DOI: 10.5152/turkjnephrol.2026.251208

Review

Turkish Journal of Nephrology

GLP-1 Receptor Agonists in Diabetic Nephropathy: Clinical Evidence, Molecular Mechanisms, and Future Perspectives

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ABSTRACT

Diabetic nephropathy (DN) remains the predominant etiology of chronic kidney disease (CKD) worldwide, significantly resulting in mortality and morbidity among individuals with diabetes mellitus. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have surfaced as transformative treatment options, offering multifaceted benefits that extend beyond glycemic control. This article explores the comprehensive role of GLP-1RAs in renoprotection and their impact on the progression of DN. Glucagon-like peptide-1 receptor agonists exhibit significant renoprotective effects through multiple mechanisms, including glycemic optimization (HbA1c reduction of 0.73%-3.01%), substantial weight reduction (14%-16% in leading clinical trials), blood pressure reduction (2-6 mmHg systolic reduction), anti-inflammatory effects, and direct albuminuria reduction (11.74%-33%). Major clinical trials, including Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN-6), Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), Evaluate Renal Function with Semaglutide Once Weekly (FLOW), Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND), consistently demonstrate cardiovascular benefits and slowed CKD progression. Glucagon-like peptide-1 receptor agonists signify a vital shift in the management of diabetic kidney disease, offering comprehensive metabolic benefits with established renoprotective and cardiovascular advantages.

Keywords: Albuminuria, cardiovascular outcomes, chronic kidney disease, diabetic nephropathy, GLP-1 receptor agonists, renoprotection

Corresponding author: Gerry George Mathew ✉ gerrygeorge007@gmail.com**Received:** September 30, 2025 **Revision Requested:** October 24, 2025 **Last Revision Received:** December 2, 2025 **Accepted:** December 3, 2025 **Publication Date:** July 6, 2026

Cite this article as: Mathew GG. GLP-1 receptor agonists in diabetic nephropathy: clinical evidence, molecular mechanisms, and future perspectives. *Turk J Nephrol.* 2026;35(3):182-193.

INTRODUCTION

Diabetic nephropathy (DN) constitutes one of the dreaded complications of systemic syndromes like diabetes mellitus, influencing about 40% of the world population with diabetes and serving as a primary source of end-stage kidney disease (ESKD) universally.[1,2] Worldwide prevalence of diabetic kidney disease (DKD) continues to rise, with projections indicating a proportionate increase in the number of affected individuals in the future decades.[3] The pathophysiology governing DN is intricate and multifactorial, involving hemodynamic changes, metabolic dysfunction, inflammatory pathways, and oxidative stress, ultimately leading to progressive kidney impairment.[4]

Traditional management strategies for DN have predominantly focused on blood pressure optimization, glycemic control through utilization of renin-angiotensin-aldosterone system (RAAS) inhibitors and lifestyle modifications.[5] However, despite these planned interventions, many patients experience a sequential decline in kidney function, underscoring the immediate need for innovative therapeutics that address the complex nature of this disease process. The development and

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innovation in glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed the standard of diabetes management, offering advantages that extend beyond blood glucose regulation.[6] This advancement began with the isolation of exenatide from salivary secretions of Gila monster by Dr. John Eng, leading to the advent of incretin-dependent therapeutics as a novel treatment option.[7] Subsequently, the development of longer-acting GLP-1RAs with enhanced pharmacokinetic profiles, such as liraglutide, semaglutide, dulaglutide, and others, has expanded treatment options and improved patient outcomes.[8]

Recent landmark clinical trials have demonstrated that GLP-1RAs confer significant kidney protection benefits independent of their hypoglycemic effects, establishing them as vital components of comprehensive DN management.[9,10] The review aims to give a comprehensive assessment of the underlying mechanisms of GLP-1RA-mediated renoprotection, evaluate clinical evidence from major trials, and discuss the integration of these agents into current treatment paradigms for DN.

PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

Hemodynamic Alterations

Pathogenesis of DN is distinguished through intricate hemodynamic modulations within the glomerular system. Chronic hyperglycemia induces an increase in kidney plasma flow or glomerular hyperfiltration, facilitated through vasodilation of afferent arterioles along with preferential efferent arteriolar vasoconstriction.[11] This leads to elevated intraglomerular pressure, glomerular injury, and the development of proteinuria. The RAAS activation further aggravates these hemodynamic disturbances, promoting sodium retention and systemic hypertension.[12]

Metabolic and Biochemical Pathways

Multiple interconnected metabolic pathways are implicated in the progression of DN. The polyol pathway activation results in sorbitol accumulation and osmotic stress within renal tubular cells and podocytes.[13] Generation of advanced glycation end products or subsequent receptor binding initiates inflammatory cascades and oxidative stress.[14] Protein kinase C pathway enhances vascular permeability and extracellular matrix accumulation.[15] Furthermore, the hexosamine pathway contributes to altered gene expression and cellular dysfunction.[16]

Inflammatory and Fibrotic Processes

Chronic inflammation is a vital factor in the advancement of DN. Pro-inflammatory cytokines, comprising IL-6 (interleukin-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1, facilitate immune cell infiltration and sustained inflammatory responses.[17] Activation of transforming growth factor-beta (TGF-β) results in increased extracellular matrix deposition and progressive fibrosis, ultimately leading to nephron loss and a decline in kidney function.[18]

MAIN POINTS

- Glucagon-like peptide-1 receptor agonists denote transformative alteration in the approach and management of diabetic nephropathy (DN), offering comprehensive metabolic, renoprotective, and cardiovascular benefits.
- Glucagon-like peptide-1 receptor agonists exhibit significant kidney benefits by glycemic optimization, substantial weight reduction, blood pressure reduction, anti-inflammatory effects, and direct albuminuria reduction.
- Glucagon-like peptide-1 receptor agonists provide renewed hope for preventing progression to end-stage kidney disease and reduce the associated mortality and morbidity in DN.
- Glucagon-like peptide-1 receptor agonists demonstrate cost-neutrality within 3-5 years of therapy initiation, with subsequent cost savings and improved outcomes.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS: PHARMACOLOGY AND CLASSIFICATION

Molecular Structure and Receptor Binding

Glucagon-like peptide-1 receptor agonists are part of the G protein-coupled receptor extended family and are extensively distributed across various organ systems, including pancreatic β-cells, kidneys, heart, brain, and gastrointestinal tract.[19] This widespread tissue distribution accounts for the multifaceted effects of GLP-1RAs beyond glucose regulation. Upon binding to GLP-1RAs, these agents activate adenylyl cyclase, leading to elevated levels of cyclic adenosine monophosphate along with activation of protein kinase A.[20]

Structural Classification and Pharmacokinetics (Figure 1)

Pharmacokinetic Properties (Table 1)

Human GLP-1 backbone agents:

- Liraglutide: Daily injection with 97% homology to human GLP-1.
- Semaglutide: Weekly injection available in subcutaneous and oral formulations.
- Dulaglutide: Weekly injection as an Fc fusion protein.
- Albiglutide: Weekly injection (discontinued in some markets).

Exendin-4 backbone agents:

- Exenatide: Available in twice-daily immediate-release and weekly extended-release formulations.
- Lixisenatide: Daily injection with rapid onset of action.

Novel dual and triple agonists:

- Tirzepatide: Dual GLP-1/GIP receptor, contrary to showing superior efficacy.
- Orforglipron: Oral non-peptide GLP-1RA with extended half-life (25-68 hours).

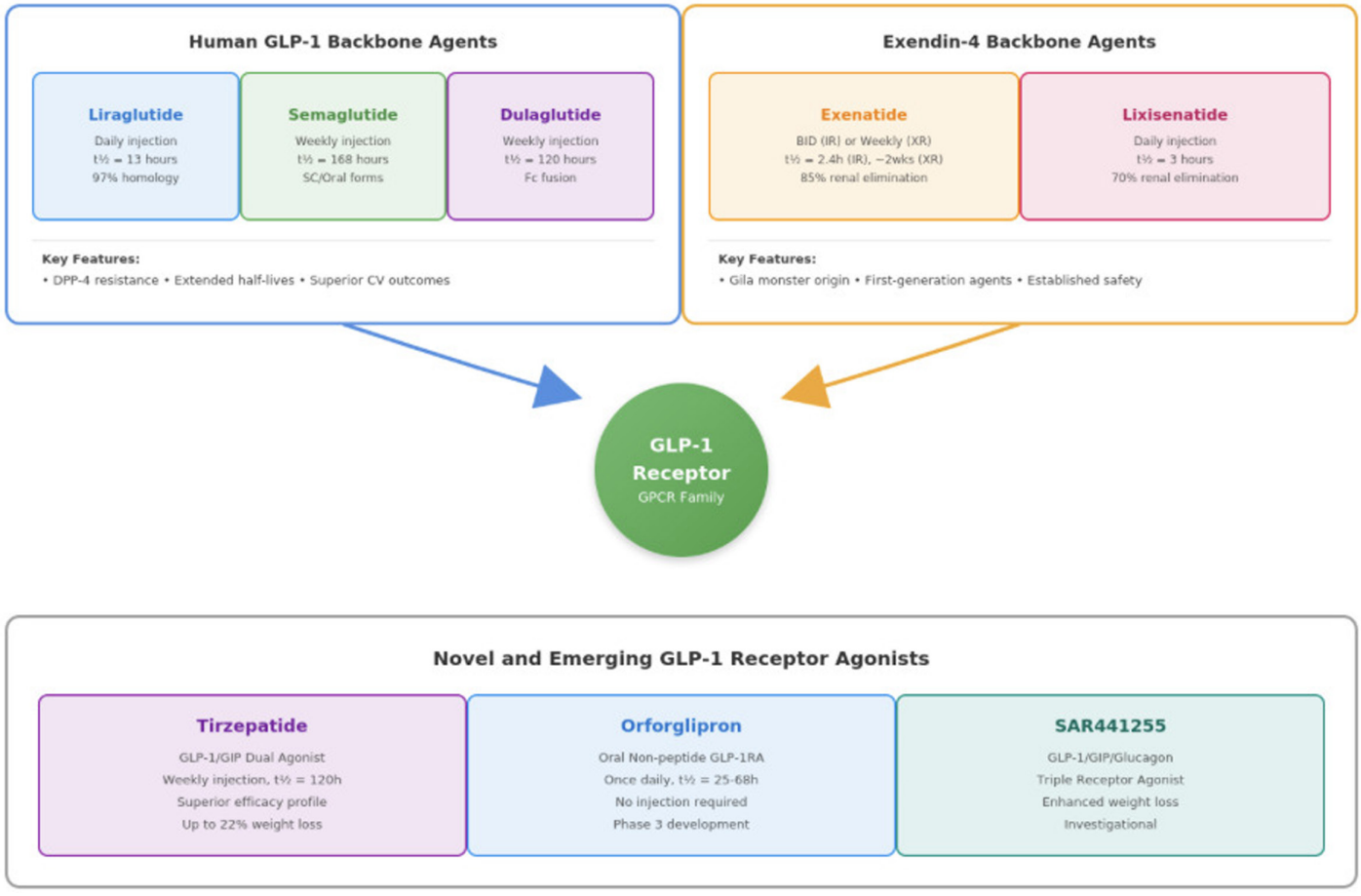

Figure 1. GLP-1 receptor agonist classification and mechanisms. The diagram illustrates the 2 main structural classes of GLP-1RAs based on their backbone (human GLP-1 vs. exendin-4), along with emerging novel agents including dual and triple receptor agonists.

- SAR441255: Investigational triple action drug directed against GLP-1/GIP/glucagon receptors.

MECHANISMS OF RENOPROTECTION BY GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (FIGURE 2)

Direct Kidney Effects

Glucagon-like peptide-1 receptor agonists are expressed in different kidney cell types, involving mesangial and tubular epithelial cells, podocytes, and endothelial cells.[21] Activation of these receptors mediates several protective mechanisms:

Podocyte protection: GLP-1RAs preserve podocyte integrity by reducing oxidative imbalance and apoptosis through activation of the *PI3K/Akt* pathway.[22] This protection is crucial for maintaining glomerular filtration barrier function and preventing proteinuria.

Table 1. Pharmacokinetic Properties of Available Glucagon-Like Peptide-1 Receptor Agonists

Agent	Half-Life	Dosing Frequency	Route	Kidney Elimination (%)	Bioavailability (%)
Exenatide IR	2.4 hours	Twice daily	SC	85	~70
Exenatide XR	~2 weeks	Weekly	SC	85	N/A
Liraglutide	13 hours	**Daily**	SC	<5	~55
Lixisenatide	3 hours	Daily	SC	70	~60
Semaglutide	168 hours	Weekly	SC/Oral	<3	~89 SC, ~1 oral
Dulaglutide	120 hours	Weekly	SC	<5	~65
Tirzepatide	120 hours	Weekly	SC	<1	~80

IR, immediate release; XR, extended release; s/c, subcutaneous; N/A, not applicable.

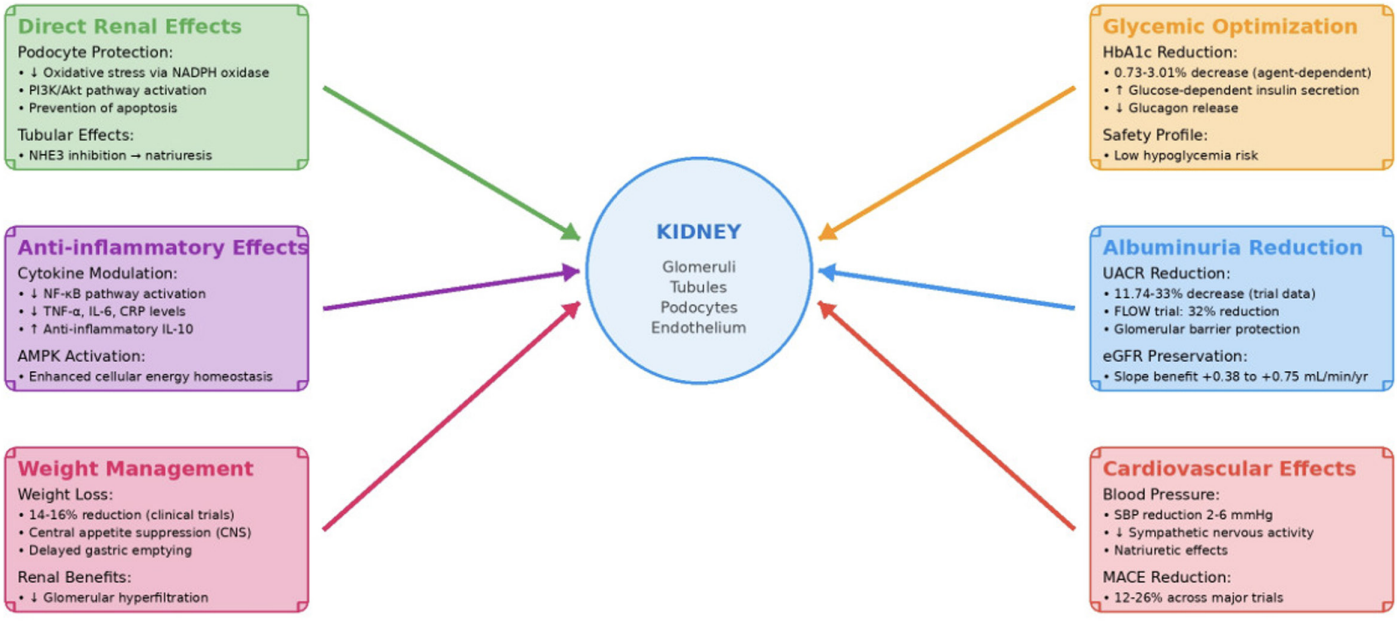

Figure 2. Multifaceted renoprotective mechanisms of GLP-1 receptor agonists. The diagram illustrates the comprehensive mechanisms through which GLP-1RAs provide renoprotection in diabetic nephropathy, including direct kidney effects, systemic metabolic improvements, anti-inflammatory actions, and cardiovascular benefits which collectively contribute to slower CKD progression.

Tubular effects: In proximal tubular cells, GLP-1RAs inhibit the Na+/H+ exchanger 3, promoting natriuresis and reducing sodium retention.[23] This mechanism contributes to lower blood pressure and reduces glomerular hyperfiltration.

Anti-fibrotic actions: Glucagon-like peptide-1 receptor agonists inhibit *TGF-β* signaling and reduce extracellular matrix protein synthesis, thereby limiting progressive fibrosis.[24] The activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway by GLP-1RAs promotes cellular energy homeostasis and reduces fibrotic gene expression.

Indirect Systemic Effects

Glycaemic optimization: Improved glucose control through enhanced insulin secretion and reduced glucagon release directly impacts DN progression. Glucagon-like peptide-1 receptor agonists achieve significant HbA1c reductions (0.73%-3.01%) across various formulations, with tirzepatide demonstrating superior efficacy.[25]

Weight management: Glucagon-like peptide-1 receptor agonists promote substantial weight loss (14%-16% in clinical trials) through central appetite suppression and delayed gastric emptying.[26] Obesity reduction alleviates glomerular hyperfiltration and reduces inflammatory burden on the kidneys.

Blood pressure reduction: Multiple mechanisms contribute to antihypertensive effects, including natriuresis, improved insulin sensitivity, and reduced sympathetic nervous system activity.[27] Systolic blood pressure reductions of 2-6 mmHg provide additional renoprotective benefits.

Anti-inflammatory effects: Glucagon-like peptide-1 receptor agonists suppress nuclear factor-κB (NF-κB) signaling, reducing pro-inflammatory cytokines.[28] Activation of anti-inflammatory pathways, including AMPK, creates a protective milieu that slows nephropathy progression.

CLINICAL EVIDENCE FROM MAJOR TRIALS

Timeline of Major Glucagon-Like Peptide-1 Receptor Agonist Kidney Outcome Trials (Figure 3)

Cardiovascular Outcome Trials with Kidney Endpoints

LEADER Trial (Liraglutide): The LEADER trial enrolled 9340 patients suffering from type 2 diabetes (T2D) and high cardiovascular risk, with a median follow-up period of 3.8 years.[29] Kidney outcomes showed:

- A 22% decrease in nephropathy progression (hazard ratio [HR] 0.78, $P = .003$, 95% CI 0.67-0.92).
- Significant decrease in development of persistent macroalbuminuria.
- Estimated glomerular filtration rate (eGFR) slope difference of +0.55 mL/min/1.73 m^2/year favoring liraglutide.
- Differences in serum creatinine doubling or ESKD onset individually were not statistically significant due to lower event rates.

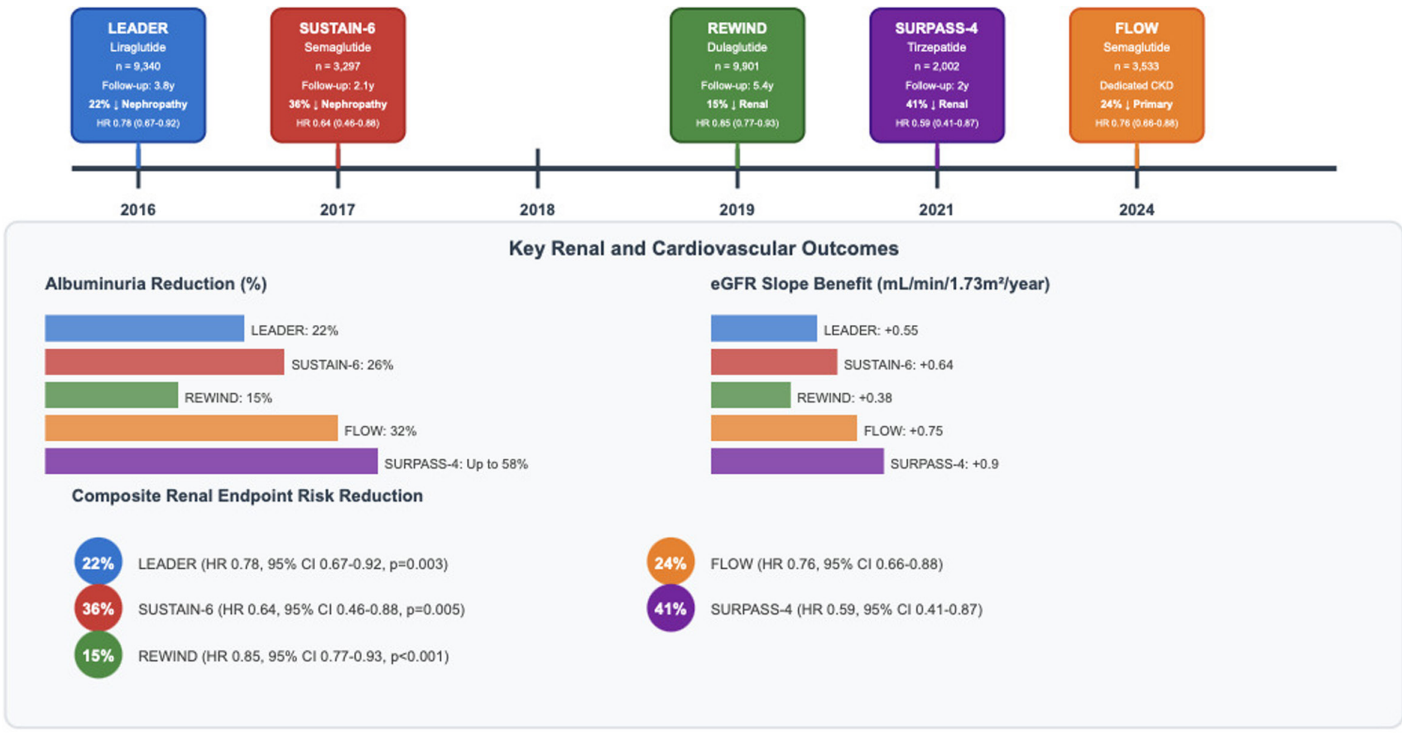

Figure 3. Timeline of major GLP-1RA trials with kidney endpoints. The timeline shows progression of evidence from cardiovascular outcome trials with kidney secondary endpoints to dedicated kidney outcome studies, demonstrating consistent benefits across different GLP-1RAs and patient populations.

- Annual eGFR decline was slightly slower with liraglutide than placebo (−2.0 vs. −2.2 mL/min/1.73 m²/year), a modest but consistent effect across subgroups.
- Early reduction in urinary albumin creatinine ratio (UACR) ending 1 year translated to better kidney outcomes.
- Modest improvements in HbA1c and systolic blood pressure translated to partial kidney protection.

SUSTAIN-6 Trial (Semaglutide): This trial included 3297 type 2 diabetic patients and cardiovascular risk factors.[30] Kidney advantages included:

- A 36% reduction in nephropathy progression (HR 0.64, *P* = .005, 95% CI 0.46-0.88).
- Substantial decrease in UACR by 26%.
- Reduced requirement for chronic kidney replacement therapy.
- Clinical end points—namely, ESKD or doubling of serum creatinine—showed fewer events and did not individually reach significance.
- The clinical benefit was determined through a 46% drastic decrease in novel onset macroalbuminuria (HR 0.54; 95% CI 0.37-0.77).
- Annual eGFR decline was −1.32 mL/min/1.73 m² with semaglutide vs −1.92 mL/min/1.73 m² with placebo (*P* < .001).
- Kidney protection has been uniformly distributed across baseline HbA1c, blood pressure, body mass index (BMI), and UACR categories, and no heterogeneity was detected in this trial.

REWIND Trial (Dulaglutide): The REWIND study followed 9901 patients for a median follow-up of 5.4 years.[31] Key findings included:

- A 15% reduction in composite kidney endpoint (HR 0.85, *P* < .001, 95% CI 0.77-0.93).
- Sustained eGFR preservation across all baseline kidney function categories.
- Benefits observed across different albuminuria levels at baseline.
- Dulaglutide curtailed the risk of kidney composite endpoint by 25% versus placebo (HR 0.75, 95% CI 0.62-0.92; *P* = .004).
- Incidence of ≥40% reduction in eGFR was reduced by 28% (HR 0.72, 95% CI 0.58-0.88; *P* = .002). Furthermore, mean annual decline in eGFR has been slower with dulaglutide (−1.37 vs −1.56 mL/min/1.73m²/year; *P* < .001), a trend that was consistent across all UACR and eGFR subgroups.

Dedicated Kidney Outcome Trials

FLOW Trial (Semaglutide): FLOW trial specifically assessed the effectiveness of semaglutide in patients suffering from T2D and chronic kidney disease (CKD).[32] Current pivotal research revealed the following outcomes:

- A 24% decrease in primary composite kidney finding (HR 0.76, 95% CI 0.66-0.88).
- A 32% reduction in albuminuria compared to placebo and a 22% reduction in kidney failure events.

- A 29% decrease in prominent adverse cardiovascular events.
- All-cause mortality has decreased by 20% (HR 0.80; 95% CI 0.67 to 0.95).
- Heart failure composite (CV [Cardiovascular] death or HF [Heart failure] events) has decreased by 27% (HR 0.73; 95% CI not reported).
- Serious adverse events have been less frequent in the semaglutide group (49.6% vs 53.8%).

SURPASS Program (Tirzepatide): Multiple SURPASS trials[25,33,34] have evaluated tirzepatide's kidney effects:

- SURPASS-4 (A Study of Tirzepatide [LY3298176] versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants with Type 2 Diabetes): 41% reduction in composite kidney outcome within high-risk patients (HR 0.59, 95% CI 0.41-0.87).
- Consistent albuminuria decreases across all studies (up to 58% in some analyses).
- Superior glycemic control and weight loss opposed to other GLP-1RAs.
- Across SURPASS 1-5 pooled post hoc analyses (n > 5200), tirzepatide produced a dose-dependent decrease in UACR compared with all control arms (placebo, semaglutide, insulin), with the most pronounced effects at 15 mg and in participants having baseline CKD (UACR ≥ 30 mg per g or eGFR < 60).
- These UACR improvements were only partially explained by decreased HbA1c levels and body weight, suggesting possible glucose- and weight-independent kidney protection.

Comparative Efficacy Among Glucagon-Like Peptide-1 Receptor Agonists (Table 2)

Meta-Analyses and Systematic Reviews

Recent comprehensive meta-analyses have confirmed the renoprotective benefits of GLP-1RAs[35,36]:

- A pooled analysis of 7 major cardiovascular outcome trials indicates a 21% reduction in kidney composite outcomes, with a relative risk of 0.79 and a 95% CI varying from 0.73 to 0.87.
- Significant albuminuria reduction across all agents with a weighted mean difference of −23.6%.
- Consistent benefits are observed irrespective of baseline kidney function or albuminuria status.
- No increased risk of acute kidney injury across trials.

SAFETY PROFILE AND CLINICAL CONSIDERATIONS

Common Adverse Events

The safety profile of GLP-1RAs was extensively investigated and verified in clinical trials and real-world experience[30,37-39] (Table 3). The most frequent side effects are predominantly gastrointestinal in nature:

Management Strategies

Gastrointestinal side effects:

1. Gradual dose titration: Start with the lowest effective dose and escalate slowly
2. Timing optimization: Administer with meals or adjust timing based on symptoms
3. Dietary modifications: Smaller, frequent meals; avoid high-fat foods
4. Temporary dose reduction: Consider dose step-down if symptoms are severe

Kidney Safety Considerations

Acute kidney injury: Large-scale trials and meta-analyses demonstrate no increased risk of Acute Kidney Injury (AKI) with GLP-1RAs.[40] In fact, some studies suggest potential protective effects against AKI.

Table 2. Comparative Kidney and Metabolic Efficacy of Glucagon-Like Peptide-1 Receptor Agonists

Parameter	Exenatide	Liraglutide	Semaglutide	Dulaglutide	Tirzepatide
Glycaemic control					
HbA1c reduction (%)	0.73-1.53	1.12-1.48	1.45-1.73	0.88-1.64	1.87-3.01
FPG reduction (mg/dL)	23-35	28-42	38-54	22-47	45-72
Weight management					
Weight loss (%)	2-6	5-8	10-15	2-5	15-22
Kidney outcomes					
UACR reduction (%)	15-20	22	26-32	15	40-58
eGFR slope benefit	+0.3	+0.55	+0.64-0.75	+0.38	+0.9
Composite renal HR	0.85	0.78	0.64-0.76	0.85	0.59
CV outcomes					
MACE reduction (%)	14	13	26	12	20

FPG, fasting plasma glucose; HR, hazard ratio; MACE, major adverse cardiac events; UACR, urine albumin creatinine ratio.

Table 3. Safety Profile and Adverse Events by Glucagon-Like Peptide-1 Receptor Agonists Class

Adverse Event	Exenatide	Liraglutide	Semaglutide	Dulaglutide	Tirzepatide	Management
Gastrointestinal						
Nausea	15%-45%	18%-28%	16%-44%	12%-21%	12%-29%	Dose titration, timing
Vomiting	8%-15%	8%-10%	5%-17%	6%-12%	6%-15%	Slow escalation
Diarrhoea	10%-18%	12%-17%	8%-16%	8%-13%	12%-16%	Dietary modification
Constipation	5%-8%	5%-10%	3%-7%	4%-8%	8%-12%	Fiber, hydration
Injection site						
Reactions	3%-5%	2%-6%	1%-3%	1%-2%	2%-4%	Rotation, technique
Rare events						
Pancreatitis	<0.2%	<0.1%	<0.1%	<0.1%	<0.1%	Discontinue
Gallbladder	1%-2%	1%-3%	1%-2%	1%-2%	2%-3%	Monitor

Dose adjustments in CKD:

- No dose adjustment required for mild-to-moderate CKD (eGFR ≥ 15 mL/min/1.73 m^2).
- Limited data in end-stage kidney disease.
- Monitor closely during illness or dehydration.

Contraindications and Precautions

Absolute contraindications:

- Medullary thyroid carcinoma in family or personal history.
- Multiple endocrine neoplasia syndrome type 2.
- Hypersensitivity to GLP-1RAs or excipients.

Relative contraindications:

- History of pancreatitis (though causal relationship unclear).[41,42]
- Severe gastroparesis or gastrointestinal disease.
- Pregnancy and breastfeeding.

INTEGRATION INTO CLINICAL PRACTICE

Current Guideline Recommendations (Figure 4)

Kidney Disease: Improving Global Outcomes 2022

Kidney Disease: Improving Global Outcomes recommends GLP-1RAs for patients with T2D, CKD, obesity, metabolic syndrome, as well as established high-risk population for cardiovascular disease.[43] The guidelines emphasize the importance of individualized treatment approaches and support combination therapy with sodium glucose co transporter 2 (SGLT2) inhibitors when appropriate.[43]

Patient Selection Criteria

Ideal candidates for GLP-1RA therapy:

- T2D with CKD (eGFR 20-60 mL/min/1.73 m^2).
- UACR ≥30 mg per g creatinine.
- Known cardiovascular disease/high cardiovascular risk patients.
- BMI ≥27 kg/m^2.
- Suboptimal glycemic control on current therapy.
- Hypertension requiring additional blood pressure lowering.

Clinical scenarios favoring GLP-1RA use:

1. Triple high-risk patient: Type 2 Diabetes Mellitus (T2DM) + CKD + Cardiovascular death (CVD).
2. Metabolic syndrome: Obesity, hypertension, dyslipidemia.
3. Progressive albuminuria: Despite optimal RAAS blockade.
4. Heart failure with preserved ejection fraction.
5. Need for therapeutic weight loss: Particularly in advanced CKD.

ECONOMIC CONSIDERATIONS AND COST-EFFECTIVENESS

Pharmacoeconomic Analysis

Multiple cost-effectiveness studies have evaluated GLP-1RAs in DN management[44-47] (Table 4).

Direct medical cost savings:

- Reduced hospitalizations for cardiovascular events (25%-35% reduction).
- Delayed need for kidney replacement therapy (potentially 2-5 years).
- Fewer diabetes-related complications requiring intervention.
- Lower long-term medication costs for complications management.

Quality-adjusted life years (QALYs):

- Significant QALY gains from improved quality of life (0.8-1.5 QALYs).

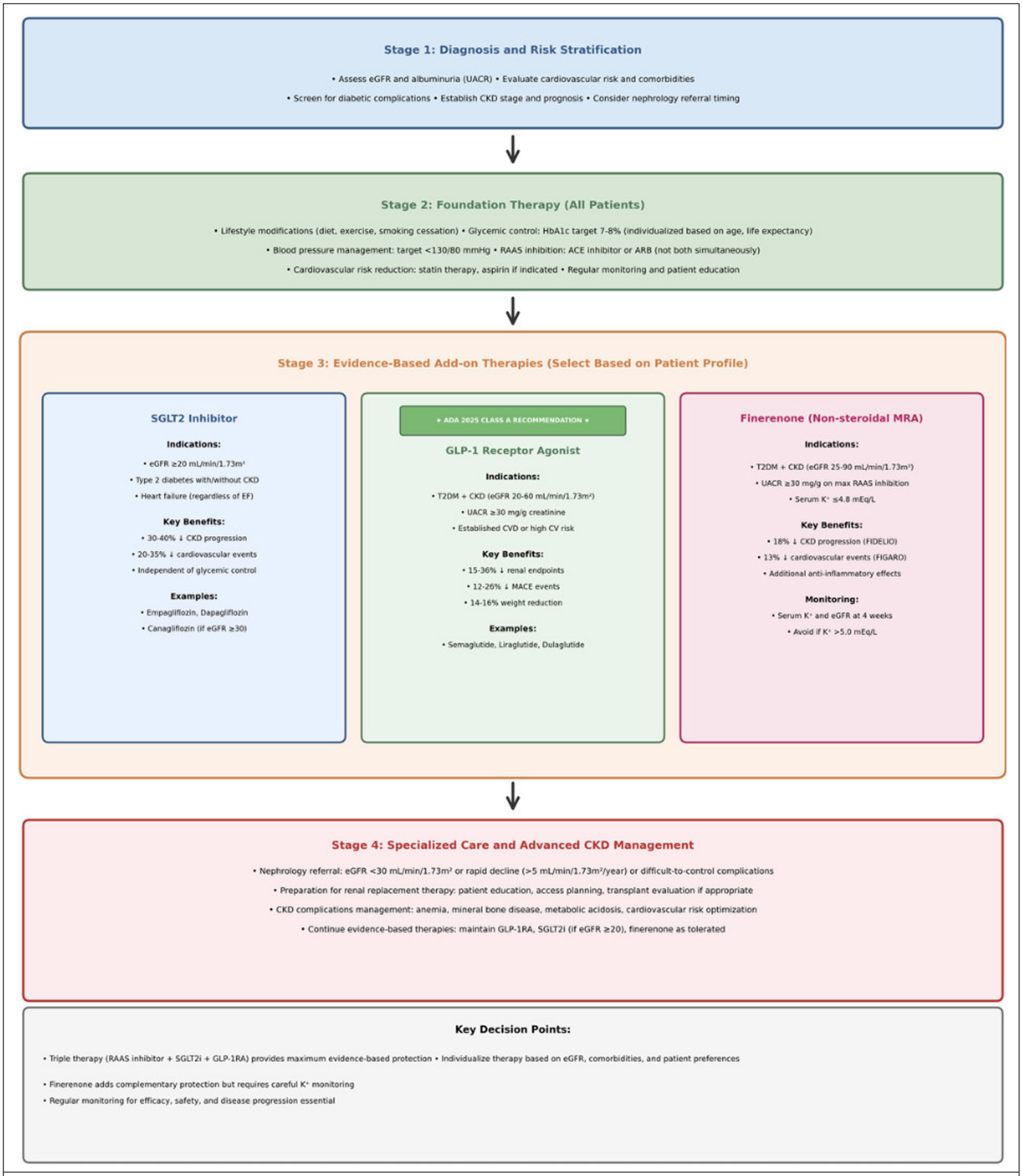

Figure 4. Evidence-based treatment algorithm for diabetic nephropathy management. The flowchart demonstrates the stepwise approach to diabetic nephropathy management, highlighting the prominent role of GLP-1RAs as Class A recommendation agents in the advanced therapy stage.

Table 4. Cost-Effectiveness Analysis of Glucagon-Like Peptide-1 Receptor Agonist Therapy in Diabetic Nephropathy

Study	Agent	Population	ICER ($/QALY)	Time Horizon	Key Findings
Gejic et al[44] (2023)	Semaglutide	T2DM + CKD	$18 450	Lifetime	Cost-effective vs. standard care
Willis et al[45] (2022)	Dulaglutide	High CV risk	$22 100	30 years	Favorable in CKD subgroup
Hunt et al.[46] (2021)	Liraglutide	Established CVD	$16 800	Lifetime	Cost-saving in CKD patients
Hwang JH(2025)[47] (2024)	Tirzepatide	Obesity + T2DM	$15 200	Lifetime	Superior cost-effectiveness

CKD, chronic kidney disease; QALY, quality-adjusted life years; ICER, Institute for Clinical and Economic review.

- Extended life expectancy from reduced cardiovascular mortality.
- Reduced disability burden from complications prevention.

Budget Impact Analysis

Healthcare systems implementing GLP-1RA therapy for DN typically observe:

- Short-term costs: Initial medication costs offset by reduced acute care utilization.
- Medium-term savings: Decreased progression to dialysis and transplantation.
- Long-term benefits: Substantial healthcare cost reduction and improved population health.

Break-even analysis: Most economic models demonstrate cost-neutrality within 3-5 years of therapy initiation, with subsequent cost savings and improved outcomes.

FUTURE DIRECTIONS AND EMERGING THERAPIES

Next-Generation Glucagon-Like Peptide-1 Receptor Agonists

Oral formulations:

- Oral semaglutide: Approved with demonstrated efficacy matching subcutaneous formulations.
- Orforglipron: Novel oral non-protein GLP-1RA in Phase 3 stage with 25-68 hour half-life.
- Patient advantages: Improved convenience, adherence, and potential for broader acceptance.

Multi-receptor agonists:

- Tirzepatide (GLP-1/GIP dual agonist): Enhanced weight loss, better efficacy, glycemic control.
- Triple agonists (GLP-1/GIP/glucagon receptors): SAR441255 and similar compounds showing enhanced metabolic benefits.
- Potential advantages: Greater weight loss (up to 25%), improved insulin sensitivity, enhanced renoprotection.

Extended-duration formulations:

- Monthly injection formulations in late-stage development.
- Implantable devices for continuous drug delivery.
- Potential for yearly administration using depot formulations.

Combination Therapy Approaches

GLP-1RA + SGLT2 inhibitor combinations:

- Synergistic mechanisms of action with complementary renoprotective effects.
- Enhanced cardiovascular benefits beyond individual agents.
- Fixed-dose combinations in development to improve adherence.
- Potential for greater albuminuria reduction and eGFR preservation.

Triple therapy (RAAS + SGLT2i + GLP-1RA):

- Maximum evidence-based nephroprotective benefit.
- Comprehensive approach targeting multiple pathways.
- Requires careful monitoring for drug interactions and side effects.
- May represent optimal therapy for high-risk patients.

Precision Medicine and Biomarker Development

Genetic polymorphisms (future avenues):

- GLP-1R gene variants affecting drug response and efficacy.
- Pharmacogenomic approaches to optimize agent selection.
- Population-specific response patterns requiring study.
- Future studies are needed to substantiate the utility of genetic polymorphisms in clinical medicine.

Inflammatory biomarkers:

- TNF-α, IL-6, and C reactive protein (CRP) levels predicting treatment response.
- Novel inflammatory markers for therapy monitoring.
- Potential for biomarker-guided dose optimization.
- However, these clinical avenues should be further studied and there is no current information regarding the applications of these biomarkers in modern day practice in the context of GLP1 receptor agonists.

Artificial intelligence integration:

- Machine learning models for treatment response prediction.
- Real-time monitoring and therapy adjustment algorithms.
- Population health management and resource allocation.
- Electronic health record integration for clinical decision support.

Novel Therapeutic Targets

Incretin system modulation:

- *Dipeptidyl peptidase-4 inhibitors (DPP-4)* resistant formulations with enhanced stability.
- Tissue-selective GLP-1R agonists for targeted effects.
- Combination with other incretin pathway modulators.

Metabolic pathway integration:

- *AMPK* activators combined with GLP-1RAs.
- Sirtuins and longevity pathway modulators.
- Mitochondrial function enhancers for cellular protection.

CLINICAL PRACTICE IMPLEMENTATION

Practical Prescribing Considerations

Initiation strategy:

1. Patient assessment: Confirm indications, screen for contraindications.
2. Agent selection: Consider efficacy, dosing frequency, cost, and patient preference.
3. Starting dose: Begin with the lowest effective dose to minimize Gastrointestinal (GI) side effects.
4. Titration schedule: Follow manufacturer guidelines for dose escalation.
5. Monitoring plan: Periodic assessment of efficacy, safety, and tolerability.

Monitoring parameters:

- Efficacy: HbA1c, weight, blood pressure, albuminuria.
- Safety: Gastrointestinal symptoms, injection site reactions.
- Kidney function: eGFR, serum creatinine, electrolytes.
- Cardiovascular: Symptoms, functional status, and any additional risk factors.

Patient Education and Support

Key educational points:

- Mechanism of action and expected benefits.
- Proper injection technique and storage.
- Prompt recognition and management of side effects.
- Importance of adherence and lifestyle modifications.
- Contact healthcare providers when indicated.

Support resources:

- Patient assistance programs for medication access.
- Diabetes educator consultations.
- Continuous glucose monitoring integration in clinical practice.
- Digital health tools and application interfaces.

CONCLUSION

Glucagon-like peptide-1 receptor agonists signify a transformative shift in the approach and management of DN, providing in-depth advantages that range far beyond traditional glucose-lowering therapies. A substantial body of evidence from major cardiovascular and dedicated kidney outcome trials consistently demonstrates significant renoprotective effects, including slowed progression of CKD, reduced albuminuria, and kidney function preservation across different stages of DN.[43]

The mechanisms responsible for these benefits are complex, involving both direct kidney effects through the activation of GLP-1RAs in kidney tissues and indirect systemic enhancements in glycemic control, weight management, blood pressure regulation, and inflammatory modulation. Glucagon-like peptide-1 receptor agonists are normally safe, with gastrointestinal side effects being a primary concern. These side effects are typically manageable through careful patient selection and gradual dose titration.

Incorporation of GLP-1RAs into clinical practice guidelines, particularly the American Diabetes Association's 2025 Class A recommendation for patients having T2D and CKD, reflects robust evidence supporting their use in this vulnerable population.[48] These agents should be considered essential components of comprehensive DN management, used in conjunction with established therapies including RAAS inhibitors and SGLT2 inhibitors to provide maximal renoprotective benefit.

Looking toward the future, emerging therapies including multi-receptor agonists, oral formulations, and combination approaches promise to further enhance outcomes for patients with DN. The development of precision medicine approaches utilizing genetic polymorphisms, biomarkers, and artificial intelligence-guided therapy selection may optimize treatment individualization and improve population health outcomes.

Economic analyses consistently reveal that GLP-1RAs exhibit favorable cost-effectiveness profiles in the management of DN. These agents contribute to significant healthcare cost savings by preventing cardiovascular events, prolonging advancement to ESKD, and eliminating the burden of complications. The economic advantages, coupled with enhanced quality of life and increased life expectancy, strongly advocate for broader implementation of GLP-1RA therapy in eligible patients. As the global prevalence of DKD continues to rise, the availability of effective therapies such as GLP-1RAs offers renewed hope for preventing progression to ESKD and mitigating associated

morbidity and mortality. Ongoing research, clinical experience, and post-marketing surveillance will undoubtedly further refine our understanding and optimize the utilization of these valuable therapeutic agents in the comprehensive care of patients with DN.

Evidence is clear: Glucagon-like peptide-1 receptor agonists have earned their place as a cornerstone therapy as one of the 4 pillars in DN management, offering patients and healthcare providers a powerful tool in the fight against DN.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.G.M.; Design – G.G.M.; Resources – G.G.M.; Materials – G.G.M.; Data Collection and/or Processing – G.G.M.; Analysis and/or Interpretation – G.G.M.; Literature Search – G.G.M.; Writing Manuscript – G.G.M.; Critical Review – G.G.M.

Declaration of Interests: The author declares that there are no competing interests.

Funding: The authors declared that this study has received no financial support.

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