Long-Term Care Updates

May 2025

The role of GLP-1 receptor agonists in chronic kidney disease (CKD)

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Introduction

Chronic kidney disease (CKD) is a progressive and often irreversible condition characterized by the gradual decline of renal function and the leaking of albumin into the urine. Over time, if renal function worsens and the kidneys can no longer effectively filter waste from the blood, this condition progresses to kidney failure, also known as end-stage renal disease (ESRD). This condition, irrespective of staging, places individuals at heightened risk for cardiovascular (CV) complications, hospitalizations, and increased mortality.[1] While there is no cure for CKD other than a kidney transplant, current treatments can help minimize damage and slow the disease's progression.

Among the many etiologies of CKD, type 2 diabetes mellitus (T2DM) stands out as one of the most prevalent and impactful contributors to disease progression. The persistent state of hyperglycemia characteristic of T2DM initiates and perpetuates a cascade of damaging physiological mechanisms within the kidneys. These include hemodynamic alterations, which lead to glomerular hyperfiltration and increased pressure within the filtering units of the kidneys; oxidative stress, which damages renal tissues at the cellular level; chronic low-grade inflammation; and ultimately, progressive fibrosis that impairs renal structure and function. Over time, these pathological changes contribute to the development of diabetic nephropathy—a specific form of CKD that is now recognized as the leading cause of ESRD and the primary reason for initiating dialysis in the United States.[2]

Managing T2DM effectively is, therefore, a critical strategy in both the prevention and progression of CKD. While traditional antihyperglycemic therapies primarily focus on glycemic control, recent advancements have emphasized the need for agents that offer additional metabolic and organ-protective benefits. This has led to growing interest in the therapeutic potential of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which have demonstrated favorable outcomes not only in glycemic control but also in weight reduction, CV protection, and most recently, preservation of renal function.

Novel Drug Approvals (May 2025)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Tryptyr	Acoltremon	Dry eye disease	TRPM8 thermoreceptor agonist	Ophthalmic solution

Overview of GLP-1 Receptor Agonists

GLP-1 RAs are a class of medications that mimic the effects of the endogenous incretin hormone glucagon-like peptide-1. This hormone is secreted by intestinal L-cells in response to nutrient ingestion, and it plays a critical role in maintaining glucose levels within the body. Its primary actions include enhancing insulin secretion from pancreatic β-cells in a glucose-dependent manner and suppressing the inappropriate release of glucagon from pancreatic α-cells following meals, both of which contribute to the regulation of postprandial blood glucose levels.[3]

In addition to their glycemic effects, GLP-1 RAs also slow gastric emptying, which helps reduce the rate at which glucose enters the bloodstream after eating. This not only aids in glycemic control but also promotes the feeling of fullness or satiety, often resulting in reduced food intake and subsequent weight loss. These multifaceted effects make GLP-1 RAs particularly beneficial for patients with T2DM, and especially those struggling with obesity or insulin resistance.[3]

Notably, this class of medications includes semaglutide, dulaglutide, and liraglutide. A related drug, tirzepatide, functions in a similar manner but also targets glucose-dependent insulinotropic polypeptide (GIP) receptors, making it a dual GLP-1/GIP receptor agonist.

Results from the FLOW Trial

The FLOW trial, published in 2024, was a landmark randomized, double-blind, placebo-controlled study evaluating the impact of semaglutide in patients with T2DM and CKD. The trial randomized over 3,500 participants to receive either semaglutide 1 mg weekly or placebo. These participants all had uncontrolled diabetes (A1c $\geq$ 10%) and high to very high risk of CKD progression (based on urine albumin-to-creatinine ratio [UACR] and estimated glomerular filtration rate eGFR).[4]

In the trial, the semaglutide group demonstrated a statistically significant 24% relative risk reduction to the primary outcome compared to placebo. This outcome was a composite that included the decline in eGFR of at least 50%, progression to kidney failure, or renal death. From this, researchers calculated that only 20 patients would need to be treated with semaglutide for 3 years to prevent one major kidney disease event. As part of the secondary outcomes, researchers found that patients receiving semaglutide experienced a significantly slower annual decline in eGFR and a 20% reduction in UACR, indicating improved kidney function and reduced proteinuria. These benefits were consistent across all subgroups analyzed. Beyond renal outcomes, semaglutide also conferred CV benefits, including an 18% lower risk of major CV events, a 29% lower risk of CV death, and a 20% lower risk of death from any cause. Semaglutide was generally well-tolerated, with gastrointestinal side effects such as nausea and vomiting being the most commonly reported. Importantly, no new safety concerns emerged from the trial.[4]

Overall, researchers concluded that semaglutide reduced the risk of clinically important kidney outcomes, major CV events, and death from any cause in participants with T2DM and CKD. Even more notably, the trial originally intended to gather data for 5 years but was stopped early during the interim analysis due to the clear benefits observed in the treatment group.[4]

Potential mechanisms of CKD benefit

The precise mechanisms by which GLP-1 RAs provide kidney protection are still not fully understood, but several key pathways have been identified. GLP-1 RAs reduce major kidney and CV risk factors such as hypertension, hyperglycemia, and dyslipidemia, helping to slow the progression of CKD over time. They also appear to reduce glomerular hyperfiltration by promoting sodium and water excretion through inhibition of the sodium-hydrogen exchanger 3 (NHE3). This action lowers intraglomerular pressure, decreasing kidney workload and mitigating further damage. Additionally, GLP-1 signaling dampens inflammation by inhibiting the activation of the receptor for advanced glycation end products (RAGE), a key player in inflammatory cascades within the kidney. Anti-inflammatory and antioxidant effects, along with reductions in oxidative stress and fibrosis, further contribute to the renal protective benefits of GLP-1 RAs. While these findings are promising, ongoing research is needed to fully elucidate the complexity of these mechanisms. [5]

Clinical Considerations

When prescribing semaglutide in patients with CKD and T2DM, the typical dosing schedule begins with 0.25 mg injections once weekly, followed by an increase to 0.5 mg, and then 1 mg. This medication can be up-titrated every four weeks if indicated. It is important to note that there is a 2 mg strength available, however, researchers did not study this higher dose in patients with T2DM and CKD.[6]

While GLP-1 RAs are generally well tolerated, adverse side effects, mainly gastrointestinal, have been known to occur. In clinical trials, nausea (15.8%), vomiting (5%), diarrhea (8.5%), abdominal pain (7.3%), and constipation (5%) were among the most commonly reported.[6] These symptoms tended to be dose-dependent and often subsided over time as patients adjusted to the medication. However, patients with CKD can be more likely to experience adverse effects. In this population, initiating therapy at the lowest dose and extending the titration window can minimize these adverse effects if experienced.[7]

In patients with CKD, volume depletion from persistent vomiting or decreased oral intake should be carefully monitored, as it can exacerbate kidney dysfunction. This, in turn, has caused reports of acute kidney injury associated with severe dehydration from gastrointestinal losses. Therefore, maintaining good hydration and close follow-up, especially during the early stages of therapy, is recommended.[8]

It is also important to be aware of contraindications when prescribing GLP-1 RAs. These agents are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2), due to observed risks in animal studies. Semaglutide should not be used in patients with acute pancreatitis, severe gastroparesis, or acute gallbladder disease.[6]

Conclusion

GLP-1 RAs are recognized in guidelines by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) for patients with T2DM and high CV or renal risk. As of January 2025, the FDA has also approved semaglutide's indication for use in patients with T2DM and CKD.

GLP-1 receptor agonists represent a promising class of medications for managing both T2DM and its renal complications. With demonstrated benefits in glycemic control, cardiovascular risk reduction, and potential renal protection, these agents offer a valuable tool in the comprehensive care of patients with CKD. Continued research will help refine their role, particularly in advanced kidney disease. Now and in the future, pharmacists will play a key role in patient education, side effect management, and sourcing affordable.

References

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