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GLP-1 Receptor Agonists – The Newest Pillar for Diabetic Kidney Disease

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GLP-1 receptor agonists (GLP1-RA) have transformed the management of obesity and are widely prescribed for treatment of diabetes to prevent and treat cardiovascular disease (CVD). Chronic Kidney Disease (CKD) is a common complication of diabetes and can lead to accelerated atherosclerotic cardiovascular disease, congestive heart failure, and progression of CKD leading to end-stage kidney disease requiring dialysis.

In the last 10 years, a number of approved therapies have been found to be safe and effective for management of diabetic kidney disease (DKD), and in particular, sodium glucose co-transport inhibitors (SGLT2i) have revolutionized treatment. More recently, non-steroidal mineralocorticoid receptor antagonists (nsMRA,) like finerenone, have been studied and also found to further reduce CVD events and CKD progression by 20-25 % on a background of renin-angiotensin aldosterone system inhibition (RAASi) or RAASi and SGLT2i therapy. As such, nephrology has embraced a pillar-based paradigm for CKD management, similar to the framework used in heart failure.

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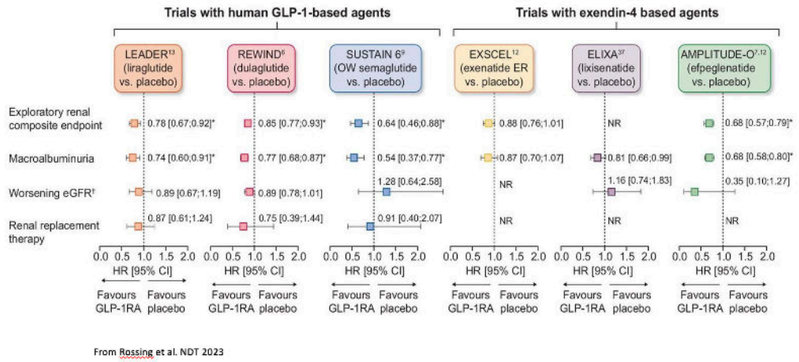
GLP1s for prevention of adverse kidney outcomes

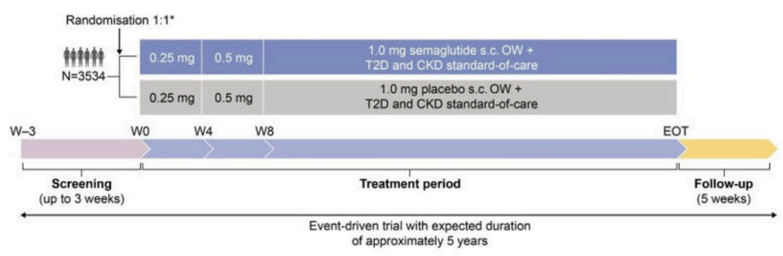
Several large cardiovascular outcomes in trials in individuals with preserved kidney function have studied the effects of GLP-1 RA on CKD progression (Figure 1). In the general population, data from the LEADER, REWIND and SUSTAIN-6 trials all showed a lower rate of progression to A3 albuminuria (> 300 mg/g or 33.6 mg/mmol) with the use of GLP-1 RA. However, these trials did not include patients at high-risk of CKD progression, and as such, had an insufficient number of CKD progression outcomes (> 40 % decline in eGFR or kidney failure). A dedicated kidney outcomes trial studying GLP RA was needed to definitively establish the role of class in the treatment of DKD.

Figure 1: Meta-Analysis of Kidney Outcomes from GLP-RA CV Outcome Trials



From Rossing et al. NDT 2023

Figure 2: FLOW - Study Design



Overview of the FLOW study

In order to provide conclusive evidence for the efficacy and safety of GLP1 agonists for the treatment of DKD, the FLOW trial was conducted, and randomized 3,533 participants at high-risk of CKD to treatment with semaglutide (1 mg SC once weekly) or placebo (Figure 2). High Risk CKD was defined as an eGFR 50-75 ml/min with urine albumin to creatinine ratio (UACR) > 300 mg/g, or an eGFR 25-50 ml/min with a UACR > 100 mg/g (Figure 2). The primary outcome was a composite of kidney failure (eGFR < 15 ml/min or receipt of dialysis or transplant) or death from cardiovascular causes. Key secondary outcomes included major adverse cardiovascular events and death from any cause. The trial was stopped early due to efficacy after 570 outcomes had accrued with a mean follow up of 3.4 years. An additional 171 outcomes occurred after the decision to stop had been made, allowing a total of 741 outcomes to occur in this high-risk population.

FLOW recruited from Asia, Europe and North America. The mean age of the participants was 66, and the average HbA1C was 7.6 %. More than 60 % of participants were on insulin at baseline. RAASi use and statin use were high (95 % and 80 % respectively), but only 15 % of the participants were on SGLT2i at baseline. The mean eGFR was 47 ml/min with a median urine ACR of 567 mg/g. More than 22 % of participants had a history of myocardial infarction or stroke at baseline, and heart failure was present in 19 % of individuals.

The primary outcome occurred in 331 participants receiving semaglutide, compared to 410 participants receiving placebo (HR 0.76, 95 % CI). There was an 18 % reduction in the risk of myocardial infarction, a 29 % reduction in the risk of CV death, and a 20 % reduction in all-cause mortality. The rate of decline of kidney function (eGFR slope) was 1.16 ml/min/year slower in the semaglutide group compared with placebo, with a 32 % reduction in UACR. A reduction in eGFR slope of > 0.75 ml/min/year is strongly associated with long term benefit in slowing CKD progression.

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There were no important differences in efficacy or safety by subgroups of age, sex, race, BMI or duration of diabetes. Importantly, efficacy was preserved in all strata of eGFR or urine ACR, suggesting that semaglutide has broad benefits in patients with CKD. Adverse events were similar in both groups and the medication was well tolerated overall.

Implications for Clinical Practice

The results of FLOW are convincing, and firmly add semaglutide as a fourth pillar in the treatment of DKD. Physicians treating these patients (family physicians, endocrinologists, cardiologists and nephrologists) need to be aware of these results and should prescribe all four pillars in patients at high-risk of CKD progression. At the same time, it is important to recognize considerations of cost/market access, polypharmacy, side effects/interactions and shared decision making when facing a treatment paradigm that includes 4 different classes of drugs. In addition, the approach to prescribing, whether that's sequential titration, two drugs at a time, or rapid sequence titration also deserves consideration.

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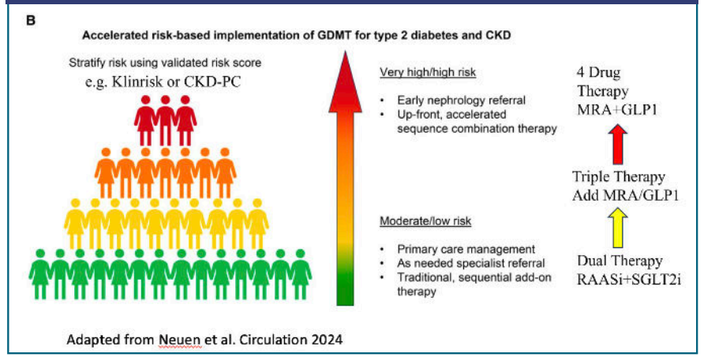
We believe that a risk-based approach to both the speed of titration and intensity of treatment can be helpful in the management of patients with DKD. RAASi and SGLT2i can be considered foundational therapy for these patients and should be prescribed for all patients with reduced eGFR or albuminuria (Figure 3). Additional agents should be added after considering residual risk, either through measurement of albuminuria alone or in combination with validated risk prediction tools. We have developed two of these tools (KFRE and KLINRISK) which include Canadian data, are externally validated, and available for clinical use.

Patients identified as intermediate or high risk for CKD progression, after starting RAASi and SGLT2i therapy, should also be considered for treatment with nsMRA, GLP-1 RA, or both. Patients with higher BMI, hyperkalemia, poor glycemic control, or those with obesity may start with the GLP-1 RA, while those with lower BMIs and adequate glycemic control should start with a nsMRA. Additional considerations such as patient preference for oral or injectable therapy as well as side effect profile/tolerability will play a role in shared decision making.

Figure 3: Foundational Therapies for Diabetic Kidney Disease



Adapted from Neuen et al. Circulation 2024

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After initial treatment with one of these agents, risk stratification could be repeated, and if residual risk remains, further treatment with another agent can be initiated to maximally reduce the risk of CV and kidney events. To date, there is no evidence of any negative interactions between the four pillars of therapy, and in fact there may even be potential benefit from a background of SGLT2i therapy to reduce the risk of hyperkalemia from finerenone.

Future Direction - Non-diabetic CKD

It is important to note that small proof of concept studies of semaglutide, with up to 6-month follow-up, demonstrate similar efficacy in albuminuria reduction in patients with obesity and non-diabetic kidney disease. Larger ongoing trials with dedicated and prespecified CKD populations and endpoints studying other GLP-1/GIP agents are ongoing and will provide definitive evidence of efficacy. If these trials are positive, they would add to similar confidence in utilizing GLP-1 RA in non-diabetic CKD, similar to both RAASi and SGLT2i. A study of finerenone is non-diabetic CKD is also ongoing and set to report in 2025.

Conclusion

In summary, the findings from the FLOW trial provide landmark evidence for the use of semaglutide as a pillar in the management of diabetic kidney disease. Patients with DKD are set to gain additional cardiovascular and kidney benefits with the use of multiple pillars of therapies that are both safe and well-tolerated. As use of these drugs increases in Canada, we expect an eventual decline in the prevalence of end-stage kidney disease, which would be cause for celebration amongst patients, physicians, and our healthcare system.

LMC Healthcare

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November is Diabetes Awareness Month, a time when we honour all those involved in the fight against diabetes – patients, their families, healthcare professionals, researchers and staff.

Managing diabetes continues to be a struggle for millions of Canadians across the country. Whether it access to specialists, fragmented care or lack of coverage, many Canadians still don't have the support they need to manage their chronic condition with confidence. That's why LMC's core purpose is centered around Making Healthy Easier for those living with diabetes and transforming diabetes care to make it more accessible, comprehensive, proactive and patient-centric than ever before.

Thank you for everything you do, day in and day out, to care for your patients and support our communities. It is all of you who allow LMC's unique care model to deliver life-changing care and support to over 70,000 patients living with diabetes each year.

HAPPY DIABETES AWARENESS MONTH!

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