Emerging role of GLP-1RAs in the management of diabetic kidney disease

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Diabetes is a leading cause of chronic kidney disease (CKD), affecting around 40% of all patients with diabetes.[1] It is estimated that almost one in three people who need dialysis or a kidney transplant have diabetes, and one in five people with diabetes will need treatment for kidney disease during their lifetime. The economic impact of CKD is considerable, and is thought to cost the NHS £7 billion annually.[2]

Until recently, interventions targeting the management of CKD in diabetes have largely relied on intensive risk factor control and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors. Although several other therapies have been evaluated for CKD management, many of these were either ineffective or had to be abandoned for safety concerns. In the last few years, trials evaluating sodium glucose transporter 2 inhibitors (SGLT2i) and selective non-steroidal mineralocorticoid receptor agonists (MRAs) have demonstrated significant reductions in the risk of cardiovascular- and renal-specific endpoints in patients with diabetes and CKD.[3,4] The availability of these agents has reduced but not eliminated the excess cardiovascular and renal risk observed in patients with CKD and diabetes, thus underscoring the need for additional therapies.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are potent glucose-lowering agents approved initially for treatment of type 2 diabetes (T2DM). Subsequent large cardiovascular (CV) outcome trials, particularly with the longer-acting GLP-1Ras, have shown significant CV benefits.[3,5] The substantial reductions in albuminuria seen in these studies prompted interest in potential role of GLP-1RAs in the management of CKD.

FLOW is the first dedicated renal outcome trial that investigated the effect of semaglutide on renal outcomes.[6] In this multicentre trial, a total of 3,533 participants with T2DM and CKD were randomised to either once-weekly semaglutide or placebo in addition to standard care. Over a period of 3.4 years, those allocated to semaglutide had a 24% (95% CI 0.66–0.88; p=0.0003) relative risk reduction in the composite primary outcome (time to first occurrence of major kidney outcomes, including onset of persistent ≥50% reduction in eGFR compared to baseline, kidney failure, kidney-related death or CV death) compared with placebo. Treatment with semaglutide was also associated with significant benefits across a number of pre-specified secondary outcomes, including a 21% reduction in the risk of kidney-specific endpoints, an 18% reduction in a first major CV event and 20% lower all-cause mortality. The benefits of semaglutide were consistent across all subgroups (age, sex, BMI, diabetes duration, HbA_{1c} and baseline use of SGLT2i). Semaglutide also had a favourable effect on the rate of decline in eGFR (mean difference between groups of 1.16ml/min/year (95% CI 0.86–1.47; p<0.001) and 32% less albuminuria compared to placebo. Overall, fewer patients treated with semaglutide experienced serious side effects (49.6% versus 53.8%), compared to placebo.

The findings of the FLOW study strengthen the growing evidence around the reno-protective effects of GLP-1RAs. Pre-specified secondary analysis of the SELECT study, a large randomised controlled trial comparing semaglutide 2.4mg once weekly with placebo in obese adults with known cardiovascular disease (CVD) and without diabetes, reported a 22% risk reduction in renal endpoint, driven largely by the ≥50% decline in eGFR and progression to macroalbuminuria.[7]

A recent meta-analysis of 11 trials, involving 85,373 participants, concluded that in participants with T2DM, GLP-1RAs reduced the composite kidney outcome by 18% compared with placebo (hazard ratio [HR] 0.82, 95% CI 0.73–0.93), kidney failure by 16% (HR 0.84, 0.72–0.99), MACE by 13% (HR 0.87, 0.81–0.93), and all-cause death by 12% (HR 0.88, 0.83–0.93).[8] These findings were consistent with a previously published meta-analysis looking at the effect of GLP-1RAs on cardiovascular and kidney outcomes in patients with T2DM, with a 21% reduction in composite renal endpoint associated with GLP-1RA treatment.[5] In a pre-specified analysis of the SURPASS-4 study looking at the effects of the dual glucose-dependent insulinotropic polypeptide (GIP)/ GLP-1RA tirzepatide, the occurrence of the composite kidney endpoint was significantly lower in those treated with tirzepatide compared with those who received insulin glargine (HR 0.58 [95% CI 0.43 to 0.80]).[9] Tirzepatide also significantly lowered albuminuria compared to insulin glargine (between-group difference -31.9% [-37.7 to -25.7]).

The precise mechanisms through which GLP-1RAs exert their

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reno-protective effects remain unclear.[10] Reductions in albuminuria would suggest alterations in glomerular haemodynamics and function. Weight loss, improvement in glycaemic control and systolic blood pressure may all be contributory but do not explain the magnitude of the benefit seen with these agents. Certainly, the findings from the SELECT study suggest that the benefits with semaglutide are independent of glucose control and that other mechanisms including reduction in renal oxidative stress, anti-inflammatory and anti-fibrotic effects may be involved.[10] The ongoing REMODEL study will hopefully provide more insights into these mechanisms.[11]

What are the implications of these findings for clinical practice? First, the ADA/EASD consensus guidelines and KDIGO guidelines recommend using GLP-1RAs in patients with CKD when SGLT2is are not tolerated or as an addition where there is need to achieve individual glycaemic targets.[12,13] Results from the FLOW study provide greater justification for this approach, particularly in those with established CVD/high CV risk or CKD. Second, considering that the reno-protective mechanisms of SGLT2is, selective non-steroidal MRAs and GLP-1RAs are thought to be complementary, it would strengthen the argument for them to be used concurrently. This has not been adequately addressed in clinical trials, however, and needs further research. Third, much of the evidence around reno-protection comes from patients with eGFR>25ml/min/year and with albuminuria. Whether these benefits extend to those with lower eGFR is not known. Finally, in clinical trials, GLP-1RAs have been generally well tolerated. Nevertheless, concerns about safety remain, particularly around the risk of progression of retinopathy, which is common amongst patients with CKD.

The rapidly changing therapeutic landscape and accumulating evidence for the role of GLP-1RAs in preventing and delaying CKD progression offer considerable hope for patients with diabetes. The goal now is to translate this evidence into clinical practice.

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