International Journal of Nephrology and Renovascular Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Current Insights and Future Directions on the Role of GLP-1 Receptor Agonists in Chronic Kidney Disease

Kavya Rajan[1], Arjun Krishen Jutley[2], Michael W Holliday Jr[3,4], Sankar D Navaneethan[3–5]

[1]Innovation Academy High School, Alpharetta, GA, USA; [2]Tomball Memorial High School, Houston, TX, USA; [3]Selzman Institute for Kidney Health, Section of Nephrology, Baylor College of Medicine, Houston, TX, USA; [4]Renal Section, Medical Care Line, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA; [5]Institute of Clinical and Translational Research, Baylor College of Medicine, Houston, TX, USA

Correspondence: Sankar D Navaneethan, Baylor College of Medicine, Department of Medicine, Renal Section, 1 Baylor Plaza, Suite 100.37D, Houston, TX, 77030, USA, Email sankar.navaneethan@bcm.edu

Abstract: Chronic kidney disease (CKD) incidence continues to rise along with obesity and diabetes, driving substantial medical, psychosocial, and economic burdens for patients. Beyond glycemic control and the recommended therapies of ACEI/ARB, SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a cornerstone therapy to benefit mortality, heart and kidney outcomes. The following review will discuss recent advances to our understanding of the kidney benefits of GLP1 agonism in high-risk populations, including patients with type 2 diabetes mellitus, obesity, those with established cardiovascular disease. Renal signals from cardiovascular outcomes trials disclosed less albuminuria and slower estimated glomerular filtration rate (eGFR) decline with GLP1RA therapy, often additive to sodium–glucose cotransporter-2 inhibition. Dedicated kidney studies now show semaglutide slows CKD progression and lowers mortality in diabetics with CKD, underscoring the relevance of new guidelines that recommend GLP1RA therapy for specific populations. Future priorities should include trials of GLP-1RA in non-diabetic patients with CKD, as well as further evaluation of dual or triple agonists (GLP-1/GIP/glucagon) and clarification of oral GLP1RA efficacy. Overall, GLP-1–based therapies represent a transformative strategy to improve weight, cardiovascular health, and kidney outcomes in diabetic CKD patients.

Keywords: cardiorenal outcomes, chronic kidney disease, diabetes, obesity, nephroprotection

Introduction

Driven by both traditional and emerging non-traditional risk factors, the prevalence of chronic kidney disease (CKD) has increased significantly in recent years.[1] Specifically, the increase in obesity and diabetes prevalence in the United States has paralleled the higher burden of CKD observed both nationally and globally.[2] The annual Medicare expenditure of 95 billion USD for kidney disease care underscores the substantial costs of medications, dialysis services, and inpatient care for individuals with kidney disease.[3] The broader psychosocial and economic burden of kidney disease on patients and their families is profound; with disease and symptom progression, patients with kidney disease have a higher prevalence of depression and greater difficulty with maintaining employment.[4,5] The development of novel therapies for kidney diseases and associated co-morbidities has improved the overall prognostic outlook for patients. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated both kidney- and heart-protective effects in individuals with CKD, and other agents, such as non-steroidal mineralocorticoid receptor antagonists (ns-MRA), provide cardio-kidney protection in patients with diabetes and kidney disease.[6] However, there is still a residual cardiorenal risk that persists when using SGLT2 and ns-MRAs such as kidney function decline, cardiovascular events, and ongoing albuminuria.[7] The residual risk highlights the need for therapies targeting additional pathophysiological pathways. GLP-1 receptor agonists (RAs) are a therapy that help complete a comprehensive cardiorenal risk prevention strategy by targeting metabolic stress, systemic and renal inflammation, vascular dysfunction, and oxidative stress.[8] Recent cardiorenal outcome trials,

https://doi.org/10.2147/IJNRD.S522424
Received: 20 October 2025
Accepted: 6 March 2026
Published: 23 March 2026

including FLOW and SELECT, have demonstrated the potential of GLP-1 receptor agonists to reduce cardiovascular events and reduce kidney disease progression.[9,10] Clinical practice guidelines now recommend the use of these agents in patients with CKD.

Multimodal treatment of obesity initially relies on lifestyle changes, with patient-centered dietary and exercise counseling augmented by psychosocial support and physician follow-up. Failure of initial multimodal therapy to achieve adequate weight loss may necessitate adjunctive treatment with medications or bariatric surgery, both of which present patient-specific risks and limitations. Among weight-loss pharmacotherapies, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including dual GLP-1 and glucose-dependent insulinotrophic polypeptide (GIP) receptor agonists, have demonstrated efficacy in patients with and without CKD, and are increasingly regarded as cornerstone therapies to improve outcomes in patients with multiple comorbidities. The pleiotrophic and kidney-specific effects of GLP1 RAs, including anti-inflammation and albuminuria reduction effects, hint at potential benefits for patients with non-diabetic kidney disease. The following will review recent evidence, including from the FLOW and SELECT trials, disclosing benefits of GLP-1 RAs, with a particular focus on kidney disease progression and cardiovascular benefits in patients with diabetes.

Mechanism of Action of GLP-1RA

GLP-1, a 30- or 31-amino-acid-long peptide hormone, is a gastrointestinal incretin hormone peptide that is secreted by L cells in the small and large intestines after stimulus from ingested glucose and food nutrients.[11] GLP-1 upregulation and secretion potentiates insulin release and reduces glucagon secretion in physiological conditions, and promotes satiety through vagally mediated slowing of gastric emptying.[12] Therapeutic GLP-1 receptor agonism has been associated with delayed gastric emptying, which aids in weight loss by reducing appetite, increasing satiety, and reducing energy intake.[12–15] GLP-1RA also reduces the inflammatory burden, which is often associated with reduction in kidney fibrosis and stabilization or improvement in the glomerular filtration rate.[16,17] Additionally, GLP-1RA lowers reactive oxygen species, thereby decreasing the imbalance between ROS production and antioxidant activity, which reduces oxidative stress and cellular damage.

Effects of GLP-1RA in the General Population

The effects of GLP-1RA on mortality and weight loss outcomes have been studied in a variety of higher-risk populations, including subjects with obesity, higher cardiovascular risk, type 2 diabetes mellitus, and metabolic dysfunction-associated steatohepatitis (Table 1). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial demonstrated that liraglutide reduced major adverse cardiovascular events (MACE) and cardiovascular death in patients with type 2 diabetes with higher baseline cardiovascular risk.[18] Additionally, the Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN) study data showed that liraglutide slowed progression of liver disease in participants with MASH, which was attributed to the weight loss and resultant liver fat reduction.[19]

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN) trials with semaglutide also demonstrated a reduction in HbA1c levels, body weight, and cardiovascular events in individuals with type 2 diabetes.[20] For obese, non-diabetic patients, the STEP study disclosed that weekly semaglutide treatment was associated with a 14.9% decrease in body weight, compared to a 2.4% increase in placebo.[24] In overweight/obese non-diabetic subjects with cardiovascular disease, the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial showed a 20% reduction in MACE, as well as reduced incidence of nonfatal myocardial infarction and stroke.[10] Overall, studies have consistently demonstrated the cardiovascular and weight loss benefits of GLP-1RAs across a variety of high-risk patient groups.

More recent trials have examined the effects and superiority of agents that exhibit both long-acting glucose-dependent insulinotropic polypeptide (GIP) and GLP1 receptor agonism. Over a 3-year follow-up, the SURMOUNT-1 trial found that treatment with tirzepatide (a dual GLP1/GIP agonist) of patients with obesity and prediabetes led to substantial and sustained weight reduction, with a lower risk of progression to type 2 diabetes.[25] In SURMOUNT-OSA, tirzepatide treatment in patients with moderate-to-severe obstructive sleep apnea and obesity reduced the apnea-hypopnea index, body weight and hypoxic

Table 1 Cardiovascular Composite Outcomes in Major GLP-1 Receptor Agonist Clinical Trials

Name of Trial/Year	Authors/Countries	Population Number/ Percent with CVD	Intervention	Primary CV Outcome	Secondary CV Outcome
LEADER (2017)[18]	Marso SP, Daniels GH, Brown Frandsen K et al. USA, Denmark, Germany, United Kingdom, Canada	9340/72.4%	Liraglutide (glucagon-like peptide analogue) vs placebo	Reduced MACE (cardiovascular death, nonfatal myocardial infarction,or nonfatal stroke) by 13% vs placebo (HR:0.87; 95% CI, 0.78 to 0.97)	Reduced MACE (CV death, nonfatal MI, nonfatal stroke), coronary revascularization, hospitalization for unstable angina pectoris, heart failure by 12% vs placebo (HR:0.88; 95% CI, 0.81–0.96)
SUSTAIN-6 (2016)[20]	Marso SP, Bain SC, Consoli A et al. USA,Italy, Spain, Brazil, Canada, Germany	3297/58.8%	Semaglutide (glucagon-like peptide analogue) vs placebo	Reduced MACE (cardiovascular death,nonfatal myocardial infarction,or nonfatal stroke) by 26% compared to placebo: HR: 0.74; 95% CI, 0.58 to 0.95	First occurrence of an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization [coronary or peripheral] and hospitalization for unstable angina or heart failure)
SURPASS-4 (2022)[21]	Heerspink HJL, Sattar N, Pavo I et al. Australia, United Kingdom, USA, Canada	3045	Tirzepatide vs Insulin Glargine	Reduced MACE-4; cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina	The primary outcome was itself composite.
SELECT (2023)[10]	Lincoff AM, Brown-Frandesn K, Colhoun HM, et al./Denmark, USA, United Kingdom, Netherlands	17,604/100%	Semaglutide vs placebo	Primary cardiovascular endpoint: 6.5% in semaglutide group and 8% in placebo group (HR: 0.80, 95% CI 0.72–0.90)	Include death from cardiovascular causes (HR 0.85, 95% CI 0.71–1.01), heart failure composite (HR 0.82, 95% CI 0.71–0.96), and death from any cause (HR 0.81, 95% CL 0.71–0.93)
FLOW-CKD[9]	Perkovic V, Tuttle KR, Rossing P, et al./ Australia, USA, Denmark, Germany	3533	Semaglutide vs placebo	N/A	Risk of major cardiovascular events 18% lower (HR, 0.82; 95% CI, 0.68 to 0.98; P=0.029)
AMPLITUDE-O[22]	Gerstein HC, Sattar N, Rosenstock J, et al/ Canada, United Kingdom, USA, Singapore, Italy	4076/89.6%	Efpeglenatide vs placebo	Major adverse cardiovascular event: 7% from efpeglenatide, 9.2% from placebo	Expanded MACE composite outcome (MACE, coronary revascularization, or hospitalization for unstable angina)
SURPASS-4[23]	Del Prato S, Kahn SE, Pavo I, et al/Italy,USA, Greece, Argentina	3045/87%	Tirzepatide vs Insulin Glargine	N/A	MACE-4 Events for tirzepatide vs glargine: 5% vs 6%, HR 0.74, 95% CI 0.51–1.08

https://doi.org/10.2147/IJNRD.S522424

burden, among additional beneficial effects.[25] Underscoring the therapeutic potential of dual agonism, a recent comparison of tirzepatide and semaglutide concluded that tirzepatide was superior in reducing body weight and waist circumference.[26]

Effects of GLP-1RA on Kidney Outcomes in General Population Studies

GLP-1RAs have emerged as promising medications for kidney protection, specifically in patients with diabetes or chronic kidney disease (CKD). Secondary analysis of multiple general population studies, including AMPLITUDE-O, SELECT, ELIXA, SURPASS, and LEADER, demonstrated significant improvements in various surrogate kidney outcomes, including slowing eGFR decline, proteinuria reduction, and decreased progression to end-stage renal disease.[9,21,22,27,28]

AMPLITUDE-O, a trial that studied efpeglenatide, disclosed a reduction in the composite kidney outcome by 32% relative to placebo in people with type 2 diabetes and a history of heart or kidney disease.[22] Efpeglenatide also lowered proteinuria, especially macroalbuminuria, by 5.4% (hazard ratio, 0.68; 95% CI, 0.57 to 0.79; P<0.001), of relevance for the observed slower decline in eGFR. The trial also showed kidney benefits in patients with and without concomitant SGLT2i use, highlighting the independent and added effects of these agents. A pre-specified analysis of SELECT also demonstrated that semaglutide reduces kidney-related adverse events, including proteinuria and eGFR decline, the latter slope lowered by 0.39 mL min^{-1} $1.73m^{-2}$ per year.[29] A post-hoc analysis of the LEADER trial disclosed that liraglutide reduced both progression of CKD and macroalbuminuria, the latter independent of baseline albuminuria or GFR.[30]

In high-risk patients with type-2 diabetes mellitus, the ELIXA trial found that lixisenatide, a short-acting GLP1RA, was safe for patients with acute coronary syndrome.[31] In exploratory analysis, lixisenatide also reduced progression of albuminuria and reduced the incidence of new-onset macroalbuminuria (HR 0.815; 95% CI, 0.665–0.999; p=0.0491). Further, the decrease in macroalbuminuria associated with lixisenatide was found to be independent of glycemic control. Despite benefits for proteinuria, there were no notable differences in eGFR decline among arms, and the risk of doubling serum creatinine was similar.

The SURPASS-4 trial examined the effects of tirzepatide, a dual GLP1 and GIP receptor agonist, on kidney outcomes in comparison to insulin glargine.[23] Tirzepatide treatment was associated with a significantly reduced annual decline in eGFR, with a 3.7 mL min^{-1} $1.73m^{-2}$ per year difference (95% CI, 2.4 to 5.1). The UACR ratio also increased by 36.9% (95% CI, −14.1 to 1.1) in the insulin glargine group, but decreased by 6.8% (95% CI, −14.1 to 1.1) in the tirzepatide group. Overall, the composite kidney outcome, defined by eGFR decline, new-onset microalbuminuria, or death from kidney failure, was lower in the tirzepatide group (HR 0.58; 95% CI, 0.43 to 0.80).

Effects of GLP-1RA on Kidney Outcomes in CKD Studies

The FLOW-CKD trial examined the benefits of semaglutide compared to a placebo in patients with diabetes and CKD, specifically focusing on long-term kidney outcomes (Table 2).[9] The clinical trial involved 3,500 participants with advanced kidney disease, who received follow-up care for a median of 3.4 years to assess the effects of the drug. The trial included patients with mild to moderate kidney disease, with estimated glomerular filtration rates ranging from 25 to 75 mL/min/1.73 m^2 and elevated UACR. The study assessed the protective effect of semaglutide on kidney function by monitoring key events, including dialysis initiation, transplant requirements, sustained eGFR decline, and kidney or cardiovascular-related deaths. By including high-risk populations, the trial provided an effective design for determining semaglutide's effectiveness in patients who may fail other conventional therapies. Notably, interim analysis found that semaglutide treatment was associated with significant improvements in kidney outcomes as well as a reduction in mortality. The study's findings revealed a 24% reduction in primary outcome events compared to patients receiving placebo, resulting in fewer cases of kidney failure and less severe declines in eGFR. Furthermore, semaglutide decreased major cardiovascular events by 18% and all-cause mortality by 20%, highlighting its benefits beyond kidney protection. The trial was stopped early due to its demonstrated efficacy, suggesting semaglutide offers a new treatment approach for CKD that benefits patients across different disease stages. These findings indicate that certain GLP1RAs may reduce the need for future renal replacement therapy, lower treatment costs, and improve quality of life for patients with diabetic kidney disease.

Table 2 Renal Composite Outcomes in Major GLP-1 Receptor Agonist Clinical Trials

Name of Trial/Year	Authors/ Countries	Population Number	Intervention	Primary Renal Outcome	Secondary Renal Outcome
SURPASS-4 (2022)[21]	Heerspink HJL, Sattar N, Pavo I et al. Australia, United Kingdom, USA, Canada	3045	Tirzepatide vs Insulin Glargine	Kidney composite (greater than or equal to 40% eGFR decline, end-stage kidney disease, death owing to kidney failure, or new-onset macroalbuminuria); (HR 0.58, [95% CI 0.43–0.80])	eGFR slope difference: 2.2 (95% CI 0.43–0.80), UACR between-group difference: −31.9% (95% CI −37.7 to −25.7)
FLOW-CKD[9]	Perkovic V, Tuttle KR, Rossing P et al. Australia, USA, Denmark, Germany	3533	Semaglutide vs placebo	Primary Outcome - major kidney disease events: 24% lower in semaglutide group than in placebo group (HR: 0.76, 95% CI 0.66–0.88)	Total eGFR slope (the annual rate of change in eGFR from randomization to the end of the trial); The mean annual slope was significantly less steep, indicating a slower decrease, by 1.16 mL per minute per 1.73m^2 in the semaglutide group (P<0.001).
AMPLITUDE-O[22]	Gerstein HC, Sattar N, Rosenstock J et al. Canada, United Kingdom, USA, Singapore, Italy	4076	Efpeglenatide vs placebo	Incident macroalbuminuria (defined as a urinary albumin-to-creatinine ratio of >300), plus an increase in the urinary albumin-to-creatinine ratio of greater than or equal to 30%	Kidney-function outcome (a decrease in the eGFR of greater than or equal to 40% for more than 30 days, end-stage kidney disease (defined as dialysis for greater than or equal to 90 days), or an eGFR of <15mL per minute per 1.73m^2

Comparison of GLP1RA to SGLT2 Inhibitors in Preserving Kidney Function

The decision to initiate GLP1RA or SGLT-2 inhibitors alone or in combination is certainly informed by patient characteristics. For example, in an obese patient, initiation of GLP1RA might be pursued first due to higher efficacy for weight loss. Both GLP1RA and SGLT2 inhibitors have benefits for both cardiovascular and kidney outcomes, and such benefits are likely independent. A meta-analysis of 12 randomized controlled trials of SGLT2 inhibitors in diabetics showed benefits to both cardiovascular and kidney outcomes whether or not patients were receiving GLP1RAs.[32] A separate meta-analysis of GLP1RA trials in diabetics as well disclosed cardiovascular and kidney outcome benefits whether or not patients were on SGLT2 inhibitors.[33] There are no randomized kidney outcome trials that examine the effect of combination GLP1RA/SGLT2 inhibitor therapies versus monotherapy. Nonetheless, with the well demonstrated kidney benefits of these agents, in combination with positive observational data, combination therapy has become an additional cornerstone of diabetic kidney disease treatment for suitable patients.

Guideline Recommendations for Use of GLP-1RA in Patients with and at Risk of Kidney Disease

AHA: The American Heart Association (AHA) recognizes glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as key agents for managing cardiovascular risk in patients with type 2 diabetes and heart failure.[34] The AHA guidelines endorse GLP-1 RAs, including semaglutide and liraglutide, because these medications have shown significant benefits in reducing major adverse cardiovascular events (MACE) and heart failure exacerbations, as demonstrated in the LEADER and SUSTAIN-6 trials (Table 3). These medications achieve their benefits through improved blood sugar control, weight

Table 3 GLP-1RA Guideline Summary Table

Organization/ Guideline Name	Guideline Statement (Specific to Kidney Disease/ Diabetes)	Strength of Evidence
KDIGO (2022) – Diabetes Management in CKD[6]	"We recommend a long-acting GLP-1 RA for patients with type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin and comprehensive lifestyle intervention, or who are unable to use metformin, to improve glycemic control and reduce risk of CKD progression and CVD."	1A - Strong recommendation, high-quality evidence from FLOW, REWIND, SUSTAIN trials
American Heart Association Clinical Practice Guidelines[34]	"GLP-1 receptor agonists with proven cardiovascular benefit are recommended for individuals with T2D and established atherosclerotic cardiovascular disease (ASCVD), indicators of high ASCVD risk, or CKD to reduce major adverse cardiovascular events and slow CKD progression."	A - High-quality RCTs and meta-analyses support efficacy
ADA Standards of Medical Care in Diabetes—2024[35]	"For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide-1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both."	A -based on data from large controlled trials demonstrating reductions in CKD progression and cardiovascular outcomes

loss, and blood pressure reduction, which together decrease hospitalizations for heart failure and lower mortality rates. The AHA recommends their use in clinical practice for patients with established cardiovascular disease because GLP1 RAs provide an effective additional treatment to standard therapies, while requiring ongoing monitoring to ensure optimal outcomes.

ADA: The American Diabetes Association (ADA) recommends GLP1RAs to reduce cardiovascular risk and kidney disease progression in people with type 2 diabetes and CKD. The guideline highlights the associated cardiovascular risk reduction associated with GLP1RA therapy.[36] The ADA also recommends GLP-1 receptor agonists for patients with type 2 diabetes who have established atherosclerotic cardiovascular disease (ASCVD), high ASCVD risk, or CKD.[35]

KDIGO: According to the KDIGO 2022 DM and CKD guidelines and the 2024 CKD guidelines, long-acting GLP-1 receptor agonists are recommended for treating type 2 diabetes patients with CKD.[7] These agents are recommended for patients who do not meet their personalized glycemic targets with metformin and lifestyle changes (or who have a contraindication to metformin) due to its benefits in controlling blood sugar, slowing CKD progression, and reducing cardiovascular disease.

Future Directions

GLP-1RAs in Non-Diabetic Kidney Disease

Up to now there are no kidney outcome trials examining the utility of GLP1RAs in non-diabetic, non-obese patients with CKD. Complementing the renal benefits disclosed in the SELECT trial, Apperloo et al examined the effect of semaglutide in non-diabetic obese patients with CKD. Treatment with semaglutide for 24 weeks was found to reduce albuminuria by 52% when compared to placebo.[37] Future kidney outcome trials of GLP1RAs in non-diabetic and non-obese CKD patients will be necessary to advance the standard of care.

New Agents

Aside from GLP-1RA, GIP agonism is also a promising treatment for obesity, with preclinical studies demonstrating improved metabolic profiles and reduced food intake. Beyond the demonstrated efficacy and benefits of the dual GLP-1/GIP receptor agonist tirzepatide, on the horizon is the question of whether a triple agonist targeting all three receptors (GLP-1/GIP/glucagon) may yield even more efficacious weight loss and glycemic control.[38] These agents are currently being studied in clinical trials, and their effects on kidney function are yet to be demonstrated. Additionally, new data

have emerged on the efficacy of oral GLP-1 RAs in the general population (demonstrating weight loss although at a lower rate compared to subcutaneous injections), but their potential benefits on kidney disease progression are yet to be established.[39,40]

Enhancing the Adoption of These Agents

Although numerous clinical trials have shown the significant benefits of cardiovascular and renal protection for individuals with diabetes and CKD, adoption of GLP-1RA in clinical practice remains low. In a cohort of 209,460 patients with CKD, type 2 diabetes, and atherosclerotic cardiovascular disease, 19,780 (9.4%) were prescribed a GLP1-RA.[41] Healthcare disparities exist, as Black and Hispanic patients are significantly less likely to be prescribed GLP-1RA compared to White and non-Hispanic patients.[42] The expanding clinical utilities of GLP-1/GIP RAs have further highlighted the barriers for patients to usage, including high costs and drug availability, as well as the need for further policy development to facilitate access for patients with medical necessity. Such barriers have contributed to the use of compounded forms of GLP-1/GIP receptor agonists, which are not recommended by the FDA.

Among patients that are initiated on GLP1RA therapy, a substantial subset discontinues the drug within the first year due to side effects and financial burdens. In a United Kingdom-based study, the overall proportion of patients who discontinued GLP-1 RA therapy at 12 months was 45.2% and 64.7% at 24 months.[43] In an obesity-centered cohort in the US, 54% of patients discontinued their GLP-1 RA within 1 year, and 72% discontinued within 2 years.[44] On review of clinical notes, gastrointestinal side effects and cost were the most cited reasons for discontinuation. On-treatment moderate or severe incident GI adverse events were associated with higher hazard of discontinuation in patients with type 2 diabetes (HR 1.38). Additionally, many patients reported a plateau in weight loss, or a lack of desired weight loss. Such adverse effects highlight the importance of careful patient selection when prescribing GLP1RA, including identifying those with prior gastrointestinal issues such as severe constipation, prior bowel obstruction or ileus.

Conclusions

In summary, several studies have reported the multiple benefits of GLP-1RA for weight loss, diabetes control, and cardiovascular and kidney outcomes. More recent evidence demonstrated kidney benefits of GLP-1RA in patients with diabetes and obesity associated kidney disease. These remarkable findings are transformative to kidney care, support the increase in utilization these agents for suitable patients, and encouraged continued work on defining benefits to wider kidney patient populations.

Funding

Dr. Navaneethan is supported by NIH/NHLBI K24 HL161414-01A and the Garabed Eknoyan MD Endowed Professorship.

Disclosure

Outside the submitted work, SDN reported serving on end point adjudication committee for clinical trials sponsored by Alnylam, Intercept, Prokidney and Vertex, and consultant for AstraZeneca, Bayer, Boehringer Ingelheim, and Novartis; and receiving research funding from the Department of Veterans Affairs Health Services Research & Development and National Institutes of Health. K. Rajan, A. Jutley, and MW Holliday Jr report no conflicts of interest in this work.

References

1. Centers for Disease Control and Prevention. Chronic kidney disease in the United States, 2023. US Department of Health and Human Services.
2. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315(21):2284–2291. doi:10.1001/jama.2016.6458
3. United States Renal Data System. 2025 USRDS annual data report: epidemiology of kidney disease in the United States. 2025;2025.
4. Villarroel MA, Wang X. Mental health symptoms and receipt of mental health care among US adults diagnosed with kidney disease. *Prev Chronic Dis*. 2025;22:E34. doi:10.5888/pcd22.240509
5. Erickson KF, Zhao B, Ho V, Winkelmayer WC. Employment among patients starting dialysis in the United States. *Clin J Am Soc Nephrol*. 2018;13(2):265–273. doi:10.2215/CJN.06470617

6. Navaneethan SD, Bansal N, Cavanaugh KL, et al. KDOQI US commentary on the KDIGO 2024 clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2025;85(2):135–176. doi:10.1053/j.ajkd.2024.08.003
7. Levin A, Ahmed SB, Carrero JJ, et al. Executive summary of the KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease: known knowns and known unknowns. *Kidney Int*. 2024;105(4):684–701. doi:10.1016/j.kint.2023.10.016
8. Mullur N, Morissette A, Morrow NM, Mulvihill EE. GLP-1 receptor agonist-based therapies and cardiovascular risk: a review of mechanisms. *J Endocrinol*. 2024;263(1). doi:10.1530/JOE-24-0046
9. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*.2024;391 (2):109–121. doi:10.1056/NEJMoa2403347
10. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221–2232. doi:10.1056/NEJMoa2307563
11. Wang JY, Wang QW, Yang XY, et al. GLP-1 receptor agonists for the treatment of obesity: role as a promising approach. *Front Endocrinol*. 2023;14:1085799. doi:10.3389/fendo.2023.1085799
12. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol*. 1997;273(5):E981–8. doi:10.1152/ajpendo.1997.273.5.E981
13. Lee YS, Jun HS. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. *Metabolism*. 2014;63(1):9–19. doi:10.1016/j. metabol.2013.09.010
14. Ikizler TA, Kramer HJ, Beddhu S, et al. ASN kidney health guidance on the management of obesity in persons living with kidney diseases. *J Am Soc Nephrol*. 2024;35(11):1574–1588. doi:10.1681/ASN.0000000512
15. Nauck MA, Meier JJ. MANAGEMENT OF ENDOCRINE DISEASE: are all GLP-1 agonists equal in the treatment of type 2 diabetes? *Eur J Endocrinol*. 2019;181(6):R211–R234. doi:10.1530/EJE-19-0566
16. Zheng Z, Zong Y, Ma Y, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2024;9 (1):234. doi:10.1038/s41392-024-01931-z
17. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. *Kidney Blood Press Res*. 2012;35(6):483–488. doi:10.1159/000337929
18. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375 (4):311–322. doi:10.1056/NEJMoa1603827
19. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387(10019):679–690. doi:10.1016/S0140-6736(15)00803-X
20. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375 (19):1834–1844. doi:10.1056/NEJMoa1607141
21. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, Phase 3 trial. *Lancet Diabetes Endocrinol*. 2022;10(11):774–785. doi:10.1016/S2213-8587(22) 00243-1
22. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med*. 2021;385 (10):896–907. doi:10.1056/NEJMoa2108269
23. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet*. 2021;398(10313):1811–1824. doi:10.1016/S0140-6736(21)02188-7
24. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384 (11):989–1002. doi:10.1056/NEJMoa2032183
25. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205–216. doi:10.1056/NEJMoa2206038
26. Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med*. 2025;393(1):26–36. doi:10.1056/NEJMoa2416394
27. Mann JFE, Fonseca V, Mosenzon O, et al. Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. *Circulation*. 2018;138(25):2908–2918. doi:10.1161/CIRCULATIONAHA.118.036418
28. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(11):859–869. doi:10.1016/S2213-8587(18)30268-7
29. Colhoun HM, Lingvay I, Brown PM, et al. Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial. *Nat Med*. 2024;30(7):2058–2066. doi:10.1038/s41591-024-03015-5
30. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377(9):839–848. doi:10.1056/NEJMoa1616011
31. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373 (23):2247–2257. doi:10.1056/NEJMoa1509225
32. Apperloo EM, Neuen BL, Fletcher RA, et al. Efficacy and safety of SGLT2 inhibitors with and without glucagon-like peptide 1 receptor agonists: a SMART-C collaborative meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2024;12(8):545–557. doi:10.1016/S2213-8587(24)00155-4
33. Neuen BL, Fletcher RA, Heath L, et al. Cardiovascular, kidney, and safety outcomes with GLP-1 receptor agonists alone and in combination with SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. *Circulation*. 2024;150(22):1781–1790. doi:10.1161/ CIRCULATIONAHA.124.071689
34. Writing Committee M, Virani SS, Newby LK, et al. AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2023;82(9):833–955. doi:10.1016/j.jacc.2023.04.003
35. American Diabetes Association Professional Practice C. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S20–S42. doi:10.2337/dc24-S002

36. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. *Diabetes Care*. 2023;46 (Suppl 1):S19–S40. doi:10.2337/dc23-S002
37. Apperloo EM, Gorriz JL, Soler MJ, et al. Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial. *Nat Med*. 2025;31(1):278–285. doi:10.1038/s41591-024-03327-6
38. Alfaris N, Waldrop S, Johnson V, Boaventura B, Kendrick K, Stanford FC. GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review. *EClinicalMedicine*. 2024;75:102782. doi:10.1016/j.eclinm.2024.102782
39. Wharton S, Lingvay I, Bogdanski P, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N Engl J Med*. 2025;393 (11):1077–1087. doi:10.1056/NEJMoa2500969
40. Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N Engl J Med*. 2025. doi:10.1056/NEJMoa2511774
41. Gregg LP, Worsley ML, Ramsey DJ, et al. Racial and ethnic disparities and facility-level variation in GLP-1 RA prescription among US veterans with CKD. *Clin J Am Soc Nephrol*. 2023;18(11):1479–1482. doi:10.2215/CJN.0000000000000266
42. Wang E, Patorno E, Khosrow-Khavar F, Crystal S, Dave CV. Racial and ethnic disparities in the uptake of SGLT2is and GLP-1RAs among medicare beneficiaries with type 2 diabetes and heart failure, atherosclerotic cardiovascular disease and chronic kidney disease, 2013-2019. *Diabetologia*. 2025;68(1):94–104. doi:10.1007/s00125-024-06321-2
43. Weiss T, Yang L, Carr RD, et al. Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. *BMJ Open Diabetes Res Care*. 2022;10(1). doi:10.1136/bmjdrc-2021-002517
44. Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw Open*. 2025;8(1):e2457349. doi:10.1001/jamanetworkopen.2024.57349