Keeping kidneys FLOWing – semaglutide improves renal outcomes

Semaglutide 1 mg demonstrated a 24% reduction in major chronic kidney disease (CKD) events, including renal or cardiovascular death, in the FLOW trial in people with type 2 diabetes and CKD, presented at the American Diabetes Association's 84th Scientific Sessions and published in the *New England Journal of Medicine* and *Nature Medicine*. This is the first dedicated randomised controlled trial of kidney outcomes with a GLP-1 receptor agonist, and the study was stopped early due to efficacy after a median follow-up of 3.4 years. Secondary endpoints favoured semaglutide and demonstrated a significant 18% lower risk of major cardiovascular events (non-fatal myocardial infarction or stroke, and cardiovascular death) and a 20% lower risk of death from any cause, as well as less steep eGFR decline in those treated with semaglutide compared to placebo.

Pam Brown
GP in Swansea

Chronic kidney disease (CKD) is defined as eGFR <60 mL/min/1.73 m^2 persisting for at least 90 days or a urinary albumin creatinine ratio (uACR) of ≥30 mg/g (≥3 mg/mmol). People with type 2 diabetes are at increased risk of developing CKD, and up to one third of people with diabetes in the UK have this comorbidity. CKD increases the risk of progression to kidney failure and of cardiovascular events and death (NICE, 2021).

ACE inhibitors, angiotensin receptor blockers and some SGLT2 inhibitors have been demonstrated to slow progression of renal disease in those with CKD, with or without type 2 diabetes, and finerenone has demonstrated benefit in those with CKD and type 2 diabetes (NICE, 2023). However, residual risk of CKD progression and cardiovascular events remain even when these drugs are used optimally; therefore, additional drug classes are being explored to identify potential benefit.

The FLOW study

In the FLOW (Evaluate Renal Function with Semaglutide Once Weekly) double-blind, randomised controlled trial, 3533 people with type 2 diabetes, CKD and HbA_{1c} <86 mmol/mol (10.0%) were randomised to semaglutide 1 mg (titrated up over 12 weeks) or placebo (Perkovic et al, 2024). Participants were followed for a median of 3.4 years before the trial was stopped early due to evidence of benefit. Participants had either:

- eGFR 50–75 mL/min/1.73 m^2 and uACR >300 mg/g to <5000 mg/g (approximately 30–500 mg/mmol), or
- eGFR 25 to <50 mL/min/1.73 m^2 and uACR >100 to <5000 mg/g (approximately 10–500 mg/mmol).

Eighty percent of both the semaglutide and placebo groups had eGFR <60 mL/min/1.73 m^2, with a mean eGFR of 47, and mean HbA_{1c} was 7.8% (around 62 mmol/mol) at baseline. Mean age was 66 years, more than 65% of the population identified themselves as White and around 12% were current smokers.

The primary outcome was the first occurrence of a composite of major kidney events:

- Onset of kidney failure (dialysis, transplantation or eGFR <15 mL/min/1.73 m^2).
- At least a 50% reduction in eGFR from baseline.
- Death from kidney-related or cardiovascular causes.

Prespecified secondary outcomes were tested hierarchically:

- Rate of decline of eGFR.
- Rate of major adverse cardiovascular events (MACE).
- All-cause mortality.

Results

Findings from the FLOW trial were published in the *New England Journal of Medicine* and *Nature Medicine* and presented at the American Diabetes Association's 84th Scientific Sessions.

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Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes

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Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial

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There was a significant 24% reduction in the composite primary outcome in the semaglutide group compared with those taking placebo, with first events occurring in 5.8 versus 7.5 people per 100 person-years of follow-up, such that 20 people would need to be treated for 3 years to prevent one primary event.

When only the renal-specific components of the primary outcome were considered, these were 21% lower in the semaglutide than the placebo group. Cardiovascular death showed a 29% reduction compared with the placebo group.

All secondary outcomes favoured semaglutide:

- The eGFR slope was less steep with semaglutide than with placebo.
- Risk of 3-point MACE was 18% lower in the semaglutide group.
- All-cause mortality was 20% lower in the semaglutide group than with placebo.

Overall, 45 people would need to be treated for 3 years to prevent one major cardiovascular event in a population similar to that in the study, and 39 would need to be treated for 3 years to prevent one death from any cause. However, it is important to understand that this was a population at very high risk of renal and cardiovascular events, and the authors warn that the outcomes in this study may not be generalisable to other populations.

Other efficacy outcomes at 104 weeks included:

- A 40% reduction in uACR with semaglutide versus 12% with placebo.
- A 4.10 kg greater mean weight loss with semaglutide versus placebo.

At the time of recruitment to the study, SGLT2 inhibitors were not specifically licensed for use to reduce CKD progression, so only 15% of participants were taking these. Thus, FLOW had limited power to test effects in those on SGLT2 inhibitors. There was no heterogeneity detected in semaglutide's renal, cardiovascular or mortality benefits, or in MACE and all-cause mortality, between those using or not using SGLT2 inhibitors (Mann et al, 2024).

Although serious adverse event rates were slightly lower in the semaglutide than the placebo arm, these occurred in around 50% in each group. Events leading to discontinuation occurred in 13.2% of the semaglutide group and 11.9% of the placebo group, and 26% of participants overall permanently discontinued semaglutide or placebo.

Several adverse events of special interest were prespecified. Gallbladder disease, retinopathy and severe hypoglycaemia did not differ significantly between the semaglutide and placebo groups.

The authors conclude that the renal benefits cannot solely be explained by weight reduction or risk factor reduction, although these may contribute, and the mechanisms of kidney protection are likely to be multifactorial and may include decreased oxidative stress, inflammation and fibrosis in the kidney.

Implications for practice

Most of the people we support with type 2 diabetes and CKD will already have received optimal therapy with the highest tolerated and licensed dose of ACE inhibitor/ARB and an SGLT2 inhibitor, and many will also be prescribed finerenone. However, people discontinue drugs and do not always share this information with their healthcare providers. This is a good reminder to optimise identification, coding and management of people with CKD (with and without type 2 diabetes) in our practices, and to check at each contact whether any drugs have been discontinued.

The ADA/EASD consensus on glycaemic management algorithm already includes GLP-1 receptor agonists with cardiovascular benefit as an option for people with CKD when SGLT2 inhibitors are contraindicated or not tolerated, in order to reduce the risk of cardiovascular disease (Davies et al, 2022). This is the first published trial to study the impact of a GLP-1 RA in a population with significant CKD, and it supports the renal benefits that had previously been suggested in some of the GLP-1 RA cardiovascular outcome trials. These findings give us another very effective tool to reduce risk of CKD progression and cardiovascular disease in this high-risk population.

The FLOW study highlights the risks of CKD progression, cardiovascular disease and death in those with type 2 diabetes and CKD, and the significant benefits of the pillars of treatment: ACE inhibitors/ARBs, SGLT2 inhibitors, finerenone and, now, semaglutide. Our challenge as clinicians is to create systems and time to support people to initiate and stay on these effective treatments. ■

References

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