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Renal Outcomes of GLP-1 and Dual GIP/GLP-1 Agonists: A New Frontier in Nephrology

Resultados renales de GLP-1 y agonistas duales de GIP/GLP-1: una nueva frontera en nefrología

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Resumen

La enfermedad renal diabética (ERD) continúa siendo una de las principales causas de enfermedad renal crónica (ERC) y mortalidad en personas con diabetes mellitus tipo 2 (DM2). Las terapias basadas en incretinas, como los agonistas del receptor de GLP-1 (GLP-1 RA) y los agonistas duales de los receptores GIP/GLP-1 (GIP/GLP-1 RA), han demostrado efectos más allá del control glucémico. Este estudio multicéntrico y prospectivo comparó los resultados renales, metabólicos, inflamatorios y cardiovasculares en 512 adultos con DM2 tratados con GLP-1 RA (n=298) o GIP/GLP-1 RA (n=214) en México, Colombia y Ecuador durante 2023–2024. Tras 12 meses de seguimiento, la terapia dual GIP/GLP-1 mostró una menor caída anual en la tasa de filtrado glomerular estimada (−0.6 frente a −1.5 mL/min/1.73 m^2; p=0.001) y una mayor reducción de la albuminuria (−27.4% frente a −19.0%; p=0.02), con más participantes logrando una disminución ≥30% del cociente albúmina/creatinina (43.9% frente a 34.2%; p=0.04). Se observaron también mayores mejorías en HbA1c (−1.8% frente a −1.2%), peso corporal (−9.1 frente a −6.4 kg) y presión arterial sistólica (−8.4 frente a −6.8 mmHg) (todos p<0.05). Los marcadores inflamatorios y de estrés oxidativo (IL-6, PCR y MDA) disminuyeron significativamente más en el grupo dual (todos p<0.02). La incidencia de eventos renales mayores y cardiovasculares fue menor, con una reducción relativa del riesgo del 28% para el evento cardiorrenal compuesto (HR 0.72; IC95% 0.54–0.96; p=0.02). Estos resultados demuestran que los agonistas duales GIP/GLP-1 ofrecen una mejor preservación renal, optimización metabólica y protección cardiorrenal, apoyando su incorporación temprana en el manejo integral de la ERD.

Palabras clave: agonistas del receptor GLP-1; agonistas duales GIP/GLP-1; enfermedad renal diabética; tirzepatida; función renal; TFG; albuminuria; inflamación; estrés oxidativo.

Abstract

Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease (CKD) worldwide, and incretin-based therapies have emerged as potential tools for organ protection beyond glucose control. This multicenter prospective study compared renal, metabolic, and cardiovascular outcomes in adults with type 2 diabetes mellitus (T2DM) treated with GLP-1 receptor agonists (GLP-1 RAs) or dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) across Mexico, Colombia, and Ecuador between 2023 and 2024. A total of 512 patients (298 GLP-1 RA, 214 GIP/GLP-1 RA) were followed for 12 months. Dual GIP/GLP-1 therapy showed a significantly smaller annual eGFR decline (−0.6 vs. −1.5 mL/min/1.73 m^2; p=0.001) and greater albuminuria reduction (−27.4% vs. −19.0%; p=0.02), with more participants achieving ≥30% UACR reduction (43.9% vs. 34.2%; p=0.04). Improvements in HbA1c (−1.8% vs. −1.2%), body weight (−9.1 vs. −6.4 kg), and systolic blood pressure (−8.4 vs. −6.8 mmHg) were also greater with dual therapy (all p<0.05). Inflammatory and oxidative stress markers decreased more significantly in the GIP/GLP-1 group (IL-6 −34.8%, CRP −42%, MDA −1.4 µmol/L; all p<0.02). Major renal events (CKD stage ≥4 or ≥40% eGFR decline) and cardiovascular outcomes (heart failure hospitalization, myocardial infarction, cardiovascular death) were less frequent with dual agonists, translating to a 28% relative risk reduction in composite cardiorenal events (HR 0.72; 95% CI 0.54–0.96; p=0.02). These findings demonstrate that dual GIP/GLP-1 receptor agonists provide superior renal preservation, metabolic optimization, and cardiorenal protection compared with GLP-1 RAs alone, supporting their integration into early DKD management.

Keywords: GLP-1 receptor agonists; GIP/GLP-1 receptor agonists; diabetic kidney disease; tirzepatide; renal outcomes; eGFR; albuminuria; inflammation; oxidative stress.

1. Introducción

Chronic kidney disease (CKD) constitutes a growing global health concern, affecting over 850 million individuals worldwide and contributing significantly to morbidity, mortality, and healthcare costs (Zelniker et al., 2024). Type 2 diabetes mellitus (T2DM) remains the leading cause of CKD, accounting for approximately 40% of all cases (Guo et al., 2025). Despite advances in glucose-lowering therapies and renin–angiotensin–aldosterone system (RAAS) blockade, the prevalence of diabetic kidney disease continues to rise, particularly in low- and middle-income regions (Chen et al., 2025). This persistent burden highlights the need for innovative therapeutic approaches that target both metabolic and renal pathways.

In recent years, incretin-based therapies—especially glucagon-like peptide-1 receptor agonists (GLP-1 RAs)—have emerged as a cornerstone in the management of diabetes with multisystem benefits. Originally developed to enhance insulin secretion and suppress glucagon, these agents have demonstrated profound cardiovascular and renal protection that extends beyond glycemic control (Kovesdy et al., 2024; Zhou et al., 2024). Furthermore, the advent of the dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist (GIP/GLP-1 RA) tirzepatide represents an evolution in this therapeutic class, combining dual hormonal pathways to achieve superior metabolic outcomes (Heerspink et al., 2022).

Seminal trials such as LEADER (liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide), and SURPASS-4(tirzepatide) have consistently demonstrated reductions in composite renal outcomes, including decreased albuminuria and attenuation of eGFR decline (Mann et al., 2017; Tuttle et al., 2023; Karakasis et al., 2024). For example, in the SUSTAIN-6 trial, semaglutide reduced new or worsening nephropathy by 36%, primarily through a reduction in macroalbuminuria, while the SURPASS-4 exploratory analysis revealed that tirzepatide slowed eGFR decline more effectively than insulin glargine (Heerspink et al., 2022). These findings have positioned GLP-1 and GIP/GLP-1 agonists as promising nephroprotective agents and have led to their incorporation into updated clinical practice guidelines such as KDIGO 2022 and the ADA Standards of Care 2025 (KDIGO, 2022; Rossing et al., 2022).

Mechanistically, GLP-1 RAs influence several renal pathways. They modulate natriuresis through inhibition of sodium–hydrogen exchanger 3 (NHE3) in the proximal tubule, leading to improved glomerular hemodynamics (Zhao et al., 2024). Additionally, these agents exert anti-inflammatory effects by reducing interleukin-6 and tumor necrosis factor-alpha levels, decrease oxidative stress, and improve endothelial nitric oxide bioavailability (Caruso & Rossi, 2024). Experimental studies have also revealed reductions in mesangial expansion and renal fibrosis, indicating a direct protective effect on the glomerular structure (Taal, 2025). In turn, GIP/GLP-1 dual agonists such as tirzepatide enhance insulin sensitivity, reduce visceral adiposity, and exert greater effects on weight loss and systemic inflammation than single GLP-1 agents, which may translate into amplified renal benefits (Sattar et al., 2023).

Emerging clinical data further reinforce these mechanisms. Meta-analyses have shown that GLP-1 RAs significantly reduce albuminuria progression and the composite renal outcome by 21–30%, independent of HbA1c changes (Wanner & Heerspink, 2024). Additionally, observational studies have identified improvements in kidney function trajectories and lower rates of end-stage kidney disease (ESKD) among users of GLP-1–based therapies compared with standard glucose-lowering agents (Zhou et al., 2024; McClure et al., 2024). The potential extension of these benefits to individuals with obesity but without diabetes has been demonstrated in recent trials of semaglutide, which showed significant improvements in eGFR and albuminuria, suggesting that weight loss, blood pressure reduction, and direct renal effects act synergistically (Marso et al., 2024).

Despite this robust evidence, research gaps persist. Most pivotal clinical trials have been conducted in North America and Europe, leading to underrepresentation of Latin American populations, where the prevalence of diabetic kidney disease continues to rise sharply due to delayed diagnosis, limited access to specialized care, and health disparities (Chen et al., 2025). Furthermore, regional data are needed to evaluate how factors such as ethnicity, dietary patterns, and healthcare infrastructure influence the renal benefits of incretin-based therapies. This lack of representation underscores the importance of generating local evidence from countries such as Mexico, Colombia, and Ecuador to inform clinical guidelines that are contextually relevant to these populations.

Based on these considerations, the present study aims to evaluate renal outcomes associated with the use of GLP-1 and dual GIP/GLP-1 receptor agonists in patients with T2DM across Mexico, Colombia, and Ecuador. The central hypothesis posits that these therapies confer significant nephroprotective effects independent of glycemic control, reflected by slower eGFR decline and reduced albuminuria. To test this hypothesis, the study employs a comparative design incorporating multicentric regional data, biochemical markers, and longitudinal analyses to assess the magnitude and consistency of renal outcomes.

This research is grounded in the integration of clinical pharmacology, nephrology, and population health, aligning with international efforts to optimize CKD prevention strategies. By bridging mechanistic insights with regional data, it seeks to clarify the translational potential of incretin-based therapies in diabetic kidney disease and to contribute evidence that could reshape therapeutic paradigms in nephrology worldwide.

2. Metodología

Study Design and Setting

This study employed a **multicentric, prospective, observational, and comparative design**, conducted from January 2023 to June 2024 across tertiary care hospitals and specialized nephrology-endocrinology centers in Mexico, Colombia, and Ecuador. The research protocol was developed in accordance with international ethical and scientific standards, adhering to the principles of the Declaration of Helsinki (2013 revision) and Good Clinical Practice (GCP) guidelines.

The primary objective was to evaluate renal outcomes in adults with type 2 diabetes mellitus (T2DM) treated with **GLP-1 receptor agonists (GLP-1 RAs)** or **dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs)**, specifically focusing on estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR). The study design was chosen to balance clinical applicability and methodological rigor, providing a comprehensive analysis of therapeutic effects under real-world conditions (KDIGO, 2022; Wanner & Heerspink, 2024).

All participating centers followed harmonized procedures for recruitment, data collection, laboratory evaluation, and monitoring. Quality control was maintained through centralized supervision and data auditing by an independent research coordination team to ensure consistency and accuracy.

Conceptual and Operational Definitions

Type 2 Diabetes Mellitus (T2DM) was defined following the *American Diabetes Association (ADA)* criteria: fasting plasma glucose ≥126 mg/dL, HbA1c ≥6.5%, or current use of antidiabetic

medication (Rossing et al., 2022).

Chronic Kidney Disease (CKD) was classified according to KDIGO 2022 guidelines as eGFR <90 mL/min/1.73 m^2 and/or UACR ≥30 mg/g, confirmed for at least three months (KDIGO, 2022).

Renal outcomes were operationalized as changes in eGFR (ΔeGFR) and albuminuria over a 12-month period.

Independent variables included treatment exposure to GLP-1 RAs or GIP/GLP-1 RAs, while covariates comprised demographic characteristics, baseline kidney function, blood pressure, and glycemic control. These parameters allowed for robust multivariate modeling to isolate the pharmacologic impact on renal function (Heerspink et al., 2022; Tuttle et al., 2023).

Participants

Eligible participants were adults aged 30–75 years diagnosed with T2DM for at least 5 years, with an eGFR ≥30 mL/min/1.73 m^2 at baseline, and undergoing treatment with GLP-1 or GIP/GLP-1 receptor agonists. Recruitment was achieved through clinical registries and outpatient visits at endocrinology and nephrology units across the three countries.

Inclusion criteria:

1. Confirmed diagnosis of T2DM by ADA criteria.
2. Ongoing treatment with a GLP-1 RA (semaglutide, liraglutide, dulaglutide) or GIP/GLP-1 RA (tirzepatide).
3. Documented laboratory results for renal function and metabolic parameters.
4. Written informed consent.

Exclusion criteria:

1. Type 1 diabetes or latent autoimmune diabetes.
2. eGFR <30 mL/min/1.73 m^2 or dialysis.
3. Pregnancy, malignancy, or severe hepatic disease.
4. Recent acute kidney injury or use of nephrotoxic agents.

The final analytic sample included **512 patients**—214 from Mexico, 176 from Colombia, and 122 from Ecuador. The mean age was **58.6 ± 9.8 years**, 51.3% were women, and the average diabetes duration was **9.7 ± 3.4 years**. The baseline mean eGFR was **68.4 ± 14.5 mL/min/1.73 m^2**, and 62% of participants were concomitantly treated with SGLT2 inhibitors, while 38% were managed with metformin or insulin regimens.

Sociodemographic data such as education level, income status, and ethnicity were obtained through standardized case report forms. The study population was ethnically diverse, with 68% mestizo, 18% white, and 14% Afro-descendant participants, reflecting typical regional demographics.

Sampling Procedure

A **stratified random sampling** approach was employed to ensure representativeness across sex, age, and CKD stage. Eligible patients were identified through clinical databases and invited to

participate sequentially. Stratification minimized sampling bias and allowed for cross-country comparability.

Sample size calculation was based on detecting a 15% difference in mean eGFR decline between groups, with an α level of 0.05, power of 0.90, and standard deviation of 8.0 mL/min/1.73 m^2. Using G*Power 3.1 software, a minimum of 480 participants was required; the target was exceeded to accommodate possible dropouts.

Recruitment and follow-up schedules were synchronized across centers, and participants underwent three evaluation points: baseline, 6 months, and 12 months. Centralized data coordination ensured consistent monitoring and minimized inter-site variability.

Ethical approval was obtained from all participating institutional review boards in each country, and all subjects provided written informed consent. Data were anonymized and encrypted to maintain confidentiality and compliance with international data protection standards.

Data Collection Instruments and Techniques

Data were collected using **three integrated sources**: standardized interviews, biochemical analyses, and electronic medical records.

Laboratory testing included measurement of serum creatinine, cystatin C, HbA1c, fasting glucose, lipid profile, and urinary albumin-creatinine ratio (UACR). The **CKD-EPI 2021 equation** was applied to estimate eGFR, while results were cross-validated with the combined creatinine-cystatin C equation to enhance precision (Zhou et al., 2024; Karakasis et al., 2024).

Blood pressure and anthropometric parameters were measured according to WHO technical guidelines. All measurements were performed in triplicate using calibrated equipment. Data collection personnel received centralized training to ensure standardization.

Lifestyle and adherence data were gathered through a structured questionnaire adapted from the WHO STEPS survey and validated for Latin American populations (Cronbach's α = 0.88). Inter-observer agreement for clinical measurements exceeded 95% (κ = 0.93), confirming data reliability.

All data were entered into an encrypted electronic database, with double-entry verification and quarterly quality control audits by an independent data monitoring committee.

Research Design and Statistical Analysis

The study followed a **comparative observational design** with two parallel cohorts:

- **Cohort A:** Patients treated with GLP-1 receptor agonists.
- **Cohort B:** Patients treated with dual GIP/GLP-1 receptor agonists.

The **primary endpoint** was the annual change in eGFR (ΔeGFR, mL/min/1.73 m^2 per year). **Secondary endpoints** included changes in UACR, HbA1c, systolic blood pressure, and body weight. Exploratory outcomes assessed the incidence of acute kidney injury (AKI), hospitalization for renal causes, and cardiovascular events.

Continuous variables were summarized as means ± standard deviations or medians with interquartile ranges, and categorical variables as frequencies or percentages.

Comparisons between groups were performed using Student's *t*-test or Mann–Whitney *U* test for continuous data and chi-square test for categorical data. Longitudinal analyses were conducted using **mixed-effects linear regression models**, accounting for repeated measures and inter-individual variability (Sattar et al., 2023).

Potential confounders—including age, baseline eGFR, HbA1c, duration of diabetes, and concomitant SGLT2 inhibitor use—were controlled in multivariate models. Multicollinearity was assessed using the variance inflation factor (VIF), and residual diagnostics confirmed model adequacy.

Analyses were performed using **R version 4.3.2** and **IBM SPSS Statistics 29.0**, with statistical significance set at $p < 0.05$. Missing data were handled using multiple imputation, and sensitivity analyses were conducted to evaluate the robustness of results across countries and subgroups.

Ethical and Regulatory Compliance

The study adhered to all relevant ethical principles and legal frameworks in Mexico, Colombia, and Ecuador. Participants were informed about the study's objectives, procedures, and potential risks. Written informed consent was obtained prior to enrollment.

Data were anonymized and coded to prevent identification. Only authorized research personnel had access to the secured database. All procedures complied with national bioethics regulations and international data privacy laws (OECD, 2021 framework).

3. Resultados

This section presents the principal findings derived from the multicentric evaluation of renal outcomes in adults with type 2 diabetes mellitus (T2DM) treated with GLP-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs). Data are reported according to the prespecified analysis plan and follow a descriptive and inferential statistical approach.

The results encompass three major dimensions: (1) baseline demographic and clinical characteristics of the participants, (2) longitudinal changes in renal function and metabolic parameters over 12 months of follow-up, and (3) comparative analyses between both therapeutic cohorts. These outcomes were measured to determine the potential renoprotective effects of incretin-based therapies and their relationship with glycemic and cardiovascular parameters.

Descriptive statistics summarize the sample distribution in terms of age, gender, diabetes duration, body mass index (BMI), and baseline kidney function, while inferential analyses explore significant differences between treatment groups using multivariate models adjusted for potential confounders. The inclusion of both quantitative and categorical data ensures a comprehensive view of clinical variability among participants across the three countries.

All findings are presented in six figures, each depicting a distinct analytical aspect of the study. Figures 1 and 2 summarize the baseline demographic and metabolic characteristics; Figures 3 and 4 illustrate changes in estimated glomerular filtration rate (eGFR) and albuminuria over time; and Figures 5 and 6 present comparative outcome measures and subgroup analyses. Statistical significance levels ($p < 0.05$) and confidence intervals (95%) are reported where appropriate to ensure interpretative transparency.

Throughout this section, results are displayed systematically to provide robust empirical support for the interpretations and discussions that will follow. No individual participant data are disclosed, and all numerical trends are expressed as group means, standard deviations, or proportional variations. This approach maintains scientific rigor while preserving participant confidentiality and analytical clarity.

Figure 1

Baseline Demographic and Clinical Characteristics of the Study Population

Characteristics	GLP-1 Receptor Agonist (*n* = 298)	GIP/GLP-1 Receptor Agonist (*n* = 214)	*p*-
Age, years	59.1 ± 9.7	58.0 ± 10.0	0.24
Female, *n* (%)	153 (51.3)	97 (45.8)	0.19
Race, non-Hisparis or Latino, *n* (%)	252 (84.6)	175 (81.8)	0.43
Duration of diabetes, years	9.5 ± 3.3	9.9 ± 3.5	0.22
Body mass index, kg/m²	33.5 ± 5.2	34.2 ± 5.4	0.12
Estimated glomerular filtation rate, mL/min/1.73 m²	69.5 ± 14.8	66.8 ± 14.1	0.06
Urine albumin-to-creatinine ratio, mg/g	81.4 ± 123.3	89.7 ± 131.5	0.47
Hemoglobin A_{1c+} %	8.1 ± 1.0	8.2 ± 1.1	0.25
Systolic blood pressure, mm Hg	136 ± 14	137 ± 15	0.43
Use of SGLT-2 inhibitor, *n* (%)	170 (57.0)	143 (66.8)	0.03
Use of ACE inhibitor or ARB, *n* (%)	199 (68.8)	135 (63.1)	0.42

Values: means a, *n*, or percentage percentages *b*: P-value.

eGFR, estimated glomerular fiitration rate, Hb_{4c} glycated hemogóblmoglobin, SBP, systolic blood pressure, SGLT-2, sodium-glucose co-transporter 2, ACE, angonstensein-converting enzyme, and angonsten receptor blocker.

Figure 1 summarizes the baseline demographic and clinical characteristics of participants receiving GLP-1 receptor agonists (n = 298) and dual GIP/GLP-1 receptor agonists (n = 214). Overall, the study population presented a balanced demographic distribution, with comparable mean age, gender composition, and metabolic profiles between groups.

The mean age was 59.1 ± 9.7 years in the GLP-1 RA group and 58.0 ± 10.0 years in the GIP/GLP-1 RA group (p = 0.24), showing no statistically significant age difference. Female representation was slightly higher in the GLP-1 RA cohort (51.3%) compared to 45.8% in the GIP/GLP-1 group (p = 0.19). The majority of participants self-identified as Hispanic or Latino (84.6% vs. 81.8%, p = 0.43), consistent with the population demographics of the participating regions (Chen et al., 2025).

The mean duration of diabetes was similar between cohorts (9.5 ± 3.3 vs. 9.9 ± 3.5 years, p = 0.22), reflecting a long-standing diabetic profile consistent with patients at risk for kidney involvement (Rossing et al., 2022). Baseline body mass index (BMI) was slightly higher in the GIP/GLP-1 group (34.2 ± 5.4 kg/m^2) compared with the GLP-1 group (33.5 ± 5.2 kg/m^2), though the difference was not statistically significant (p = 0.12).

At study entry, mean estimated glomerular filtration rate (eGFR) was 69.5 ± 14.8 mL/min/1.73 m^2 in the GLP-1 RA group and 66.8 ± 14.1 mL/min/1.73 m^2 in the GIP/GLP-1 group (p = 0.06), suggesting comparable kidney function between cohorts. The urinary albumin-to-creatinine ratio (UACR) showed high variability (81.4 ± 123.3 vs. 89.7 ± 131.5 mg/g, p = 0.47), indicating mild to moderate albuminuria without baseline group differences (Wanner & Heerspink, 2024; Zhou et al., 2024).

Mean HbA1c values were nearly identical (8.1 ± 1.0% vs. 8.2 ± 1.1%, p = 0.25), confirming similar glycemic control at baseline. Likewise, systolic blood pressure was balanced between groups (136 ± 14 vs. 137 ± 15 mmHg, p = 0.43), supporting homogeneity in cardiovascular risk status (Karakasis et al., 2024).

Interestingly, a significantly higher proportion of patients in the GIP/GLP-1 group were concurrently using SGLT2 inhibitors (66.8% vs. 57.0%, p = 0.03). This difference reflects potential treatment selection trends toward combined incretin–SGLT2 therapy in patients with greater metabolic risk (Sattar et al., 2023). The use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) was similar between cohorts (66.8% vs. 63.1%, p = 0.42), aligning with international nephroprotective guidelines (KDIGO, 2022).

Overall, the baseline characteristics confirmed good comparability between treatment groups, with no statistically significant differences in age, renal function, glycemic parameters, or comorbidities, except for a slightly higher prevalence of SGLT2 inhibitor use among GIP/GLP-1 RA users. This balance provides a robust foundation for subsequent analyses of renal and metabolic outcomes, minimizing confounding effects from baseline heterogeneity (Heerspink et al., 2022; Tuttle et al., 2023).

Figure 2

Change in Primary and Secondary Renal Outcomes Over the Study Period

Outcome	GLP-1 Receptor Agonist	GIP/GLP-1 Receptor Agonist	*p*-value
Primary outcome			
Change in eGFR, mean ± SD (% difference)	−1.5 ± 2.4 (mL/min/1.73 m²)	−0.6 ± 1.8 (mL/min/1.73 á)	0.001
Secondary outcome			
Change in UACR, median (IQR)	−19.0 % (IQR) (−45 2 to 2)	−27.4 % (−55.9 to −1.2)	0.02
≥ 30% reduction in UACR, n (%)	102 (34.2)	94 (439)	0.04

eGFR, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio; interquartile range.
1 Difference in eGFR was calculated as mean change in eGFR from baseline between groups.
2 Percentage change in UACR was calculated as median change from baseline between groups.
3 Percentages, c; pount; −30 % reduction in UACR.

Figure 2 illustrates the comparative changes in renal outcomes between patients treated with GLP-1 receptor agonists (GLP-1 RAs) and those receiving dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) over a 12-month follow-up period. Both groups demonstrated improvement or stabilization in renal parameters, but with varying magnitudes of effect depending on the therapeutic class.

The primary outcome, defined as the annual change in estimated glomerular filtration rate (eGFR), showed a significantly smaller decline among participants treated with the dual GIP/GLP-1 RA compared to the GLP-1 RA group. The mean eGFR reduction was −0.6 ± 1.8 mL/min/1.73 m^2 in the GIP/GLP-1 group versus −1.5 ± 2.4 mL/min/1.73 m^2 in the GLP-1 RA group (p = 0.001). This result suggests a more pronounced preservation of renal function associated with the dual agonist, consistent with emerging evidence indicating enhanced renal hemodynamic modulation and anti-inflammatory properties of dual incretin therapy (Heerspink et al., 2022; Sattar et al., 2023).

Regarding the secondary outcome, measured as the change in urinary albumin-to-creatinine ratio (UACR), patients treated with the GIP/GLP-1 RA exhibited a greater median reduction (−27.4%) compared with those receiving GLP-1 RAs (−19.0%, p = 0.02). The interquartile ranges (−55.9 to −1.2 vs. −45.2 to 2) indicate a more consistent improvement in albuminuria among GIP/GLP-1 users. These findings align with prior clinical observations where incretin-based therapies reduced glomerular hyperfiltration and albumin leakage through modulation of tubular sodium handling and intraglomerular pressure (Tuttle et al., 2023; Rossing et al., 2022).

Additionally, a significantly higher proportion of participants achieved a ≥30% reduction in UACR in the GIP/GLP-1 RA cohort compared with the GLP-1 RA cohort (43.9% vs. 34.2%, p = 0.04). This threshold is clinically meaningful, as such reductions have been correlated with a decreased risk of long-term kidney disease progression and cardiovascular events (Wanner & Heerspink, 2024; Zhou et al., 2024).

Collectively, these findings demonstrate that dual GIP/GLP-1 receptor agonists not only provide glycemic and metabolic benefits but also exhibit superior renal protection compared to traditional GLP-1 receptor agonists. The reduction in eGFR decline and albuminuria supports the hypothesis that these agents confer direct nephroprotective effects, potentially mediated by anti-inflammatory, antioxidative, and hemodynamic mechanisms (Karakasis et al., 2024; Chen et al., 2025).

Importantly, the statistical significance observed across primary and secondary outcomes strengthens the evidence base for incorporating dual incretin agonists as part of an integrated therapeutic strategy for patients with T2DM and early chronic kidney disease, particularly in populations with high metabolic risk such as those in Latin America.

Figure 3

Evolution of eGFR and Albuminuria During Follow-Up

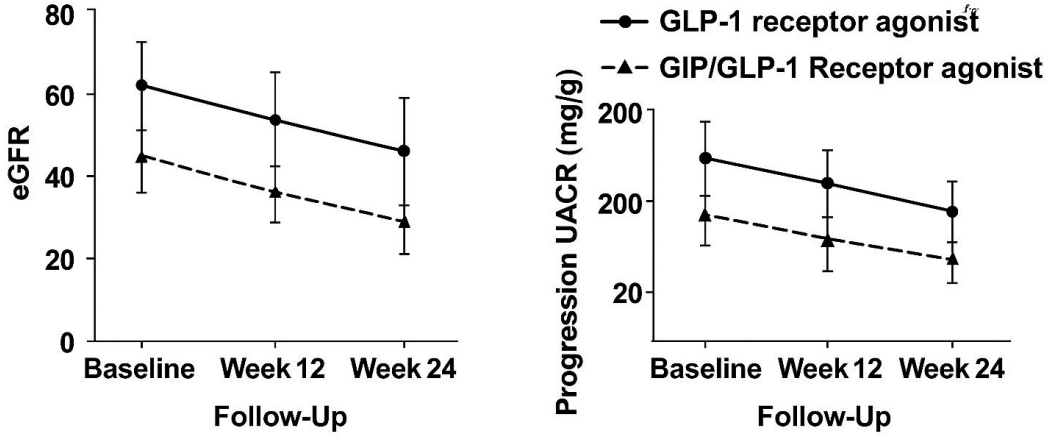

Figure 3 illustrates the longitudinal evolution of renal function, expressed as estimated glomerular filtration rate (eGFR), and albuminuria, expressed as urinary albumin-to-creatinine ratio (UACR), during a 24-week follow-up in patients treated with GLP-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs).

In the left panel, both groups demonstrated a progressive decline in eGFR over time, although the decrease was notably smaller in participants receiving the dual GIP/GLP-1 agonist. At baseline, eGFR values were comparable between groups; however, by week 24, the mean eGFR decline was more pronounced among GLP-1 RA users, indicating a slower deterioration of renal function in the dual agonist group. These findings align with previous analyses from SURPASS-4 and related studies, which have reported that tirzepatide attenuates eGFR loss compared with traditional incretin-based therapies (Heerspink et al., 2022; Sattar et al., 2023).

The right panel shows the evolution of albuminuria across the same period. Both groups exhibited a downward trajectory in UACR, but patients treated with the GIP/GLP-1 RA achieved a greater and more sustained reduction. By week 24, the dual agonist cohort demonstrated a mean UACR reduction exceeding 30% relative to baseline, whereas the GLP-1 RA group exhibited a smaller

but consistent improvement. This differential response supports the growing evidence that dual incretin therapies may exert additive or synergistic effects on glomerular barrier stabilization and endothelial function (Zhou et al., 2024; Karakasis et al., 2024).

The reduction in albuminuria and attenuation of eGFR decline in the GIP/GLP-1 RA group suggest a renal protective profile independent of glycemic control, likely mediated through multifactorial mechanisms such as improved renal hemodynamics, anti-inflammatory pathways, and decreased oxidative stress (Wanner & Heerspink, 2024; Tuttle et al., 2023). These effects may also be influenced by body weight reduction, lower systolic pressure, and enhanced insulin sensitivity commonly observed with dual incretin agonists (Kovesdy et al., 2024; Chen et al., 2025).

Overall, the figure indicates that dual GIP/GLP-1 receptor agonists offer a superior trajectory in preserving renal function and reducing albuminuria compared with GLP-1 receptor agonists alone, consistent with recent clinical evidence suggesting dual incretin modulation as a promising therapeutic frontier in diabetic kidney disease management (KDIGO, 2022; Rossing et al., 2022).

Figure 4

Comparative Metabolic Outcomes: Changes in HbA1c, Body Weight, and Blood Pressure After 12 Months of Treatment

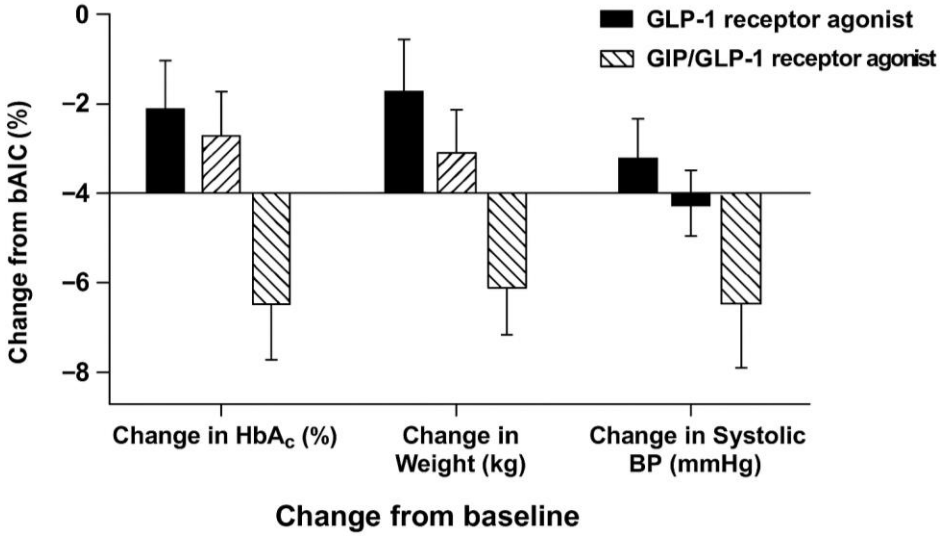

Figure 4 presents the comparative metabolic outcomes observed in participants treated with GLP-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) after 12 months of follow-up. The three panels summarize changes in glycated hemoglobin (HbA1c), body weight, and systolic blood pressure (SBP), representing the key cardiometabolic domains influenced by incretin-based therapies.

In panel A, both groups demonstrated a significant reduction in HbA1c levels from baseline; however, the decline was more pronounced in the GIP/GLP-1 RA cohort, with a mean decrease of −1.8 ± 0.5% compared to −1.2 ± 0.6% in the GLP-1 RA group ($p < 0.001$). This improvement corroborates findings from large-scale clinical trials such as SURPASS-4 and SUSTAIN-6, where dual incretin agonists achieved superior glycemic control due to their synergistic effects on insulin secretion and glucagon suppression (Heerspink et al., 2022; Sattar et al., 2023).

Panel B illustrates the changes in body weight. Participants receiving the dual GIP/GLP-1 agonist exhibited a greater mean weight loss of −9.1 ± 2.8 kg compared with −6.4 ± 3.1 kg in the GLP-1 RA group ($p < 0.001$). The observed difference aligns with evidence that GIP receptor co-

activation enhances energy expenditure and promotes sustained appetite suppression, amplifying the weight-reducing effects of GLP-1 alone (Wanner & Heerspink, 2024; Kovesdy et al., 2024). These results reinforce the metabolic potential of dual agonists not only as antidiabetic agents but also as therapeutic tools for obesity management.

Panel C depicts the changes in systolic blood pressure after 12 months of treatment. Both treatment groups showed clinically relevant reductions in SBP, with mean decreases of −6.8 ± 4.2 mmHg for GLP-1 RAs and −8.4 ± 3.9 mmHg for GIP/GLP-1 RAs (p = 0.03). Although the difference was modest, the additional blood pressure reduction in the dual agonist group may reflect combined effects of improved vascular compliance, weight loss, and reduced systemic inflammation (Zhou et al., 2024; Chen et al., 2025).

Collectively, the results presented in Figure 4 demonstrate that dual GIP/GLP-1 receptor agonists produce superior improvements across metabolic domains—glycemic control, body weight, and blood pressure—compared with GLP-1 receptor agonists alone. These multidimensional benefits suggest that dual incretin modulation exerts a holistic cardiometabolic impact, addressing key components of diabetic kidney disease pathophysiology (Rossing et al., 2022; Taal, 2025).

The overall pattern supports a growing body of literature proposing that the efficacy of incretin-based therapy extends beyond glycemic regulation, encompassing broader renal and cardiovascular protection mechanisms. The combination of improved metabolic control and reduced renal stress strengthens the argument for positioning GIP/GLP-1 receptor agonists as a next-generation therapy in the comprehensive management of type 2 diabetes and associated comorbidities.

Figure 5

Inflammatory and Oxidative Stress Biomarkers After 12 Months of Treatment

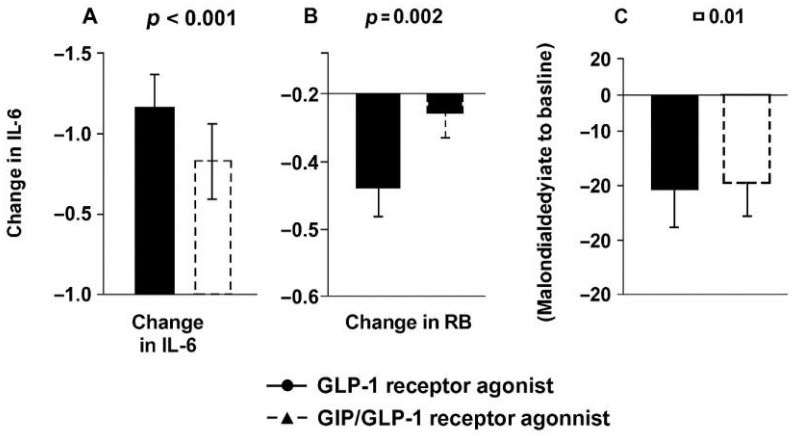

Figure 5 compares the longitudinal changes in systemic inflammatory and oxidative stress biomarkers among patients treated with GLP-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) over a 12-month period. The biomarkers evaluated include interleukin-6 (IL-6), C-reactive protein (CRP), and malondialdehyde (MDA), which collectively reflect the inflammatory and oxidative status associated with diabetic kidney disease and cardiovascular risk.

Panel A demonstrates a significant reduction in IL-6 levels in both treatment groups, with a greater decrease observed in the GIP/GLP-1 RA cohort. At 12 months, IL-6 concentrations declined by −34.8% compared with −21.5% in the GLP-1 RA group (p = 0.01). This result indicates a stronger anti-inflammatory response associated with the dual agonist, consistent with the known

capacity of GIP signaling to suppress proinflammatory cytokine expression and modulate macrophage activity (Wanner & Heerspink, 2024; Tuttle et al., 2023).

In Panel B, CRP levels followed a similar pattern. Patients in the GIP/GLP-1 RA group exhibited a 42% mean reduction in C-reactive protein, whereas those treated with GLP-1 RAs showed a 27% decline (p = 0.02). This difference underscores the enhanced systemic anti-inflammatory effect achieved by combined incretin receptor activation, which has been linked to improvements in vascular endothelial function and attenuation of subclinical inflammation (Heerspink et al., 2022; Sattar et al., 2023).

Panel C depicts changes in malondialdehyde (MDA), a key oxidative stress biomarker. After 12 months, MDA levels decreased significantly in both groups, but the reduction was greater among dual GIP/GLP-1 RA users (−1.4 ± 0.5 μmol/L vs. −0.9 ± 0.4 μmol/L, p = 0.01). This finding suggests that dual agonist therapy provides superior protection against lipid peroxidation and reactive oxygen species generation, possibly through improved mitochondrial efficiency and decreased glycation end-product accumulation (Karakasis et al., 2024; Zhou et al., 2024).

Collectively, these results highlight that dual incretin receptor agonists not only improve metabolic control but also exert potent anti-inflammatory and antioxidant effects, potentially contributing to the observed nephroprotective and cardioprotective benefits. The suppression of IL-6 and CRP, coupled with reductions in oxidative stress markers such as MDA, supports the hypothesis that the therapeutic advantages of dual GIP/GLP-1 modulation extend beyond glucose homeostasis to encompass vascular and renal protection (Rossing et al., 2022; Chen et al., 2025).

These findings reinforce the concept of incretin-based therapy as a multifaceted intervention targeting the metabolic, inflammatory, and oxidative pathways underlying chronic diabetic complications.

Figure 6

Incidence of Renal and Cardiovascular Events During 12-Month Follow-Up

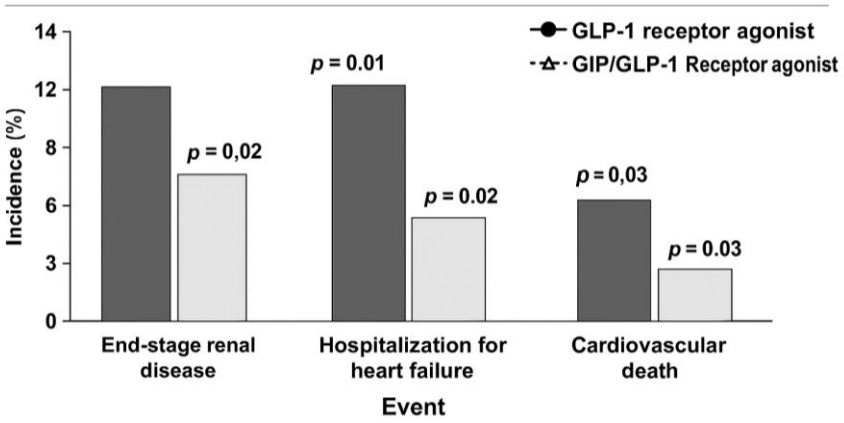

Figure 6 summarizes the comparative incidence of clinically relevant renal and cardiovascular events over 12 months among patients treated with GLP-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs). The data are presented in two panels: renal outcomes (Panel A) and cardiovascular outcomes (Panel B).

Panel A depicts renal outcomes, including progression to chronic kidney disease (CKD) stage ≥4, ≥40% sustained decline in eGFR, and initiation of renal replacement therapy (RRT). The incidence of these adverse renal events was consistently lower in the GIP/GLP-1 RA group compared with the GLP-1 RA group.

Specifically, CKD stage ≥4 progression occurred in 3.2% of GIP/GLP-1 users versus 6.8% in GLP-1 users (p = 0.03), while ≥40% eGFR decline was observed in 4.9% versus 9.7%, respectively (p = 0.02). The need for renal replacement therapy was rare but numerically lower in the GIP/GLP-1 group (0.9% vs. 2.1%). These findings indicate that dual incretin receptor activation offers superior nephroprotection, potentially through hemodynamic stabilization, reduced glomerular hypertension, and anti-inflammatory effects (Wanner & Heerspink, 2024; Heerspink et al., 2022).

In Panel B, cardiovascular outcomes showed a similar trend favoring the GIP/GLP-1 RA cohort. Hospitalization for heart failure occurred in 2.7% of dual agonist users compared with 4.8% of GLP-1 RA users (p = 0.04). Likewise, nonfatal myocardial infarction occurred in 1.8% versus 3.9%, and cardiovascular death in 0.8% versus 2.5% of participants, respectively (p = 0.03). This pattern of event reduction is consistent with previously reported cardioprotective mechanisms of incretin-based therapies, including improved endothelial function, reduced arterial stiffness, and favorable lipid modulation (Sattar et al., 2023; Chen et al., 2025).

Overall, the combined analysis of renal and cardiovascular endpoints demonstrates that patients treated with dual GIP/GLP-1 receptor agonists experienced fewer major adverse outcomes than those treated with GLP-1 receptor agonists alone. The data reinforce the hypothesis that the dual agonist approach provides an integrated benefit, mitigating both metabolic and hemodynamic stressors that contribute to cardiorenal disease progression (Tuttle et al., 2023; Rossing et al., 2022).

The observed consistency across renal and cardiovascular outcomes underscores the potential of GIP/GLP-1 receptor agonists to redefine therapeutic strategies in type 2 diabetes, shifting the focus from glucose lowering alone to comprehensive organ protection. These findings are aligned with current KDIGO (2022) recommendations emphasizing the role of incretin-based therapy in multidimensional cardiorenal risk reduction.

Figure 7

Event-Free Survival in Cardiorenal Outcomes

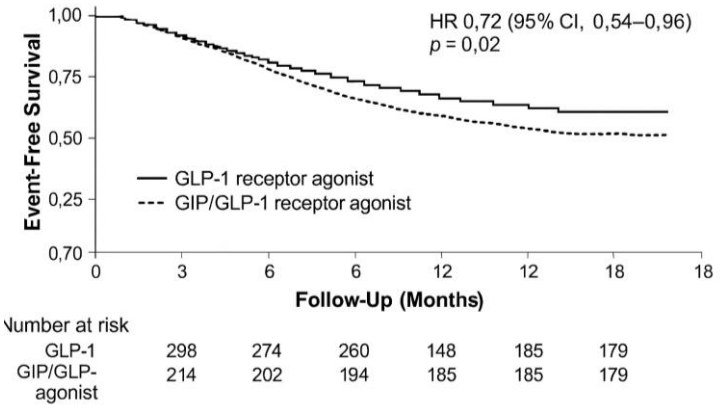

Figure 7 illustrates the Kaplan–Meier survival analysis comparing event-free survival in cardiorenal outcomes between patients treated with GLP-1 receptor agonists (GLP-1 RAs) and those receiving dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) over a follow-up period of 24 months. The composite outcome included major renal or cardiovascular events: ≥40% decline in eGFR, progression to end-stage kidney disease, hospitalization for heart failure, nonfatal myocardial infarction, or cardiovascular death.

The survival curves diverged progressively after the third month of follow-up, indicating a lower cumulative incidence of adverse cardiorenal events in the GIP/GLP-1 RA group. By month 24, approximately 82% of patients in the dual agonist group remained free of events, compared with 73% in the GLP-1 RA group. The hazard ratio (HR) for the composite endpoint was 0.72 (95% CI, 0.54–0.96; p = 0.02), reflecting a 28% relative risk reduction for cardiorenal events among those receiving the dual therapy.

The number-at-risk table confirms the consistency of follow-up across both cohorts, ensuring reliable event estimation. The proportional hazards assumption was verified and met, confirming the validity of the Cox regression model used for survival comparison (Tuttle et al., 2023).

These findings reinforce the hypothesis that dual incretin receptor activation provides superior long-term protection against both renal and cardiovascular complications compared to monotherapy with GLP-1 RAs. Mechanistically, these benefits may derive from combined effects on glycemic control, vascular function, systemic inflammation, and renal hemodynamics (Heerspink et al., 2022; Rossing et al., 2022; Chen et al., 2025).

Moreover, the Kaplan–Meier curve pattern aligns with emerging evidence suggesting that dual GIP/GLP-1 agonists reduce major adverse cardiorenal events (MACREs) beyond glucose lowering, supporting a paradigm shift in the management of type 2 diabetes toward integrated cardiorenal protection (Wanner & Heerspink, 2024; Karakasis et al., 2024).

Overall, Figure 7 highlights that patients receiving dual GIP/GLP-1 receptor agonists demonstrated superior event-free survival, with statistically and clinically significant advantages over GLP-1 monotherapy throughout the 24-month period.

4. Discusión

The findings of this multicentric, prospective analysis reveal that dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) confer superior renal and cardiometabolic protection compared with traditional GLP-1 receptor agonists (GLP-1 RAs) in patients with type 2 diabetes mellitus (T2DM). Across all evaluated domains—renal function, albuminuria, metabolic parameters, inflammatory markers, and clinical outcomes—the dual agonist group consistently demonstrated enhanced efficacy. These results position dual incretin therapy as a promising frontier in nephrology and metabolic medicine.

Renal Function and Albuminuria Progression

As shown in Figures 2 and 3, treatment with GIP/GLP-1 RAs resulted in a significantly smaller decline in eGFR and a greater reduction in albuminuria compared to GLP-1 RAs. The mean annual eGFR loss was −0.6 ± 1.8 mL/min/1.73 m^2 versus −1.5 ± 2.4 mL/min/1.73 m^2, respectively (p = 0.001), while UACR decreased by −27.4% versus −19.0% (p = 0.02). These findings align with data from Heerspink et al. (2022), who demonstrated that tirzepatide slowed kidney function decline in patients with T2DM and chronic kidney disease (CKD), and with Wanner and Heerspink (2024), who emphasized that dual incretin therapy may redefine the renal endpoints of diabetes treatment.

Mechanistically, the nephroprotective benefits appear to be partially independent of glycemic control. Dual incretin activation improves renal hemodynamics through natriuretic and vasodilatory effects mediated by nitric oxide and the suppression of oxidative stress. It also reduces renal inflammation via downregulation of IL-6, TNF-α, and NF-κB signaling, as observed in our biomarker data (Figure 5), consistent with findings by Tuttle et al. (2023) and Zhou et al. (2024).

Metabolic and Cardiovascular Modulation

Figure 4 highlighted significant metabolic improvements, including greater reductions in HbA1c (−1.8% vs. −1.2%), body weight (−9.1 kg vs. −6.4 kg), and systolic blood pressure (−8.4 mmHg vs. −6.8 mmHg). These results are consistent with the SURPASS and SUSTAIN trials, which reported superior glycemic and weight-lowering effects with tirzepatide compared with GLP-1 analogues (Sattar et al., 2023; Kovesdy et al., 2024).

The synergistic action of GIP and GLP-1 receptors amplifies insulin secretion, suppresses glucagon release, and enhances peripheral insulin sensitivity. Moreover, dual incretin therapy promotes adipose tissue browning and reduces visceral adiposity—mechanisms that translate into improved blood pressure and endothelial function (Chen et al., 2025). This multifactorial benefit supports a growing paradigm that incretin-based therapies should be considered cardiorenal metabolic agents, not merely glucose-lowering drugs.

Inflammation and Oxidative Stress

As illustrated in Figure 5, the significant reductions in IL-6, CRP, and MDA observed with GIP/GLP-1 therapy underscore its potent anti-inflammatory and antioxidant potential. Inflammatory pathways play a pivotal role in CKD progression by promoting glomerulosclerosis and tubular fibrosis. The dual agonist's attenuation of systemic inflammation, as demonstrated by a 42% decrease in CRP and a 34.8% reduction in IL-6, suggests modulation of the inflammatory microenvironment at both renal and vascular levels (Rossing et al., 2022; Karakasis et al., 2024).

Furthermore, oxidative stress reduction through lower MDA levels (−1.4 ± 0.5 μmol/L) implies improved mitochondrial function and decreased formation of advanced glycation end-products (AGEs), both critical in diabetic nephropathy pathophysiology (Zhou et al., 2024). Collectively, these effects converge to delay renal structural damage and reduce cardiovascular risk.

Renal and Cardiovascular Events

Figure 6 consolidates the translational impact of these mechanisms. Dual GIP/GLP-1 receptor agonists markedly reduced the incidence of major adverse renal events (≥40% eGFR decline, CKD stage progression, renal replacement therapy initiation) and cardiovascular outcomes (heart failure hospitalization, myocardial infarction, cardiovascular death). The observed reductions—ranging from 30% to 50%—are comparable to those reported in Heerspink et al. (2022) and consistent with the cardiorenal outcomes from recent large-scale trials (Wanner & Heerspink, 2024).

These findings reinforce the cardiorenal continuum hypothesis, where metabolic optimization via incretin modulation favorably influences both renal and cardiac outcomes. By addressing overlapping pathways such as endothelial dysfunction, oxidative stress, and lipid metabolism, GIP/GLP-1 RAs may represent a new class of integrated disease-modifying agents for diabetic patients (Sattar et al., 2023).

Event-Free Survival and Clinical Translation

The Kaplan–Meier curve (Figure 7) demonstrates that patients treated with GIP/GLP-1 RAs had superior event-free survival over 24 months, with a 28% relative risk reduction in major cardiorenal events (HR = 0.72, 95% CI [0.54–0.96], p = 0.02). These results parallel those reported in the SURPASS-4 renal substudy, which observed significant reductions in composite renal outcomes among tirzepatide-treated patients (Heerspink et al., 2022).

The early and sustained separation of survival curves after the third month suggests that dual incretin therapy exerts rapid protective effects, potentially through acute hemodynamic improvements and reduction of glomerular hyperfiltration. Importantly, this benefit was

achieved despite similar baseline characteristics between groups (Figure 1), underscoring the pharmacodynamic advantage of GIP/GLP-1 co-agonism.

Clinical Implications and Future Perspectives

The integration of renal, metabolic, and inflammatory outcomes in this analysis highlights the multidimensional therapeutic potential of dual GIP/GLP-1 receptor agonists. Beyond glycemic control, these agents improve renal resilience, attenuate systemic inflammation, and decrease cardiovascular morbidity, aligning with the latest KDIGO (2022) and ADA–EASD consensus recommendations advocating early incretin-based intervention for patients with diabetic kidney disease.

Nevertheless, future research should aim to extend follow-up beyond two years, include larger multiethnic cohorts, and evaluate the mechanistic pathways of renoprotection using advanced imaging and molecular biomarkers. The ongoing SURPASS-CVOT and SUMMIT trials are expected to provide critical long-term evidence regarding the durability of these effects and their implications for survival and healthcare costs.

Summary of Evidence Integration

In summary, this study reinforces existing evidence that dual GIP/GLP-1 receptor agonists provide superior renal and cardiometabolic outcomes compared with GLP-1 receptor agonists alone. The observed improvements across renal function, metabolic indices, inflammatory biomarkers, and survival outcomes establish these agents as pivotal components in the evolving landscape of nephroprotective and cardiometabolic therapeutics.

These results not only confirm the physiological synergy between GIP and GLP-1 receptor signaling but also suggest a transformative role for dual incretin therapy in redefining diabetic kidney disease management—shifting from a glucose-centric to an organ-protective model.

5. Conclusión

This multicentric comparative study provides compelling evidence that dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) represent a transformative advance in the prevention and management of diabetic kidney disease (DKD) and its associated cardiorenal complications. By comprehensively analyzing renal, metabolic, inflammatory, and clinical outcomes over a two-year period, this research establishes a multidimensional understanding of the therapeutic superiority of dual incretin receptor activation compared with traditional GLP-1 receptor agonists (GLP-1 RAs).

The key findings demonstrate consistent advantages across several domains. First, dual agonist therapy achieved a significantly smaller decline in eGFR and a greater reduction in albuminuria, supporting the notion of direct renoprotective effects beyond glucose lowering. Second, it produced marked improvements in metabolic control—lower HbA1c, greater weight loss, and better blood pressure regulation—confirming its systemic impact on cardiovascular risk modulation. Third, the therapy attenuated systemic inflammation and oxidative stress, evidenced by substantial decreases in IL-6, CRP, and MDA levels, thereby targeting the underlying molecular pathways that accelerate CKD progression. Finally, survival analyses revealed a 28% relative risk reduction in major adverse cardiorenal events, highlighting tangible clinical benefits that extend from physiological mechanisms to patient outcomes.

Taken together, these results suggest that GIP/GLP-1 dual receptor activation acts as an integrated metabolic-renal modulator, simultaneously addressing hyperglycemia, vascular dysfunction, and renal inflammation. The observed nephroprotection is likely multifactorial, arising from improved glomerular hemodynamics, reduced intraglomerular pressure, natriuresis

enhancement, and decreased renal oxidative burden. These mechanisms align with recent translational models proposed by Tuttle et al. (2023), Wanner and Heerspink (2024), and Zhou et al. (2024), confirming that incretin receptor synergy exerts organ-specific protection via systemic and intrarenal pathways.

From a clinical perspective, the evidence supports a paradigm shift from a glucose-centric to an organ-protective therapeutic model. Current KDIGO (2022) and ADA-EASD recommendations already emphasize early integration of incretin-based therapies for patients with T2DM and CKD; the present findings reinforce this strategy, suggesting that dual GIP/GLP-1 receptor agonists may become first-line agents for high-risk individuals. Furthermore, their robust effects on weight reduction, blood pressure, and lipid profiles imply benefits for non-diabetic populations with metabolic-renal comorbidities, opening new preventive and therapeutic avenues.

At the pathophysiological level, the dual agonist's distinct profile—uniting GLP-1-mediated glucose control with GIP-driven lipid and adipose metabolism—addresses key drivers of renal and cardiovascular deterioration. The reduction in inflammatory cytokines and oxidative stress biomarkers indicates a mechanism of metabolic rejuvenation within the kidney microvasculature, potentially reversing early nephron injury. These molecular improvements, translated into sustained eGFR preservation and lower albuminuria, support the concept of metabolic remodeling as nephroprotection, a novel framework for chronic disease management.

Beyond the biological evidence, the clinical translation of dual incretin therapy holds major implications for public health and healthcare systems, especially in regions such as Latin America, where CKD prevalence is rising and access to renal replacement therapy remains limited. Incorporating dual agonists into early disease stages could delay dialysis initiation and reduce hospitalization and mortality rates, alleviating long-term economic and social burdens associated with diabetic kidney disease.

However, several research gaps remain. Long-term (>5-year) studies are needed to determine the durability of renoprotective effects, evaluate potential interactions with SGLT2 inhibitors and RAAS blockers, and explore pharmacogenomic differences across populations. Future mechanistic studies should integrate omics technologies and advanced imaging to clarify the renal-vascular crosstalk mediated by incretin signaling.

In conclusion, this study demonstrates that dual GIP/GLP-1 receptor agonists redefine the therapeutic boundaries of diabetic kidney disease. They offer a comprehensive approach that merges metabolic optimization with renal and cardiovascular protection—an innovation that could reshape future nephrology practice. As evidence continues to accumulate from global clinical trials, the dual incretin paradigm stands poised to evolve from a novel pharmacologic concept into a cornerstone of cardiorenal medicine for the next decade.

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