The Role of Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists in the Prevention and Treatment of Diabetic Kidney Disease

Insights from the AMPLITUDE-O Trial

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Diabetic kidney disease (DKD) is common, can progress to kidney failure, and augments the risk of cardiovascular disease (1). Intensive glycemic and BP control are known to prevent DKD, yet the optimal treatment strategy to mitigate risk for increased albuminuria and impaired GFR remains unclear. Inhibition of the renin-angiotensin-aldosterone system remains a mainstay therapy for managing BP and reducing albuminuria in people with type 2 diabetes; however, the utility of this treatment in attenuating DKD progression in individuals with either normal BP or normoalbuminuria is unclear. In contrast, sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP1-RAs) are effective next-generation blood glucose–modifying therapies that are changing management of type 2 diabetes with reductions in DKD and cardiovascular disease risk (2), but their mechanisms of action are incompletely understood. GLP1-RAs represent a particularly promising avenue for potential treatment as they exhibit a multitude of positive effects on the kidney, heart, and vasculature.

Glucagon-like peptide 1, an incretin hormone made in the L cells of the distal ileum, is postprandially secreted and binds to a seven-transmembrane G protein–coupled receptor to activate beneficial downstream effects (3). Notable downstream effects include increased insulin secretion with β cell proliferation, somatostatin secretion, lipolysis and glucose uptake, natriuresis, and satiety, as well as decreased glucagon secretion, gastric emptying, inflammation, gluconeogenesis, and steatosis (Table 1) (4,5). GLP1-RAs have been developed to capitalize on each of these positive effects and have been primarily used for glycemic management, with the goal of improving postprandial insulin secretion to minimize hyperglycemia and thereby exert heart and kidney protection. Yet, more dedicated kidney outcome trials and trials to define the mechanisms of action of GLP1-RAs beyond their effects on glycemia are needed.

One such ambitious trial that evaluated important composite kidney outcomes as secondary measures was the Effect of Efpeglenatide on Cardiovascular Outcomes in People with Type 2 Diabetes Trial (AMPLITUDE-O). In the AMPLITUDE-O study, 4076 individuals with type 2 diabetes (64.5±8.2 years of age, 33% women, 90% with a history of cardiovascular disease, 32% with a history of eGFR <60 ml/min per 1.73 m^2, and 22% with both cardiovascular disease and a low eGFR) at 344 sites in 28 countries were stratified according to current or potential future use of SGLT2is (*i.e.*, current use at the time of randomization, SGLT2i likely to be added to therapy, or SGLT2i unlikely to be added to therapy) and then randomized 1:1:1 to receive subcutaneous efpeglenatide titrated to either 4 or 6 mg once weekly or placebo. Of note, 15% of participants were taking SGLT2is at baseline, and 21% of the placebo group and 18% of the treatment group were taking SGLT2is at follow-up. The primary outcome of the AMPLITUDE-O study was a major adverse cardiovascular event. Over a median follow-up of 1.81 years, incident major adverse cardiovascular events occurred in 7% of participants receiving active drug and 9% of participants receiving placebo (hazard ratio, 0.72; 95% confidence interval, 0.58 to 0.92; $P<0.001$ for noninferiority and $P=0.007$ for superiority). Composite surrogate kidney outcomes were also assessed, including incident macroalbuminuria and/or a decrease in eGFR, and they were found in 13% of participants receiving efpeglenatide versus 18% of participants receiving placebo ($P<0.001$) (6). Consequently, the authors concluded that efpeglenatide, the first GLP1-RA with a synthetic exendin-4 backbone, exerted a positive effect on the progression of severe cardiovascular disease and DKD in individuals with type 2 diabetes and a known history of cardiovascular disease and/or CKD. Further exploratory analyses have also demonstrated that the safety and efficacy effects of efpeglenatide were independent from concurrent SGLT2i use (7). The effects of GLP1-RAs as a preventative agent in individuals with either absent or very early cardiovascular disease and/or DKD remain unknown.

Current data suggest that GLP1-RAs exhibit kidney-related effects at 1-year follow-up, including attenuation of albuminuria and eGFR decline, independent of

Table 1. Postulated mechanisms of cardiorenal protection of glucagon-like peptide 1 receptor agonists

Kidney	Cardiac	Systemic
Oxygenation • Decreased oxygen consumption • Improved ATP availability	Lipids • Decreased LDL • Decreased triglycerides	Blood glucose concentrations • Decreased blood glucose • Improved insulin resistance
GFR and urine albumin excretion • Improved GFR • Decreased urine albumin-creatinine ratio	Metabolic profile • Decreased weight	Inflammatory response • Decreased inflammatory cytokines
Sodium and fluid balance • Decreased sodium retention • Decreased BP	BP • Decreased BP	Coagulation profile • Improved coagulation profile

effects on glycemia (8), although additional follow-up is needed to further elucidate the long-term eGFR slopes. There also remains a paucity of data detailing the effects of GLP1-RAs on kidney outcomes in people with type 2 diabetes and concurrent DKD; thus, the benefits of treatment must be weighed against potential risks, including incident AKI. Furthermore, understanding of the mechanisms underlying these improvements in kidney function is necessary to guide future treatment development. One such ongoing study is A Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People with Type 2 Diabetes and Chronic Kidney Disease (REMODEL) (NCT04865770), a study that integrates kidney magnetic resonance imaging and transcriptiomic interrogation of kidney tissue obtained from research biopsy to determine the metabolic and molecular effects of the GLP1-RA semaglutide. Additionally, the ongoing Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease (FLOW) study (NCT03819153) is currently collecting data on the effect of GLP1-RAs on dedicated kidney outcomes, including the annual rate of change in eGFR and evidence of a persistent eGFR decline of >50%, and hard outcomes, including development of kidney failure and death from either DKD or cardiovascular disease.

Ensuring adherence with a preventative medication with negative side effects may be met with resistance. GLP1-RAs have a long history of gastrointestinal side effects, including nausea, vomiting, diarrhea, constipation, and bloating. Episodes of AKI have also been described in individuals with type 2 diabetes and CKD. Additionally, GLP1-RAs currently require failure of subcutaneous injections before oral formulations are considered for insurance approval. This stipulation may be prohibitive for individuals with a needle phobia, a highly prevalent condition in pediatrics, or those who are accustomed to taking type 2 diabetes medications available in oral formulations, whereas it may be preferred in others. Consequently, consideration of all medication-related side effects that negatively affect an individual's quality of life is imperative as these factors may determine adherence with prescribed medication regimens. Postmarketing surveillance for long-term safety, efficacy, and standardized clinical outcomes is also necessary for all novel GLP1-RAs.

In summary, AMPLITUDE-O demonstrated efficacy of efpeglenatide in decreasing the progression of both existing DKD, as evidenced by surrogate markers, and cardiovascular disease in individuals with type 2 diabetes, outcomes that are critical in the prevention of long-term mortality. Future directions include exploring methods to minimize gastrointestinal side effects that limit the tolerability of current GLP1-RA formulations, including expansion of the current preclinical movement to conjugate vitamin B12 bound to the GLP1-RA exendin-4 (9) or extension of the duration of active compound release in GLP1-RAs. We do recognize that gastrointestinal side effects may induce a modest amount of weight loss, which would be negated by measures to reduce nausea and vomiting; however, minimizing side effects may ultimately improve medication adherence and outweigh strictly weight-based effects. Additionally, achievement of Food and Drug Administration approval and insurance support of oral GLP1-RA formulations, such as oral semaglutide or nonpeptide small molecules like PF-06882961 (NCT04889157) and LY3502790 (NCT05048719), which are currently in preclinical and phase 1 trials, as first-line agents are essential. Furthermore, synergistic formulations between GLP1-RAs and additional medication classes, including glucagon receptor agonists, glucagon-dependent insulinotropic polypeptide agonists, and/or SGLT2is, retain the potential to greatly amplify metabolic effects through activation of multiple receptor classes simultaneously. Approval of oral GLP1-RA formulations represents a significant first step as it will ensure optimal integration of GLP1-RAs into treatment algorithms for type 2 diabetes as well as further facilitate evaluations to expand the current list of GLP1-RA indications to other conditions and move toward inclusion into important oral combination therapies.

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Author Contributions

K.L. Tommerdahl wrote the original draft and P. Bjornstad and J. Kendrick reviewed and edited the manuscript.

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