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Glucagon-like Peptide Receptor Agonists (GLP-1 receptor agonists): A Powerful Addition to Foundational Therapy Kidney Care in Patients with Type 2 Diabetes Mellitus

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About the Author

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Current State of Therapy in CKD with Type 2 Diabetes Mellitus

There has been a veritable explosion in therapeutic options for patients with chronic kidney disease (CKD) and Type 2 diabetes mellitus (T2DM). For the past several decades, therapy for this condition has been limited to glycemic control, blood pressure control and utilization of angiotensin converting enzyme inhibitors (ACEi's) or angiotensin 2 receptor blockers (ARBs). Recently, the emergence of therapies with organ protective effects has completely altered the landscape of therapy and outcomes for CKD in T2DM.[1] Specifically, several large randomized clinical trials have demonstrated the positive impact of sodium glucose luminal transporter 2(SGLT2) inhibitors on the progression of kidney disease, end-stage kidney disease (ESKD), major adverse cardiovascular events (MACE), cardiovascular (CV) death, hospitalization for heart failure(HHF), all-cause hospitalization, and all-cause mortality.[2] Furthermore, finerenone, a non-steroidal mineralocorticoid receptor (nsMRA), has also been established as a component of foundational kidney therapy in patients with T2DM.[3] A robust clinical trial program demonstrated kidney protection, CV protection and reductions in HHF in patients with CKD and T2DM. International guidelines have been updated to incorporate these agents as standards of care in this group of patients.[4] CKD in T2DM is a complex disease and it stands to reason that multi-targeted therapy could result in better outcomes for patients, similar to the management of patients with chronic heart failure.[1] Those who follow this field will have noted that GLP-1 receptor agonists are listed as a component of guideline-directed management. However, these recommendations are based on the CV protective

effect of these agents.[4] Until recently, it was not clear if GLP-1RA's possessed kidney protective properties. The recent publication of the FLOW trial confirms that GLP-1 receptor agonists are, in fact, kidney protective.[5]

Mechanisms Contributing to the Pathogenesis of CKD in T2DM

The development of kidney disease in patients with T2DM is quite complex. The ensuing discussion will focus on diabetic nephropathy (DN). It is, however, important to recognize that patients with T2DM may develop other kidney diseases apart from DN. For example, patients with T2DM often have overlapping risk factors for small vessel ischemic renovascular disease and may manifest this condition.[6]

Given that dysglycemia is a requirement for the development and progression of DN, not surprisingly, there are metabolic factors that influence DN. First, the advanced glycation end products and glucose metabolism by-products lead to several disturbances, including endothelial dysfunction, dysregulated angiogenesis (similar to diabetic retinopathy), dysregulated cell growth, and the generation of reactive oxygen species. These deleterious alterations have been associated with the development of tissue fibrosis and vascular disease in the kidney. Second, there is evidence to demonstrate that various growth factors become over-expressed, including vascular endothelial growth factor, which leads to abnormal angiogenesis. Third, there are hemodynamic factors that contribute to kidney disease progression in T2DM. These hemodynamic perturbations include systemic hypertension and intraglomerular hypertension. Intraglomerular hypertension appears to be a terminal pathway of many kidney diseases, including DN. It leads to progressive glomerular sclerosis and its development is heralded by albuminuria.[6] It remains an important clinical practice point to highlight that care providers must order an assessment of albuminuria when screening patients with T2DM for CKD. Not only is it an earlier marker of kidney disease when compared with eGFR, but it also portends much worse kidney and CV outcomes. The identification of albuminuria also represents an opportunity for meaningful therapeutic intervention. Many of the existing therapies for CKD in T2DM target intraglomerular hypertension, including ACEi's/ARBs, SGLT2 inhibitors, and finerenone.[7] Finally, there are several proinflammatory and profibrotic factors that lead to kidney inflammation and fibrosis. Clearly, this is a complex interaction of pathogenic processes, and this may explain why multi-targeted therapy is required to best address CKD in T2DM.[6]

GLP-1 receptor agonists have many potential mechanisms that address the pathogenesis of kidney disease in T2DM, and these mechanisms appear to complement other therapies in this space (**Figure 1**). GLP-1 receptor agonists are powerful anti-hyperglycemic agents and additionally have powerful weight loss properties well suited to addressing the derangements caused by AGE's and glucose metabolism byproducts. Additionally, GLP-1 receptor agonists appear to stimulate pathways in the kidney that enable degradation of reactive oxygen species. Both basic science and human research have demonstrated the anti-atherosclerotic properties of this class of medication. It has become apparent that obesity itself can result in kidney disease and there is emerging research to suggest that perinephric fat may result in maladaptive hormone signalling, resulting in negative kidney impacts. Thus, the weight loss properties of these agents could have added an independent benefit in overweight patients. Regarding hemodynamic perturbations, GLP-1 receptor agonists have been shown to reduce systemic blood pressure by approximately 2.2 mmHg. Perhaps, surprisingly, GLP-1 receptor agonists also possess a natriuretic effect that not only reduces blood pressure but may also favourably regulate intraglomerular hypertension. This is thought to be mediated by sodium hydrogen exchanger 3. Interestingly, SGLT2 inhibitors are also thought to interact with this exchanger. The inflammation associated with kidney disease in T2DM may also be at least partially addressed by GLP-1 receptor agonists. Research in this area indicates that GLP-1 receptor agonists downregulate various inflammatory cytokines and prevent the infiltration of inflammatory cells into the kidney.[1] Certainly, this is a various complex area, but GLP-1 receptor agonists have multiple mechanisms that make them well suited to treat kidney disease in T2DM and these mechanisms are likely complemented by other therapies for this condition.

Efficacy of GLP-1 receptor agonists

Cardiovascular protection

Patients with CKD in T2DM are at very high risk of CV disease and this is often their most common cause of mortality. Both clinical trials and

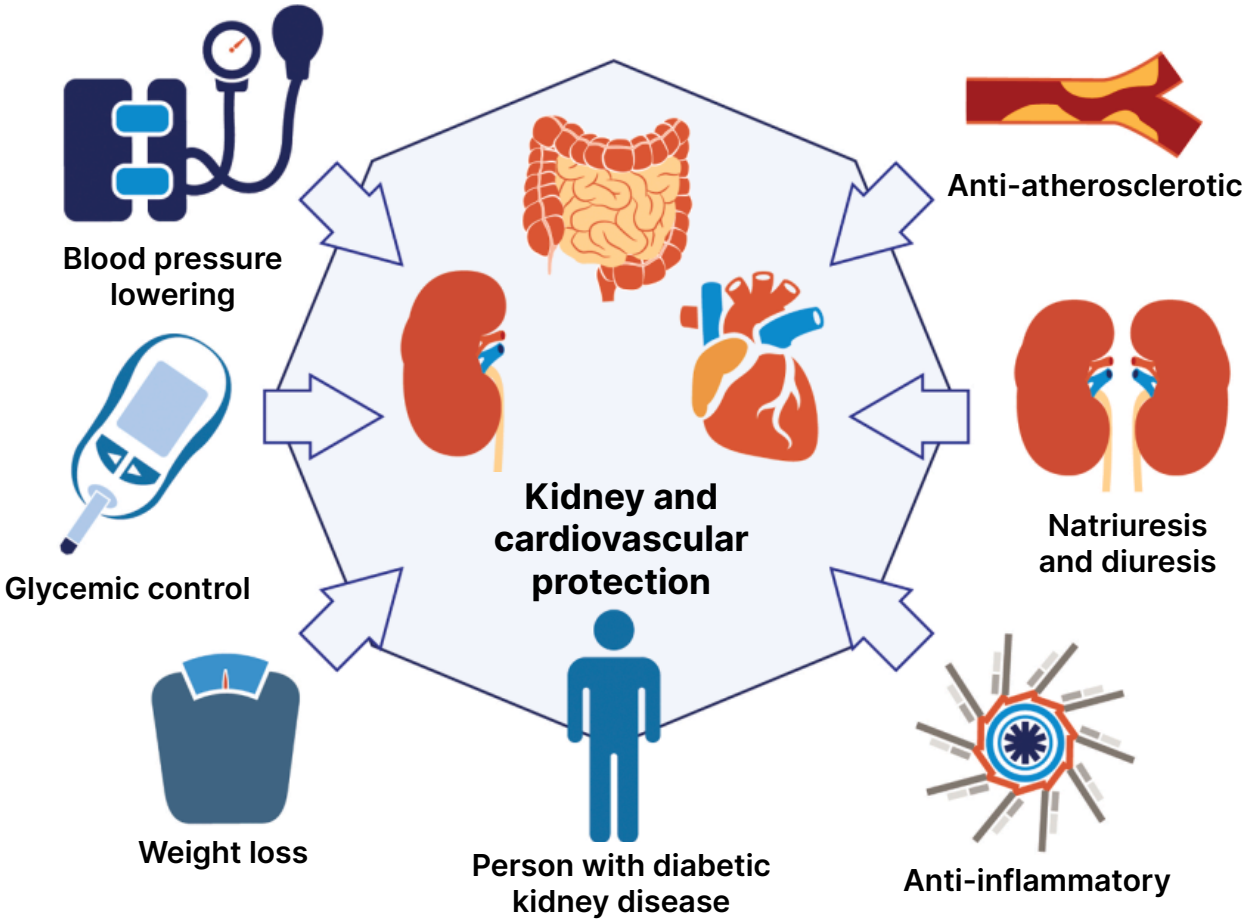

Figure 1. Potential mechanisms by which GLP1-RA confer kidney and cardiovascular protection; *adapted from Michos ED, et al., 2023.*

epidemiologic data indicate that having moderate CKD and albuminuria increases a patient's risk of CV disease by 50%, even in the context of T2DM, which is already a high-risk condition.[8] Albuminuria accounts for a large portion of this risk and beyond predicting the risk of CKD progression and CV disease, it also predicts the development of new HF and worse outcomes for patients with established HF.[9] Therefore, it is important to not only address the risk of progressive CKD, but also, if possible, reduce CV risk. In addition to SGLT2 inhibitors and finerenone, GLP-1 receptor agonists reduce CV risk in many populations, including those with CKD. A meta-analysis of CV outcome trials (CVOT's) from 2021 revealed a 17% (HR 0.83; 0.74–0.93) relative risk reduction in MACE events for patients with an eGFR <60. This data led to the inclusion of GLP-1 receptor agonists in international guidelines.[10] Additionally, GLP-1 receptor agonists have been shown safe in patients with lower GFRs (>15), have low rates of hypoglycemia, are effective at reducing HbA1C, and result in beneficial metabolic benefits, including weight loss.[1]

Kidney protection

A meta-analysis of secondary kidney outcomes from large CVOT's with GLP1-RA therapy demonstrated a reduction in albuminuria but failed to demonstrate statistically significant eGFR preservation. However, the point estimate (HR 0.86; 0.72–1.02) suggested that a reduction in eGFR decline was possible.[10] Therefore, the FLOW trial was conceived and recently completed to definitively examine the effects of semaglutide on kidney function in patients with CKD in T2DM. This trial enrolled 3533 participants with T2DM , an eGFR of 25–75 and albuminuria to be randomized to receive semaglutide in addition to standard of care vs. placebo. The primary outcome of the trial was a composite of kidney failure (ESKD, transplantation, or eGFR <15), a 50% reduction in eGFR from

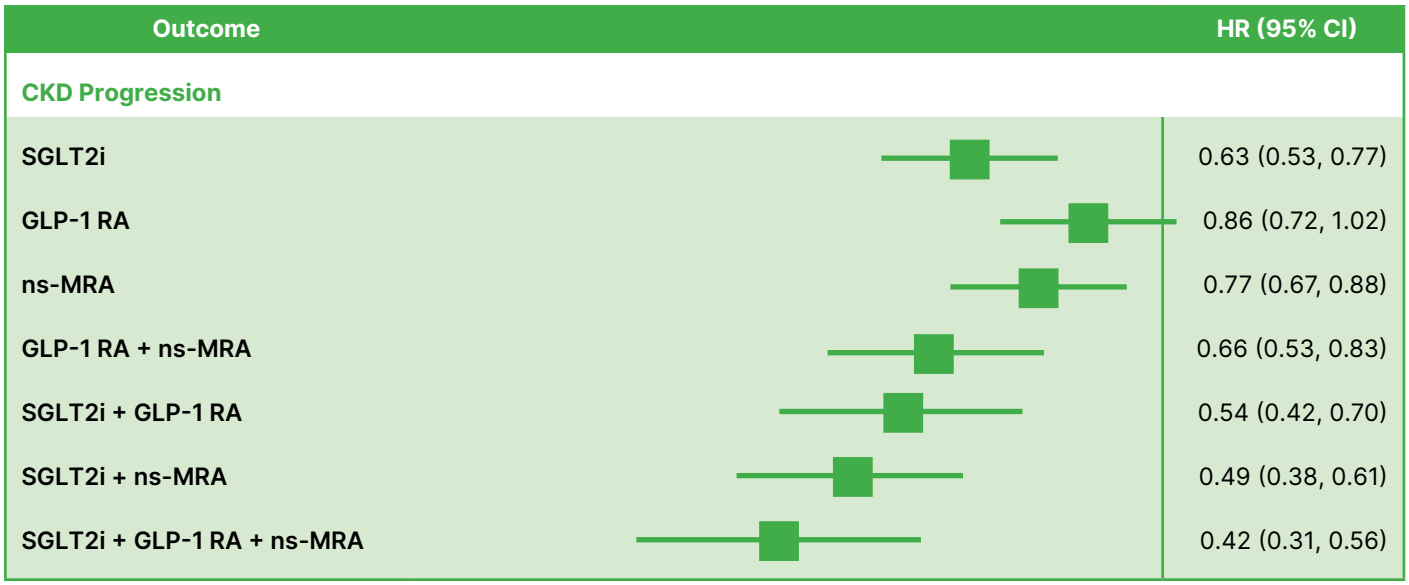

Figure 2. Estimated treatment effects on CKD progression of SGLT2i, GLP-1RA, and ns-MRA, alone and in combination, when added to renin-angiotensin system blockage in patients with type 2 diabetes; adapted from Neuen, BL, et al., 2024.

baseline, kidney-related death, or CV death. Notably, this outcome did not include albuminuria. Greater than 95% of the cohort were on ACEi or ARB therapy. This landmark, first kidney outcome trial of GLP-1 receptor agonists confirmed that semaglutide is a kidney protective agent with 23% (HR 0.76; 0.66–0.88) relative risk reduction in the primary outcome. Given that GLP-1 receptor agonists are known to be CV protective, the primary outcome was converted to a kidney-specific outcome by removing CV death from the analysis and this kidney-specific outcome remained statistically significant in favour of semaglutide (HR 0.79; 0.66–0.94). Additionally, eGFR slope was preserved by 1.16 mL/min/year, which is significant.[5] To put this into context, ACEi's or ARBs have a 0.75–1.0 mL/min/year preservation of eGFR slope. A preservation of 0.75 mL/min/year is accepted as a surrogate for delaying ESKD.[11,12] Therefore, this trial confirms that semaglutide is kidney protective and that GLP-1 receptor agonists should be prioritized for patients with CKD in T2DM and risk factors for CV disease. Reassuringly, the FLOW trial also demonstrated important and significant reduction in CV death, MACE and all-cause mortality in this high-risk kidney group.[5]

Conclusion

As clinicians, we have entered the HF realm where we have 4 evidence based pillars of care for CKD therapy in T2DM. It is incumbent upon the community of care providers (primary care, diabetes educators, nurses, pharmacists, and specialists) to pursue the implementation of guidelines to direct quadruple therapy (ACE/ARB, SGLT2 inhibitor, nsMRA and GLP-1 receptor agonist) in all patients with CKD and T2DM where indicated. Recent modelling analyses suggest that combination therapy has meaningful and sequential reductions in kidney, CV and mortality outcomes (**Figure 2**).[13] Furthermore, a recent meta-analysis of the landmark trial in T2DM indicates that addition of an SGLT2 inhibitor in the presence or absence of GLP-1 receptor agonist therapy has the same beneficial effects on these outcomes.[14] This means that current data suggests that the effects of these therapies are not diminished when added to other outcomes reducing agents as background therapy. Care providers often have questions about the sequencing of these therapies. However, this is likely not as important as ultimately initiating patients on guideline-directed medical therapy for CKD.[15] Patient and clinical priorities may also dictate this sequence. For example, if a patient is quite dysglycemic, GLP-1 receptor agonist and SGLT2 inhibitor therapy may be prioritized. If the patient is primarily concerned with weight loss, a GLP-1 receptor agonist would likely be added sooner. Therefore, tailoring of individualized approaches for patients may result in better success and compliance with the delivery of this package of care. As an easy reminder, if a patient has residual albuminuria, this represents an opportunity to add additional therapies to further reduce the patient's kidney risk.

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