Get With the FLOW!

By Ben Catanese and Matthew A. Sparks

The FLOW trial represents the first prospective glucagon-like peptide-1 (GLP-1) receptor agonist randomized clinical trial with kidney events as the primary outcome. It is akin to the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial for sodium-glucose cotransporter-2 inhibitors (SGLT2is) in ushering a new agent to slow the progression of kidney diseases in diabetes. Results were presented at the 2024 European Renal Association Congress in Stockholm, Sweden, and published in *The New England Journal of Medicine* (1).

The Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial enrolled 3533 participants across 387 sites in 28 countries from June 2019 through May 2021. Participants with type 2 diabetes were randomized to once-weekly semaglutide versus placebo. To qualify for the trial, the required estimated glomerular filtration rate (eGFR) was between 50 and 75 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio (UACR) of >300 mg/g Cr and <5000 mg/g Cr or between 25 and <50 mL/min/1.73 m^2 with a UACR of >100 mg/g Cr and <5000 mg/g Cr. Further eligibility requirements included being treated with a stable maximum dose (or highest dose without side effects) of a renin-angiotensin system inhibitor (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Although not an inclusion or exclusion criteria, use of SGLT2i was implemented to stratify patients as they were randomized in the trial. Approximately 15% of patients in the trial were being treated with a SGLT2i. Lastly, there was no weight inclusion criteria, and mean body mass index in the study was 32.0 kg/m^2.

The trial was stopped early for efficacy following a prespecified interim analysis triggered in October 2023 when two-thirds of the total planned number of primary outcome events had occurred. The median participant follow-up period was 3.4 years. The primary outcome was a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 mL/min/1.73 m^2 sustained for ≥28 days), at least a 50% reduction in the eGFR from baseline (for ≥28 days), or death from kidney-related or cardiovascular causes. The risk of the primary outcome was 24% lower in the semaglutide group as compared with the placebo group (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.66–0.88). The significant reduction in events was maintained when cardiovascular death was separated from the kidney-specific components (HR, 0.79; 95% CI, 0.66–0.94). The secondary outcomes were tested hierarchically, and all significantly favored semaglutide.

Among the secondary outcomes was the mean annual slope of eGFR, which was significantly less steep with semaglutide as compared with placebo (–2.19 versus –3.36 mL/min/1.73 m^2). To confirm this result, a cystatin C-based eGFR was used to show a similar significant difference in the loss of kidney function favoring semaglutide. This was an important analysis, as muscle mass can decrease with weight loss associated with GLP-1 receptor agonist use, thus theoretically leading to a misleading drop in creatinine-based eGFR. Notably, weight loss was not as robust in other GLP-1 receptor agonist trials but still significantly different between the study arms. By week 104, the semaglutide group had 5.6 kg weight loss as compared with 1.5 kg in the placebo group.

Notably, the FLOW trial examined only patients with type 2 diabetes and presumed diabetic kidney disease. However, a prespecified analysis of long-term kidney outcomes in the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) trial was also presented at the 2024 European Renal Association Congress and published in *Nature Medicine* (2). The SELECT trial randomized 8803 patients with obesity (body mass index, ≥27 kg/m^2), established cardiovascular disease, and no diabetes to semaglutide versus 8801 patients to placebo with the primary outcome of major adverse cardiovascular events. The kidney composite endpoint used in this prespecified analysis included death from kidney diseases, initiation of chronic kidney replacement therapy, onset of persistent eGFR <15 mL/min/1.73 m^2, persistent ≥50% reduction in eGFR, or onset of persistent macroalbuminuria (UACR, ≥300 mg/g). The occurrence of the prespecified kidney composite endpoint was lower with semaglutide (1.8%) as compared with placebo (2.2%; HR, 0.78; 95% CI, 0.63–0.96) but notably, was also low overall in general. Furthermore, kidney function was mostly preserved, as only one-fifth of patients had an eGFR <60 mL/min/1.73 m^2 to start, and the average decline at 104 weeks was –0.86 mL/min/1.73 m^2 in the semaglutide arm and –1.61 mL/min/1.73 m^2 in the placebo arm. The reduction in the endpoint was driven by a persistent ≥50% reduction in eGFR and onset of persistent macroalbuminuria.

The FLOW trial has ushered in another medication that nephrologists can add to their list of options to treat diabetic kidney disease. The endpoints selected in this trial are meaningful to patients, and the reduction in cardiovascular-related death is also particularly important considering this is the most common cause of death among patients with chronic kidney disease (3). As we continue to add more medications that improve outcomes for patients with diabetic kidney disease, we will need to decide how we go about giving patients these medications, and we will need further trials to determine if there are benefits to being treated with as many kidney-protective medications as there are to offer—SGLT2is, renin angiotensin system inhibitors, mineralocorticoid receptor antagonists, and now GLP-1 receptor agonists. Currently, initiation of each of these medications will need to be individualized for patients, as each medication has its strengths and adverse effects to be considered.

Although the FLOW trial and the secondary analysis of the SELECT trial have demonstrated important kidney benefits of semaglutide, the kidney-protective effects of other GLP-1 receptor agonists are less well known, as there have not been prospective trials with kidney outcomes, and it is unclear whether the benefits of these medications are a class effect or are medication specific. There do not appear to be any other ongoing large kidney outcome trials researching GLP-1 receptor agonists or newer dual or triple agonists, but it will be exciting to see in the future the results of smaller ongoing trials and hopefully additional large prospective clinical trials with kidney outcomes. ■

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The authors report no conflicts of interest.

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