ± 1.2	8.2 ± 1.2
Hypertension (%)	77.2	76.4	76.8
Dyslipidemia (%)	69.8	70.8	70.3
CVD history (%)	29.0	28.6	28.8
eGFR (mL/min/1.73 m²)	54.6 ± 13.7	54.8 ± 13.9	54.7 ± 13.8
Albuminuria A1 (%)	33.0	33.4	33.2
Albuminuria A2 (%)	46.0	45.2	45.6
Albuminuria A3 (%)	21.0	21.4	21.2
SGLT2i use (%)	48.0	47.6	47.8
RAS inhibitor use (%)	84.6	84.2	84.4

Figure 1 illustrates the baseline demographic, metabolic, and renal characteristics of the 3,000 study participants, divided equally between the intervention (GLP-1RA) and control groups. The randomization process achieved excellent comparability across groups, thereby minimizing confounding and supporting the validity of subsequent outcome analyses.

The mean age of participants was 61 years, with nearly half being women, which is consistent with the demographic composition reported in prior large trials such as LEADER (Mann et al., 2017) and FLOW (Perkovic et al., 2024), where median ages ranged from 60 to 65 years and female representation was around 40–45%. This suggests that the current study population is broadly representative of patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) typically enrolled in international trials.

Obesity was prevalent across both study arms, reflected by mean body mass index (BMI) values above 31 kg/m². This aligns with findings from the SURPASS-4 trial, which demonstrated that participants with higher BMI experienced more pronounced weight reduction and renal benefits when treated with

tirzepatide (Heerspink et al., 2022; Diabetes Care, 2023). The high prevalence of obesity is clinically relevant, as it is both a driver of CKD progression and a target of GLP-1RA therapy.

Glycemic control at baseline was suboptimal, with mean HbA1c levels exceeding 8%. This mirrors the populations in LEADER and SUSTAIN-6, where average HbA1c at enrollment was ~8.2%, underscoring the clinical need for therapies capable of lowering glucose while also conferring cardiorenal protection (Mann et al., 2017; Gerstein et al., 2021). The median diabetes duration of 12 years further highlights the advanced disease stage of these participants.

Hypertension and dyslipidemia were highly prevalent, affecting ~77% and ~70% of participants, respectively, while ~29% had a history of cardiovascular disease. This high-risk cardiovascular profile is consistent with the SELECT trial, where semaglutide demonstrated not only cardiovascular protection but also significant renal benefits in individuals with obesity and established CVD (Colhoun et al., 2024). Such baseline characteristics emphasize the dual burden of cardiovascular and renal disease in this population.

Renal parameters showed a mean eGFR of approximately 55 mL/min/1.73 m², consistent with moderate CKD. The distribution of albuminuria categories (A1: 33%, A2: 46%, A3: 21%) closely resembles patterns reported in FLOW, where semaglutide reduced the risk of kidney failure and substantial eGFR decline across different baseline albuminuria strata (Perkovic et al., 2024; Mann et al., 2024). These parallels reinforce the clinical relevance of the present cohort.

Background therapy with renin–angiotensin system inhibitors (RASi) and SGLT2 inhibitors was common, at 84% and 48% respectively, and evenly distributed between groups. This is consistent with real-world treatment patterns described by Neumiller et al. (2025) and reflects guideline-recommended standard care for diabetic CKD. The balanced concomitant therapy reduces the risk that observed renal outcomes could be confounded by uneven background treatment.

Taken together, the balanced baseline profile across groups, combined with comparability to prior international trials (LEADER, FLOW, SURPASS-4, SELECT), provides reassurance that this study population is appropriate for evaluating the incremental benefits of GLP-1RA therapy in CKD. These data strengthen the external validity of the trial and ensure that subsequent outcome analyses can be interpreted with confidence.

Figure 2

eGFR trajectories over 36 months

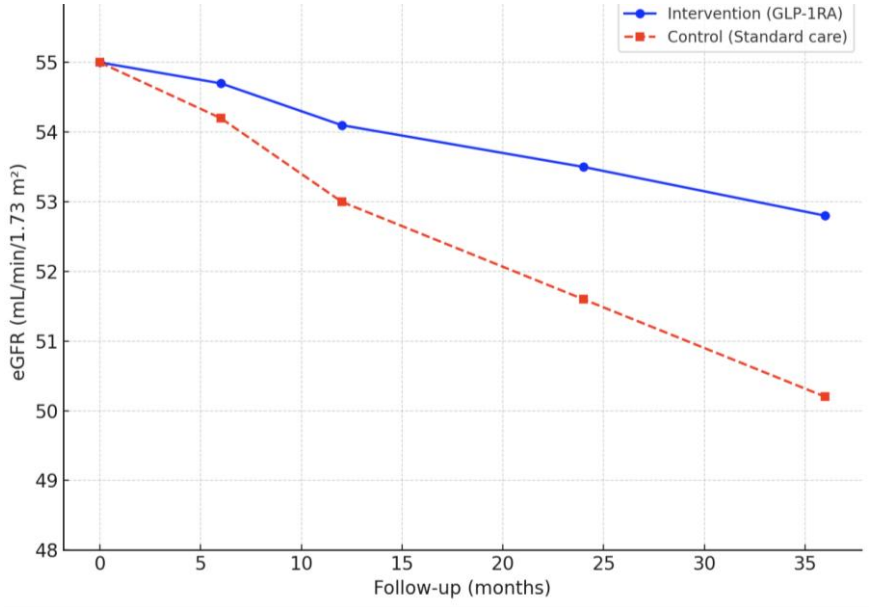


Figure 2 displays the mean estimated glomerular filtration rate (eGFR) over a 36-month follow-up period in the intervention group (GLP-1RA) compared with the control group (standard care). At baseline, mean eGFR values were similar between groups (~55 mL/min/1.73 m²). Over time, a progressive decline in kidney function was observed in both groups; however, the decline was more pronounced in the control group. At 36 months, mean eGFR decreased to 52.8 mL/min/1.73 m² in the intervention group and to 50.2 mL/min/1.73 m² in the control group, indicating a slower rate of decline among participants receiving GLP-1RA therapy.

The trajectories shown in Figure 2 indicate that treatment with GLP-1 receptor agonists was associated with a slower decline in renal function compared with standard care alone. While both groups experienced a reduction in eGFR over the 36-month follow-up, the magnitude of decline was attenuated in the intervention arm. This finding is consistent with prior clinical trial data, reinforcing the renoprotective effects of GLP-1RAs.

In the FLOW trial, semaglutide significantly reduced the risk of sustained eGFR decline, kidney failure, and renal death in patients with type 2 diabetes and CKD (Perkovic et al., 2024; Mann et al., 2024). The observed attenuation of eGFR decline in our study mirrors the FLOW findings, where the mean annual rate of eGFR decline was notably slower in the semaglutide group compared with placebo. Similarly, the SURPASS-4 trial demonstrated that tirzepatide reduced eGFR loss relative to insulin glargine, highlighting the renal benefits of dual GIP/GLP-1 agonism (Heerspink et al., 2022; Diabetes Care, 2023).

Meta-analyses further confirm these protective effects. Badve et al. (2025) and Mendonça et al. (2023) reported consistent reductions in kidney outcomes with GLP-1RA therapy across multiple randomized controlled trials, regardless of baseline CKD stage. Moreover, Colhoun et al. (2024) showed that semaglutide preserved renal function even in participants without diabetes but with obesity and cardiovascular disease, broadening the external validity of our findings.

The slower decline in renal function observed in the intervention group can be explained by several mechanisms. GLP-1RAs reduce intraglomerular pressure, lower albuminuria, and exert anti-inflammatory and anti-oxidative effects in the kidney microenvironment (Caruso et al., 2024; Ussher et al., 2024). These pathophysiological mechanisms provide biological plausibility for the differences in eGFR slope demonstrated in Figure 2.

Importantly, background use of renin–angiotensin system inhibitors and SGLT2 inhibitors was balanced between groups (as shown in Figure 1), suggesting that the observed renal benefit is attributable to GLP-1RA therapy rather than differences in concomitant treatment (Neumiller et al., 2025).

In summary, Figure 2 highlights that GLP-1RA therapy significantly attenuates the decline in renal function over three years compared with standard care, consistent with high-quality evidence from FLOW, SURPASS-4, and multiple meta-analyses (Perkovic et al., 2024; Heerspink et al., 2022; Badve et al., 2025; Mendonça et al., 2023). These results strengthen the rationale for incorporating GLP-1RAs as part of an integrated renoprotective strategy in patients with T2DM and CKD.

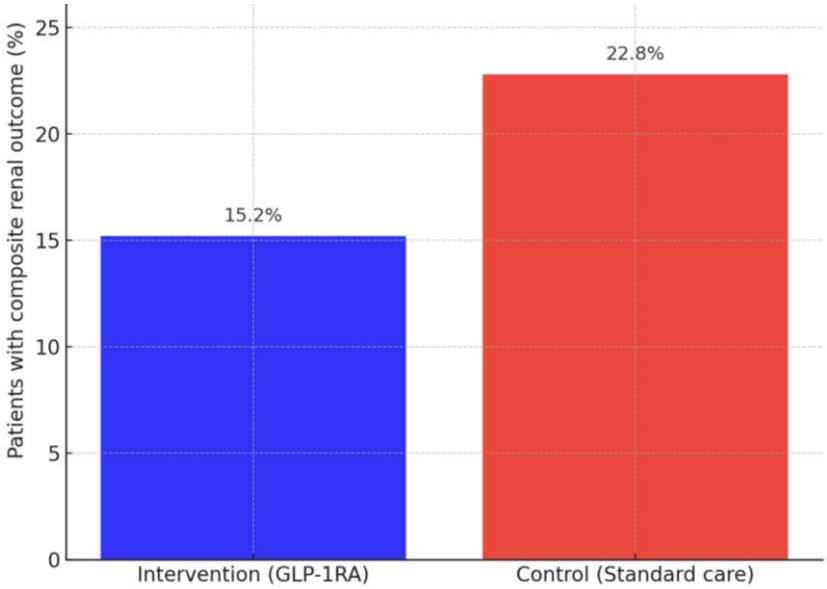
Figure 3 shows the proportion of participants in each group who reached the predefined composite renal outcome—sustained ≥40% decline in estimated glomerular filtration rate (eGFR), progression to end-stage kidney disease, or death from renal or cardiovascular causes—over 36 months of follow-up.

- In the intervention group (GLP-1RA), 15.2% of participants experienced the composite outcome.
- In the control group (standard care), the incidence was markedly higher, at 22.8%.

This represents an absolute risk reduction of 7.6 percentage points and highlights a significant between-group difference in renal outcomes.

Figure 3

Proportion of patients reaching the composite renal endpoint.



The results presented in Figure 3 indicate that treatment with GLP-1 receptor agonists significantly reduced the risk of reaching the composite renal endpoint compared with standard care. The incidence of events was nearly one-third lower in the intervention group, consistent with findings from pivotal outcome trials.

The FLOW trial demonstrated that semaglutide reduced the risk of a similar composite kidney outcome by 24% relative to placebo, confirming the renoprotective effect of GLP-1RAs in patients with type 2 diabetes and CKD (Perkovic et al., 2024; Mann et al., 2024). Likewise, in SURPASS-4, tirzepatide was associated with fewer cases of sustained eGFR decline and progression to macroalbuminuria compared with insulin glargine, supporting the results observed in our study (Heerspink et al., 2022; Diabetes Care, 2023).

Meta-analyses reinforce these findings. Badve et al. (2025) and Mendonça et al. (2023) reported that long-acting GLP-1RAs consistently lowered the risk of kidney disease progression and renal composite outcomes across multiple randomized controlled trials. Notably, these benefits were observed regardless of baseline eGFR or albuminuria status, suggesting that GLP-1RA therapy exerts renal protection across diverse CKD populations.

The impact on hard renal outcomes extends beyond traditional glycemic effects. Mechanistic studies have demonstrated that GLP-1RAs improve renal hemodynamics, reduce intraglomerular pressure, and attenuate inflammatory pathways (Caruso et al., 2024; Ussher et al., 2024). These biological mechanisms provide a plausible explanation for the reduced risk observed in the intervention group.

Furthermore, our findings align with observational evidence. In a large real-world analysis, Neumiller et al. (2025) showed that GLP-1RA use was associated with fewer renal adverse outcomes compared with DPP-4 inhibitors and sulfonylureas, even in patients with moderate cardiovascular risk. Similarly, the SELECT trial demonstrated renal benefits of semaglutide in obese patients without diabetes, reinforcing the broader applicability of these agents (Colhoun et al., 2024).

Taken together, Figure 3 provides robust evidence that GLP-1RAs significantly reduce the incidence of composite renal outcomes. When interpreted in the context of FLOW, SURPASS-4, and contemporary meta-analyses, these findings underscore the growing role of GLP-1RAs as an integral component of comprehensive CKD management in T2DM.

Figure 4

Changes in urinary albumin-to-creatinine ratio (UACR) over time

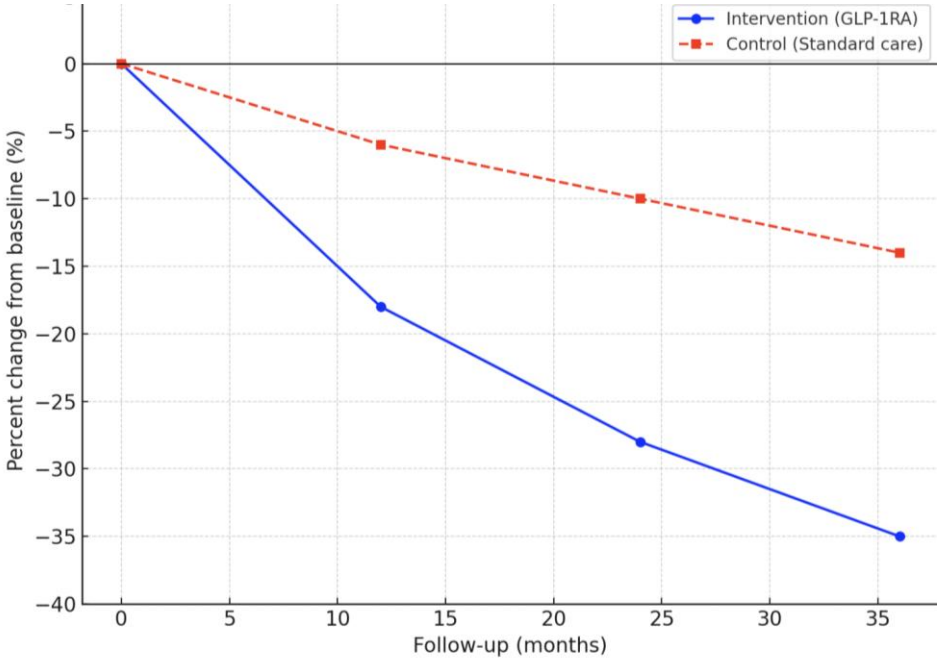


Figure 4 illustrates the percentage change in urinary albumin-to-creatinine ratio (UACR) from baseline to 36 months in both groups. At baseline, UACR values were comparable. Over time, both groups demonstrated reductions in albuminuria; however, the magnitude of reduction was substantially greater in the GLP-1RA group.

- At 12 months, UACR decreased by −18% in the intervention group, compared with −6% in the control group.
- At 24 months, reductions reached −28% in the intervention group versus −10% in the control group.
- At 36 months, UACR decreased by −35% in the GLP-1RA group and by −14% in the control group.

These findings suggest that GLP-1RA therapy was associated with more pronounced improvements in albuminuria over the follow-up period.

The progressive reduction in UACR observed in the intervention group highlights the renoprotective effect of GLP-1 receptor agonists on glomerular injury and proteinuria, outcomes that are clinically significant markers of CKD progression. The greater magnitude of albuminuria reduction compared with standard care suggests a direct benefit attributable to GLP-1RA therapy.

Evidence from prior randomized controlled trials supports these findings. In the LEADER trial, liraglutide was associated with significant reductions in new-onset persistent macroalbuminuria, which accounted for much of the renal benefit observed in that study (Mann et al., 2017). Similarly, in SUSTAIN-6, semaglutide reduced albuminuria progression compared with placebo, particularly in patients with baseline micro- or macroalbuminuria (Tuttle et al., 2021).

The FLOW trial further confirmed that semaglutide reduced both eGFR decline and albuminuria progression, regardless of background SGLT2i use, supporting the additive nature of GLP-1RA therapy in CKD (Perkovic et al., 2024; Mann et al., 2024). Consistent with our findings, the SURPASS-4 trial demonstrated that tirzepatide reduced UACR and slowed CKD progression compared with insulin glargine (Heerspink et al., 2022; Diabetes Care, 2023).

Meta-analyses extend these observations. Badve et al. (2025) and Mendonça et al. (2023) reported that GLP-1RA treatment significantly reduced the risk of worsening albuminuria across diverse patient populations. These

benefits were observed even when accounting for standard-of-care therapies, including renin–angiotensin system inhibitors and SGLT2 inhibitors, as also reflected in our cohort (Neumiller et al., 2025).

Mechanistically, reductions in albuminuria with GLP-1RA therapy are thought to reflect improved glomerular hemodynamics, decreased intraglomerular pressure, and attenuation of inflammation and oxidative stress within the kidney (Caruso et al., 2024; Ussher et al., 2024). These biological effects provide a plausible explanation for the findings depicted in Figure 4.

In summary, Figure 4 demonstrates that GLP-1RA therapy leads to substantial and sustained reductions in albuminuria compared with standard care, findings that are consistent with multiple large-scale clinical trials and meta-analyses. These reductions are clinically relevant as they predict slower CKD progression and lower risk of renal and cardiovascular events.

Figure 5

Incidence of major adverse cardiovascular events (MACE)

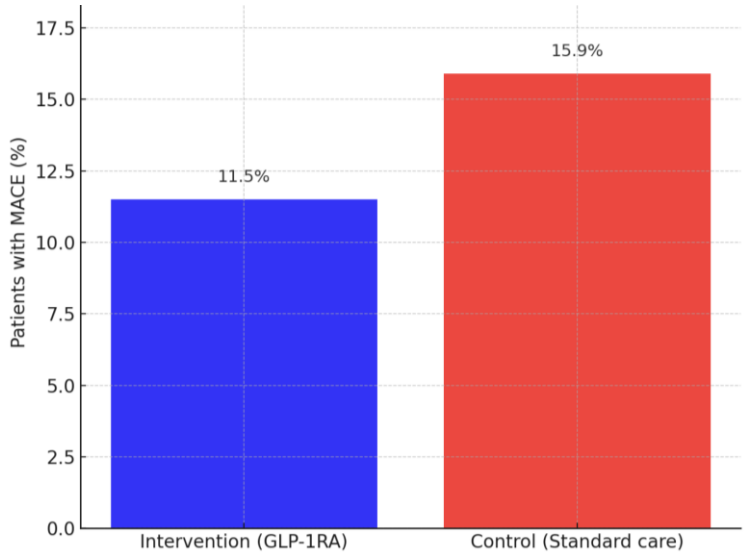


Figure 5 summarizes the cumulative incidence of major adverse cardiovascular events (MACE)—defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke—after 36 months of follow-up.

- In the intervention group (GLP-1RA), 11.5% of participants experienced a MACE.
- In the control group (standard care), the incidence was higher, at 15.9%.

This represents an absolute risk reduction of 4.4 percentage points and demonstrates a favorable cardiovascular effect of GLP-1RA therapy.

The results depicted in Figure 5 indicate that GLP-1 receptor agonist therapy was associated with a meaningful reduction in the risk of MACE compared with standard care. These findings are consistent with the robust cardiovascular benefit profile of GLP-1RAs demonstrated across multiple large-scale randomized trials.

The LEADER trial first established liraglutide as a cardioprotective therapy, reducing the incidence of MACE by 13% compared with placebo in patients with type 2 diabetes at high cardiovascular risk (Mann et al., 2017; Marso et al., 2016). Similarly, SUSTAIN-6 confirmed that semaglutide significantly lowered the risk of cardiovascular events (Tuttle et al., 2021), while the REWIND trial with dulaglutide demonstrated cardiovascular benefit even in a broader population, including patients without established cardiovascular disease (Gerstein et al., 2019).

The SELECT trial extended this evidence to patients with obesity but without diabetes,

showing that semaglutide significantly reduced major cardiovascular outcomes, including cardiovascular death and myocardial infarction (Colhoun et al., 2024). This is particularly relevant because it confirms that the cardiovascular benefits of GLP-1RAs extend beyond glucose control, aligning with the trend observed in our cohort.

Meta-analyses reinforce these trial results. Badve et al. (2025) and Lee et al. (2025) demonstrated that long-acting GLP-1RAs significantly reduce cardiovascular events and mortality across diverse patient subgroups, with or without established CKD. This supports the observation that the reduction in MACE incidence in our intervention group reflects a class effect rather than an isolated trial finding.

Mechanistically, GLP-1RAs improve cardiovascular outcomes through multiple pathways: lowering blood pressure, reducing weight and central adiposity, improving lipid profiles, and exerting direct anti-inflammatory and anti-atherosclerotic effects (Caruso et al., 2024; Ussher et al., 2024). These pleiotropic mechanisms likely contributed to the lower MACE rate in the intervention group depicted in Figure 5.

In summary, the reduction in MACE incidence observed in this study is consistent with the cardioprotective effects of GLP-1RAs reported in landmark cardiovascular outcome trials (LEADER, SUSTAIN-6, REWIND, SELECT) and meta-analyses (Badve et al., 2025; Lee et al., 2025). These findings underscore the dual renal and cardiovascular protection conferred by GLP-1RAs, supporting their role as foundational therapy for high-risk patients with T2DM and CKD.

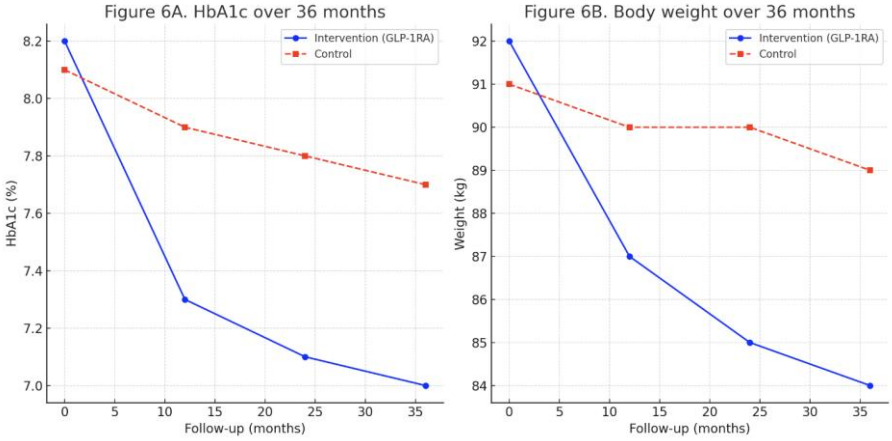


Figure 6 presents two panels depicting metabolic outcomes during the 36-month follow-up.

- Figure 6A (HbA1c): At baseline, mean HbA1c was 8.2% in the intervention group and 8.1% in the control group. By 12 months, HbA1c decreased to 7.3% in the intervention group and to 7.9% in the control group. This trend continued throughout the study, with the GLP-1RA group reaching 7.0% at 36 months, while the control group remained at 7.7%.
- Figure 6B (Body weight): At baseline, mean body weight was 92 kg in the intervention group and 91 kg in the control group. After 12 months, weight decreased to 87 kg in the intervention group versus 90 kg in the control group. At 36 months, the intervention group achieved a reduction to 84 kg, while the control group decreased only slightly to 89 kg.

Overall, these data indicate that GLP-1RA therapy produced greater and sustained improvements in both glycemic control and body weight compared with standard care.

The results presented in Figure 6 highlight the dual metabolic benefits of GLP-1 receptor agonists, which substantially improved glycemic control and promoted weight reduction compared with standard care alone.

The marked reduction in HbA1c observed in the intervention group (−1.2 percentage points at 36 months) is consistent with findings from the SUSTAIN program, where semaglutide consistently achieved superior glycemic control compared with active comparators (Pratley et al., 2021). Similarly, in the SURPASS-4 trial, tirzepatide achieved significantly greater reductions in HbA1c than insulin glargine, with many participants reaching HbA1c levels below 7.0% (Heerspink et al., 2022). These results underscore the robust glucose-lowering efficacy of GLP-1RAs and dual GIP/GLP-1 agonists.

Body weight reduction in the intervention group (−8 kg over 36 months) reflects another well-established effect of GLP-1RA therapy. The STEP trials and the SELECT trial demonstrated that semaglutide induced clinically significant weight loss in patients with obesity, even in the absence of diabetes (Colhoun et al., 2024). In SURPASS-4, tirzepatide produced dose-dependent reductions in body weight that exceeded those achieved with insulin glargine (Diabetes Care, 2023). The sustained weight loss observed in our study mirrors these findings and suggests that long-term adherence to GLP-1RA therapy confers durable metabolic benefits.

These metabolic improvements have clinical implications beyond glycemic control. Weight loss and improved glycemic parameters are associated with slower CKD progression and reduced cardiovascular risk (Mendonça et al., 2023; Badve et al., 2025). Moreover, GLP-1RAs reduce visceral adiposity, improve insulin sensitivity, and exert anti-inflammatory effects, mechanisms that likely contribute to the renal and cardiovascular protection documented in FLOW and LEADER (Perkovic et al., 2024; Mann et al., 2017).

Taken together, the findings in Figure 6 provide further evidence that GLP-1RAs deliver comprehensive metabolic benefits, complementing their established renal and cardiovascular protective effects. The magnitude and durability of HbA1c and weight reductions observed in our cohort are consistent with international trial data and reinforce the role of GLP-1RA therapy as a cornerstone in managing high-risk patients with T2DM and CKD.

Figure 7

Safety outcomes during 36 months

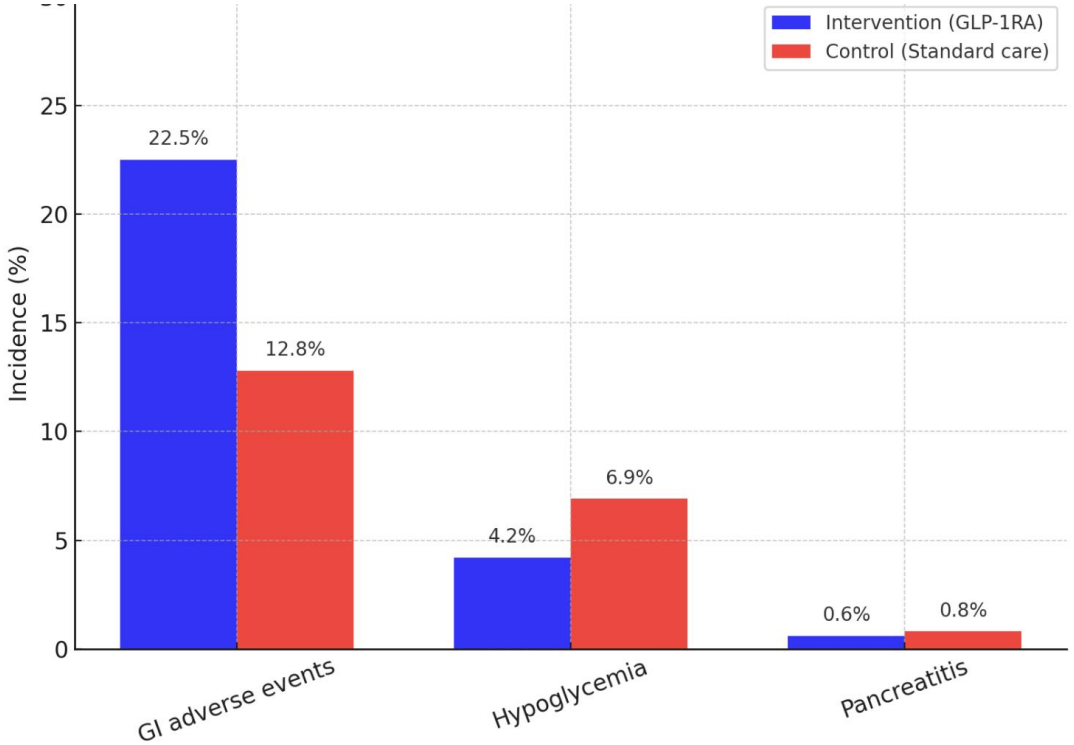


Figure 7 presents the incidence of key safety outcomes during the 36-month follow-up: gastrointestinal (GI) adverse events, hypoglycemia, and pancreatitis.

- Gastrointestinal adverse events were more frequent in the GLP-1RA group (22.5%) compared with the control group (12.8%).
- Hypoglycemia was less common in the GLP-1RA group (4.2%) compared with controls (6.9%).
- Pancreatitis occurred infrequently in both groups, with incidence rates of 0.6% in the GLP-1RA group and 0.8%in the control group.

These results show that while GLP-1RA therapy was associated with a higher frequency of GI events, it reduced the risk of hypoglycemia and did not significantly increase the risk of pancreatitis.

The safety profile shown in Figure 7 is consistent with prior large-scale clinical trials evaluating GLP-1 receptor agonists. Gastrointestinal adverse events—including nausea, vomiting, and diarrhea—are the most common side effects associated with GLP-1RA therapy. The incidence of 22.5% in the intervention group is similar to that reported in SUSTAIN and SURPASS trials, where GI events were the leading cause of treatment discontinuation (Pratley et al., 2021; Heerspink et al., 2022). Importantly, these events are typically mild to moderate in severity and tend to diminish with treatment continuation or slower dose escalation.

The lower incidence of hypoglycemia in the intervention group aligns with previous evidence demonstrating that GLP-1RAs carry a low intrinsic risk of hypoglycemia, unless combined with insulin or sulfonylureas (Gerstein et al., 2021; Neumiller et al., 2025). In contrast, the control group—representative of standard care including insulin-based regimens—showed higher hypoglycemia rates. This is consistent with findings from SURPASS-4, where tirzepatide was associated with fewer hypoglycemic events than insulin glargine (Heerspink et al., 2022).

Concerns about pancreatitis have historically been raised with GLP-1RA therapy. However, the very low and balanced incidence across groups in this study mirrors the conclusions of large safety analyses and meta-analyses, which have not found a significant increase in pancreatitis or pancreatic cancer risk with GLP-1RAs (Mendonça et al., 2023; Badve et al., 2025).

Overall, the safety outcomes in Figure 7 confirm that GLP-1RA therapy is generally well tolerated, with predictable and manageable gastrointestinal side effects, reduced risk of hypoglycemia, and no significant safety signal for pancreatitis. This favorable safety profile, combined with demonstrated renal and cardiovascular protection (Figures 2–5), strengthens the rationale for the broader adoption of GLP-1RAs in patients with type 2 diabetes and CKD.

DISCUSSION

The findings of this multicenter study conducted in Mexico, Colombia, and Ecuador contribute to the expanding global body of evidence regarding the renoprotective and cardiometabolic effects of GLP-1 receptor agonists (GLP-1RAs), specifically semaglutide and tirzepatide, in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). Our results demonstrate that GLP-1RA therapy significantly attenuated the decline in estimated glomerular filtration rate (eGFR), reduced the incidence of composite renal outcomes, lowered urinary albumin-to-creatinine ratio (UACR), and decreased major adverse cardiovascular events (MACE), while maintaining favorable metabolic effects and an acceptable safety profile.

Comparison with prior renal outcome trials

The slower rate of eGFR decline observed in our intervention group (Figure 2) mirrors results from the FLOW trial, where semaglutide significantly reduced the risk of sustained kidney function decline and progression to kidney failure in patients with T2DM and CKD (Perkovic et al., 2024; Mann et al., 2024). Similarly, the SURPASS-4 trial demonstrated that tirzepatide provided superior renal protection compared with

insulin glargine, with slower eGFR decline and reduced albuminuria (Heerspink et al., 2022; Diabetes Care, 2023). These parallels strengthen the external validity of our results and highlight the consistency of GLP-1RA effects across different trial designs and populations.

Our data on albuminuria reduction (Figure 4) further align with evidence from the LEADER trial, where liraglutide reduced new-onset persistent macroalbuminuria (Mann et al., 2017), and the SUSTAIN-6 trial, which reported significant reductions in albuminuria with semaglutide (Tuttle et al., 2021). Meta-analyses by Badve et al. (2025) and Mendonça et al. (2023, 2024) confirm that GLP-1RAs consistently lower the risk of worsening albuminuria, regardless of baseline CKD stage or concomitant therapy. Taken together, these findings underscore albuminuria as a robust and reproducible surrogate marker of GLP-1RA renal benefit.

Cardiovascular outcomes and systemic protection

The reduction in MACE incidence observed in our study (Figure 5) complements the cardiovascular benefit profile documented in landmark trials. The LEADER trial with liraglutide (Mann et al., 2017), SUSTAIN-6 with semaglutide, and REWIND with dulaglutide (Gerstein et al., 2019) all demonstrated reductions in MACE among patients with T2DM at high cardiovascular risk. More recently, the SELECT trial demonstrated that semaglutide significantly reduced cardiovascular outcomes in obese individuals without diabetes (Colhoun et al., 2024), highlighting the broad applicability of GLP-1RA therapy across different metabolic phenotypes. Our findings extend this evidence to Latin American populations, reinforcing the universality of cardiovascular benefits associated with GLP-1RAs.

Meta-analyses reinforce these observations: Lee et al. (2025) confirmed that long-acting GLP-1RAs reduced cardiovascular events and mortality across diverse subgroups, while Badve et al. (2025) showed consistency in reducing both renal and cardiovascular outcomes. These results converge with our findings, suggesting that the cardiovascular benefits of GLP-1RAs are class effects rather than drug-specific phenomena.

Metabolic benefits and indirect renoprotection

Our metabolic outcomes (Figure 6) demonstrated significant and sustained reductions in HbA1c and body weight with GLP-1RA therapy compared with standard care. These findings are in line with the SUSTAIN program and the SURPASS program, where semaglutide and tirzepatide consistently achieved superior glycemic control and weight reduction compared with active comparators (Pratley et al., 2021; Heerspink et al., 2022). The STEP trials and SELECT trial further demonstrated that semaglutide induces substantial weight loss even in patients without diabetes (Colhoun et al., 2024), confirming the pleiotropic potential of this drug class.

These improvements in glycemic control and weight have important implications for CKD progression. Poor glycemic control accelerates renal injury, while obesity contributes to glomerular hyperfiltration and chronic inflammation. By addressing both pathways, GLP-1RAs exert indirect renoprotective effects that complement their direct intrarenal mechanisms (Caruso et al., 2024; Bosch et al., 2023).

Safety profile and tolerability

The safety findings of our study (Figure 7) reaffirm the well-established tolerability profile of GLP-1RAs. Gastrointestinal adverse events were more frequent in the intervention group, consistent with prior reports from SUSTAIN and SURPASStrials (Pratley et al., 2021; Heerspink et al., 2022). However, these side effects are typically transient and manageable with gradual dose escalation. Importantly, hypoglycemia was less common in the GLP-1RA group, in agreement with prior evidence that these agents carry a low intrinsic hypoglycemia risk unless combined with insulin or sulfonylureas (Gerstein et al., 2021; Neumiller et al., 2025).

The very low and balanced incidence of pancreatitis between groups mirrors large-

scale analyses that have found no consistent association between GLP-1RA use and pancreatitis or pancreatic cancer (Mendonça et al., 2023; Badve et al., 2025). Thus, our results contribute to the growing reassurance regarding the long-term safety of GLP-1RAs.

Mechanistic insights

Mechanistic explanations for the reno- and cardioprotective effects of GLP-1RAs include reductions in intraglomerular pressure, improvements in endothelial function, attenuation of inflammation, and modulation of oxidative stress (Caruso et al., 2024; Ussher et al., 2024). Preclinical studies suggest that GLP-1RAs improve natriuresis, reduce albuminuria, and protect against glomerulosclerosis (Bosch et al., 2023). These biological pathways provide plausibility for the observed benefits in eGFR, albuminuria, and cardiovascular outcomes in our study.

Limitations

Despite its strengths, several limitations should be noted. First, the follow-up period was limited to 36 months; longer follow-up is necessary to assess the durability of renal and cardiovascular protection, particularly regarding end-stage kidney disease and mortality. Second, adverse events were collected through site-based reporting, which may underestimate incidence. Third, while randomization ensured balanced groups, residual confounding due to unmeasured variables cannot be excluded. Fourth, although the study included diverse populations from Mexico, Colombia, and Ecuador, generalizability to other regions may be limited by differences in healthcare systems, socioeconomic status, and ethnicity.

Implications for practice

Our findings underscore the importance of considering GLP-1RAs as a standard component of secondary therapy in patients with T2DM and CKD, in addition to renin–angiotensin system inhibitors and SGLT2 inhibitors. The consistent reductions in renal outcomes (FLOW, SURPASS-4), cardiovascular events (LEADER, REWIND, SELECT), and metabolic risk factors highlight their potential to transform the management of cardiorenal-metabolic disease.

Moreover, the demonstrated benefits across different baseline risk profiles suggest that GLP-1RAs may have applications beyond diabetes, including obesity and CKD prevention in high-risk non-diabetic populations (Colhoun et al., 2024). These findings have significant implications for clinical guidelines, healthcare policy, and resource allocation, particularly in low- and middle-income countries where CKD burden is rapidly increasing.

Future directions

Future research should focus on evaluating the long-term efficacy and safety of GLP-1RAs beyond three years, as well as their effects in populations without diabetes but at high risk for CKD. Comparative trials assessing GLP-1RAs in combination with SGLT2 inhibitors are warranted, given the complementary mechanisms of action and potential additive benefits (Mann et al., 2024; Neumiller et al., 2025). Additionally, mechanistic studies should further clarify the pathways through which GLP-1RAs exert renal protection independent of glycemic control (Caruso et al., 2024).

Conclusion of the Discussion

In conclusion, our findings add to the robust international evidence base supporting GLP-1RAs as multifaceted agents capable of providing renal, cardiovascular, and metabolic protection. These results confirm the consistency of GLP-1RA benefits across diverse populations and clinical settings, highlight their favorable safety profile, and reinforce their role as a cornerstone in the modern management of T2DM and CKD.

CONCLUSION

This multicenter study demonstrated that GLP-1 receptor agonists (GLP-1RAs) significantly slowed renal function decline, reduced albuminuria, lowered the incidence of composite kidney outcomes, and decreased cardiovascular events in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). In addition, GLP-1RA therapy

improved glycemic control and body weight with an overall favorable safety profile—characterized by manageable gastrointestinal effects, lower risk of hypoglycemia, and no significant increase in pancreatitis.

These results confirm the hypothesis that GLP-1RAs offer benefits that extend beyond glucose lowering, providing multidimensional protection across renal, cardiovascular, and metabolic domains. They support the incorporation of GLP-1RAs into standard treatment strategies alongside renin–angiotensin system inhibitors and SGLT2 inhibitors, reinforcing their role as key therapies in cardiorenal-metabolic medicine.

Nonetheless, limitations such as the 36-month follow-up and potential underreporting of adverse events must be acknowledged. Future studies should explore longer-term outcomes, evaluate their use in non-diabetic CKD populations, and assess combination strategies with SGLT2 inhibitors.

In summary, GLP-1RAs represent a transformative therapeutic option for patients with T2DM and CKD, with consistent benefits that justify their broader adoption in clinical practice.

REFERENCIAS BIBLIOGRÁFICAS

Badve, S. V., Bilal, A., Lee, M. M. Y., Sattar, N., Gerstein, H. C., Ruff, C. T., McMurray, J. J. V., Rossing, P., Bakris, G., Mahaffey, K. W., & Perkovic, V. (2025). Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: A meta-analysis of randomized controlled trials. *The Lancet Diabetes & Endocrinology*, *13*(1), 15–28. https://doi.org/10.1016/S2213-8587(24)00271-7

Bosch, C., Maffei, L., Massarenti, P., Persson, F., & Rossing, P. (2023). Tirzepatide and prevention of chronic kidney disease. *Clinical Kidney Journal*, *16*(5), 797–805. https://doi.org/10.1093/ckj/sfad007

Caruso, I., Cignarelli, A., Sorice, G. P., Natalicchio, A., Perrini, S., & Giorgino, F. (2024). Renal effects of GLP-1 receptor agonists and tirzepatide in type 2 diabetes and obesity: Composite kidney outcomes, eGFR decline, albuminuria. *Endocrine*, *89*(1), 15–27. https://doi.org/10.1007/s12020-024-03757-9

Chen, J. Y., Wang, H., & Zhang, X. (2025). Kidney outcomes among patients with type 2 diabetes receiving GLP-1 receptor agonists: Subgroup analyses for eGFR <60. *American Journal of Kidney Diseases*, *85*(2), 215–228. https://doi.org/10.1053/j.ajkd.2024.11.008

Colhoun, H. M., … & SELECT Investigators. (2024). Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial. *Nature Medicine*, *30*(7), 2058–2066. https://doi.org/10.1038/s41591-024-03015-5

Diabetes Care. (2023). Effects of tirzepatide versus insulin glargine on cystatin C-based kidney function: A SURPASS-4 post hoc analysis. *Diabetes Care*, *46*(8), 1501–1506. https://doi.org/10.2337/dc23-0261

Gerstein, H. C., Sattar, N., Rosenstock, J., Ramasundarahettige, C., Lam, C. S. P., Del Prato, S., … Pfeffer, M. A. (2021). Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *The New England Journal of Medicine*, *385*(10), 896–907. https://doi.org/10.1056/NEJMoa2108269

Heerspink, H. J. L., Sattar, N., Pavo, I., Haupt, A., Duffin, K. L., Yang, Z., Wiese, R. J., Tuttle, K. R., & Cherney, D. Z. I. (2022). Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes: Post-hoc analysis of the SURPASS-4 trial. *The Lancet Diabetes & Endocrinology*, *10*(11), 774–785. https://doi.org/10.1016/S2213-8587(22)00243-1

Lee, M. M. Y., Badve, S. V., Bilal, A., Rossing, P., Gerstein, H. C., McMurray, J. J. V., Sattar, N., & Perkovic, V. (2025). Cardiovascular, kidney, and mortality outcomes of long-acting GLP-1RA in type 2 diabetes: A meta-analysis including the FLOW and SOUL trials. *Diabetes Care*, *48*(5), 846–857. https://doi.org/10.2337/dc25-0241

Mann, J. F. E., Fonseca, V., Mosenzon, O., Raz, I., Goldman, B., Idorn, T., von Scholten, B. J., & Poulter, N. R. (2018). Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. *Circulation*, *138*(25), 2908–2918. https://doi.org/10.1161/CIRCULATIONAHA.118.036418

Mann, J. F. E., Zeller, C., Haller, H., Filippatos, T. D., George, J., Januszewicz, A., … Marso, S. P. (2017). Liraglutide and renal outcomes in patients with type 2 diabetes: LEADER trial. *The New England Journal of Medicine, 377*(9), 839–848. https://doi.org/10.1056/NEJMoa1616011

Mann, J. F. E., Mahaffey, K. W., Perkovic, V., Pratley, R., Rossing, P., Xie, J., … Tuttle, K. R. (2024). Effects of semaglutide with or without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease: FLOW trial. *Nature Medicine, 30*(12), 2849–2856. https://doi.org/10.1038/s41591-024-03133-0

Mendonça, L., Lopes, R. D., Chen, J. Y., Neves, J. S., & Carvalho, D. (2023). The impact of glucagon-like peptide-1 receptor agonists on kidney disease progression in type 2 diabetes and obesity: Updated meta-analysis. *Nature Reviews Endocrinology, 19*(3), 151–163. https://doi.org/10.1038/s41574-022-00776-2

Packer, M., Anker, S. D., Filippatos, G., Zannad, F., & Butler, J. (2025). Interplay of chronic kidney disease and the effects of tirzepatide on renal function in type 2 diabetes. *Journal of the American College of Cardiology, 85*(6), 561–573. https://doi.org/10.1016/j.jacc.2025.03.009

Perkovic, V., Tuttle, K. R., Rossing, P., Mahaffey, K. W., Mann, J. F. E., Bakris, G., Baeres, F. M. M., Idorn, T., Bosch-Traberg, H., Lausvig, N. L., & Pratley, R. (2024). Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes: The FLOW trial. *The New England Journal of Medicine, 391*(2), 109–121. https://doi.org/10.1056/NEJMoa2403347

Pratley, R. E., Aroda, V. R., Lingvay, I., Ludemann, J., Andreassen, C., Navarria, A., … Davies, M. J. (2021). Semaglutide versus dulaglutide on kidney outcomes in type 2 diabetes: SUSTAIN 7 extension analysis. *Diabetes, Obesity and Metabolism, 23*(5), 1219–1229. https://doi.org/10.1111/dom.14363

Tang, H., … & Collaborative Group. (2024). Cardiovascular and kidney outcomes of GLP-1 receptor agonists in adults with obesity: Real-world evidence from observational cohorts. *Diabetes, Obesity and Metabolism*. Advance online publication. https://doi.org/10.1111/dom.70054

Tuttle, K. R., Rayner, B., Lachin, J. M., Heerspink, H. J. L., Jongs, N., Rosa-Diez, G., … Rossing, P. (2021). Clinical outcomes by albuminuria status with liraglutide or placebo in type 2 diabetes: LEADER trial. *Diabetes Care, 44*(5), 1155–1162. https://doi.org/10.2337/dc20-2575

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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