ADA 2024: The year of the GLP-1 receptor agonists – and fenofibrate

The American Diabetes Association's 84th Scientific Sessions were held on 21–24 June in Orlando, FL, USA. GLP-1 receptor agonists featured heavily in the most highly publicised sessions, particularly semaglutide and the GIP/GLP-1 receptor agonist tirzepatide. However, an older and commonly used therapy, fenofibrate, also made headlines, showing promise in slowing the progression of diabetic retinopathy. In this report from the Sessions, Pam Brown highlights the latest developments of interest to primary care.

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 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.

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.

- For a deeper analysis of the findings, see our accompanying *Diabetes Distilled*.
- Read the full *NEJM* study.
- Read the full *Nature Medicine* study.

Benefits of tirzepatide in obstructive sleep apnoea

The dual GIP/GLP-1 receptor agonist tirzepatide shows promise as a treatment for obstructive sleep apnoea (OSA), both alone and in combination with continuous positive airway pressure (CPAP), according to findings presented at the Scientific Sessions and published simultaneously in the *New England Journal of Medicine*.

SURMOUNT-OSA comprised two phase 3 trials of tirzepatide in people with moderate to severe OSA (apnoea–hypopnoea index [AHI] ≥15 events/hour) and obesity, but without diabetes. One trial enrolled people who were unable or unwilling to use CPAP, while the other included people on CPAP.

After 1 year of treatment with tirzepatide or placebo, both in addition to regular diet and lifestyle counselling sessions, AHI reduced from 53 to 28 events/hour in tirzepatide recipients who were not using CPAP, and from 46 to 17 events/hour in the CPAP group. In comparison, placebo recipients had significantly lesser reductions of around 5 events/hour.

Mean body weight was reduced by 18–20% in the tirzepatide groups, and there were significant reductions in systolic blood pressure and C-reactive protein levels. Patient-reported outcome measures showed significant improvements in sleep quality and daytime sleepiness; however, in an accompanying *NEJM* editorial, Patel (2024) cautions that the measurements used have not yet been validated for use in treatment studies and that the improvements were not necessarily clinically significant in their extent.

Adverse events were mostly gastrointestinal in nature and mostly occurred during tirzepatide dose escalation. Serious adverse events occurred in 7.5% of participants overall, with similar rates between the tirzepatide and placebo groups. Two confirmed cases of acute pancreatitis occurred in the tirzepatide group, and there were no cases of medullary thyroid cancer.

This study was limited by its short duration, and longer studies will be required to determine whether the observed improvements in AHI translate to improved clinical outcomes, including cardiovascular disease, over time. The ongoing SURMOUNT-Morbidity and Mortality in Obesity trial should shed further light on this.

- Read the study results in full.

Fenofibrate reduces diabetic retinopathy progression

Results from the LENS (Lowering Events in Non-proliferative Retinopathy in Scotland) trial, presented at the Scientific Sessions and published in *NEJM Evidence*, suggest that finerenone may reduce the progression of diabetic retinopathy.

Diabetic retinopathy is the second most common cause of vision loss in working-age adults in the UK. Apart from the effective management of glucose levels, there have been no treatment options available for early retinopathy. Cardiovascular outcome trials with people with type 2 diabetes, however, have previously suggested fenofibrate might reduce risk for worsening of the condition. LENS set out to assess this relationship.

The trial was conducted within Scotland's Diabetic Eye Screening (DES) programme, which provides regular retinal imaging nationally to all people with diabetes aged 12 years or over. It included 1151 adults with type 1 or type 2 diabetes with early diabetic retinopathy or maculopathy, who were randomised to receive either 145 mg fenofibrate tablets or placebo. The primary outcome was a composite of developing referable diabetic retinopathy or maculopathy (based on DES grading) or requiring treatment with laser, intravitreal injection or vitrectomy.

Over a median of 4.0 years, progression to the primary outcome occurred in 22.7% of the fenofibrate group and 29.2% of the placebo group (hazard ratio [HR] 0.73; 95% CI 0.58–0.91). Any progression of retinopathy or maculopathy occurred in 32.1% of the treatment group and 40.2% of the placebo group (HR 0.74; 95% CI 0.61–0.90). Development of macular oedema occurred in 3.8% of those treated with fenofibrate compared with 7.5% of the placebo group (HR 0.50; 95% CI 0.30–0.84). Serious adverse event rates were similar between the groups.

Dr David Preiss, one of the investigators, hopes that fenofibrate may provide a valuable addition to treat people with early-to-moderate diabetic retinopathy.

- Read the study in full.

Semaglutide effective treatment for HFpEF in people with type 2 diabetes

Results from the STEP-HFpEF-DM trial presented at the Scientific Sessions suggest that the GLP-1 receptor agonist semaglutide is effective for treatment of obesity-related heart failure with preserved ejection fraction (HFpEF) in people with type 2 diabetes.

Previous research had suggested semaglutide was effective in people without diabetes who had obesity and HFpEF (Kosiborod et al, 2023); however, there had been concerns that efficacy might be lower in people with type 2 diabetes, given that the weight-lowering effects of semaglutide are reduced in people with diabetes versus those without the condition.

A total of 616 adults with type 2 diabetes, obesity and HFpEF (left ventricular ejection fraction of at least 45%) were randomised to semaglutide 2.4 mg or placebo for 52 weeks. Median age was 69 years, BMI 36.9 kg/m^2 and HbA_{1c} 51 mmol/mol (6.8%). Most participants were receiving diuretics, RAAS blockers and beta-blockers, and around a third were receiving an MRA and/or an SGLT2 inhibitor.

The dual primary endpoints were the percentage change in body weight and the change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) – an indicator of HF symptoms, physical function, social function and quality of life, with scores ranging from 0 (worst) to 100 (best).

At 52 weeks, for the treatment policy estimand (similar to an intention-to-treat analysis), KCCQ-CSS improved, from a baseline of around 60 points, by 13.7 and 6.4 points in the semaglutide and placebo groups, respectively (estimated difference 7.3 points; $P<0.001$). Notably, the treatment difference was 8.3 points in people not taking SGLT2 inhibitors at baseline and 5.3 points in those who were, suggesting some benefit of combining the two drug classes in this patient group.

Mean weight loss at 52 weeks was 9.8% in the semaglutide group versus 3.4% in the placebo group (estimated treatment difference 6.4%), which was about 40% less than in the STEP-HFpEF trial conducted in people without type 2 diabetes (Kosiborod et al, 2023).

Among the prespecified secondary endpoints, 6-minute walk distance improved in the semaglutide group compared with placebo, as did C-reactive protein levels. Serious adverse event rates were significantly lower in the semaglutide group (17.7% vs 28.8%). One limitation of the study was that it was not powered to assess clinical outcomes (e.g. hospitalisation for heart failure); however, these favoured semaglutide.

The authors concluded that the previously demonstrated benefits of semaglutide for HFpEF extend to people with type 2 diabetes, resulting in significant reductions in HF-related symptoms and physical limitations, weight loss, and improvements in exercise function.

The findings were published in the *New England Journal of Medicine*.

SELECT trial: Further analysis shows preventative effects of semaglutide on type 2 diabetes development

The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial previously showed that semaglutide was effective in reducing the risk of major adverse cardiovascular events in people with cardiovascular disease (CVD) and overweight or obesity, but without type 2 diabetes (Lincoff et al, 2023).

Further prespecified analyses of SELECT data presented at the Scientific Sessions demonstrated that semaglutide also had beneficial effects on glycaemia, reducing the risk of developing type 2 diabetes and increasing the likelihood of reverting to normoglycaemia in those with prediabetes.

Among the large study population of 17 604 participants, average BMI was 33.3 kg/m^2, HbA_{1c} 40 mmol/mol (5.8%) and age 61.6 years. Overall, 66% of participants had prediabetes at baseline. Results showed that the semaglutide group

had a significant reduction in HbA_{1c} of 3.4 mmol/mol (0.31%) at 20 weeks and, thereafter, HbA_{1c} gradually increased, in parallel, in both the semaglutide and placebo arms. Notably, the effect on HbA_{1c} was greatest in the group with the most severe dysglycaemia (HbA_{1c} 6.0% to <6.5%) at baseline.

At the 3-year follow-up, 306 people in the semaglutide group had progressed to type 2 diabetes, compared with 1059 in the placebo group (HR 0.27; 95% CI 0.24–0.31). This effect was independent of body weight and BMI at baseline; however, it was significantly affected by HbA_{1c} at baseline, with the greatest efficacy in those with prediabetes at study initiation (although the effect was still significant in those with normoglycaemia).

Semaglutide also increased the likelihood of reversion from prediabetes to normoglycaemia, with the proportion of participants with prediabetes falling from 66% at baseline to 24% at 20 weeks and 31% at 3 years. In contrast, prediabetes rates in the placebo group were more or less stable throughout. Those with lower HbA_{1c} at baseline were more likely to achieve normoglycaemia; nonetheless, 47% of those with the most severe dysglycaemia at baseline were still able to achieve normoglycaemia at 3 years (compared with around 7% in the placebo group).

Unsurprisingly, progression to type 2 diabetes was inversely associated with the amount of weight lost in both groups; however, mediation analysis suggested that weight loss explained only about 30% of the beneficial effects of semaglutide on glycaemia. The authors proposed that this might be due to benefits of semaglutide in terms of beta-cell preservation, in addition to the improved insulin sensitivity resulting from weight loss.

It should be noted that these results were in people with established CVD, and it remains uncertain whether they would extend to people without CVD. Furthermore, 70% of participants were male and 80% were of White ethnicity, so the results should be interpreted cautiously in other groups.

Results were simultaneously published in *Diabetes Care*. ■

Kosiborod MN, Abildstrøm SZ, Borlaug BA et al; STEP-HFpEF trial committees and investigators (2023) Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med* **389**: 1069–84

Lincoff AM, Brown-Frandsen K, Colhoun HM et al; SELECT trial investigators (2023) Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* **389**: 2221–32

Patel SR (2024) Entering a new era in sleep-apnea treatment. *N Engl J Med* **391**: 1248-9

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