News in brief: Highlights of the American Diabetes Association 82nd Scientific Sessions

The American Diabetes Association 82nd Scientific Sessions were held in New Orleans and presented online from 3rd to 7th June. Here, we share some of the breaking stories from the conference.

Tirzepatide achieves comparable weight loss to bariatric surgery in SURMOUNT-1

Treatment with tirzepatide 15 mg once weekly achieved more than 20% mean sustained weight loss and one third of those treated with 10 or 15 mg of tirzepatide achieved at least 25% weight loss over 72 weeks in the SURMOUNT-1 phase 3 trial, evaluating the safety and efficacy for the treatment of obesity. Results were presented at the *82nd Scientific Sessions of the ADA*, and published simultaneously in the *New England Journal of Medicine*. Weekly doses of 5 mg and 10 mg tirzepatide achieved mean weight loss of 15% and 19.5%, respectively, compared to 3.1% weight loss in the placebo group.

SURMOUNT-1

Tirzepatide is a once-weekly dual GIP (glucose-dependent insulinotropic peptide)/GLP-1 receptor agonist ("twincretin") approved by the US Food and Drug Administration for the treatment of type 2 diabetes in May 2022, but not yet licensed in the UK. The SURMOUNT-1 trial recruited 2539 adults with obesity (BMI ≥30 kg/m^2) or BMI ≥27 kg/m^2 and at least one weight-related complication (hypertension, dyslipidaemia, obstructive sleep apnoea or CVD) who had made at least one previous unsuccessful attempt to lose weight. Participants (mean baseline weight 104 kg, mean BMI 38 kg/m^2), but no type 2 diabetes (40.6% with prediabetes) were randomised 1:1:1:1 to once-weekly injections of tirzepatide (5 mg, 10 mg or 15 mg) or placebo. Co-primary endpoints were percentage change in weight from baseline to 72 weeks and weight reduction of ≥5% at 72 weeks. Key secondary endpoints included:

- Weight reduction of ≥10%, ≥15% and ≥20% at 72 weeks.
- Change in weight from baseline to 20 weeks.
- Change from baseline to week 72 in waist circumference, systolic blood pressure, fasting insulin and lipid levels, and physical function scores (SF-36).

An exploratory endpoint of ≥25% weight reduction at 72 weeks was also included. Percentage change in body-fat mass from baseline to week 72 was assessed using DXA scans in a subgroup of 255 participants.

Those without pre-diabetes at randomisation continued for a 4-week safety follow-up, the results of which are included here. Those with prediabetes continue in their treatment or placebo group for an additional 2-year period.

Results

After 72 weeks of treatment:

- Mean body weight was reduced by 15.0%, 19.5% and 20.9% in the tirzepatide 5 mg, 10 mg and 15 mg groups, respectively. In comparison, the placebo group lost a mean 3.1% of body weight.
- 50% of those treated with 10 mg and 57% of those treated with 15 mg of tirzepatide achieved at least 20% weight loss, compared with only 3% of the placebo group.
- Around 90% of those treated with tirzepatide lost at least 5% of body weight, compared with 35% of placebo recipients.
- 15%, 32% and 36% of those treated with 5 mg, 10 mg and 15 mg tirzepatide achieved the exploratory weight loss goal of ≥25%, compared with 1.5% of the placebo group.

Among participants with prediabetes, over 95% of those in the tirzepatide groups reverted to normoglycaemia; this was achieved by 61.9% treated with placebo. Clinically significant improvements in waist circumference, lipid levels and systolic blood pressure were also observed with tirzepatide compared to placebo.

Amongst those who underwent DXA scan measurement of body composition, mean reduction in total body fat mass was almost 34% in those treated with tirzepatide compared to just over 8% in the placebo group.

The safety profile of tirzepatide was consistent with the GLP-1 RA class and with tirzepatide use in the SURPASS trials for type 2 diabetes. Adverse events were principally gastrointestinal, occurred mainly during the 20-week dose escalation and were similar between the tirzepatide 10 mg and 15 mg doses. Despite around 80% of those on tirzepatide and 72% of those in the placebo group reporting at least one adverse event, only 7.1% and 6.2% in the 10 mg and 15 mg tirzepatide groups, respectively, discontinued treatment due to adverse events, compared with 2.6% in the placebo treated group. Gallbladder-

related events occur more commonly in those who achieve significant weight loss with, for example, metabolic surgery or GLP-1 RA use. Gallstones were equally common in the tirzepatide and placebo groups. Cholecystitis occurred more frequently in those taking tirzepatide, but was uncommon (≤0.6%). The trial took place during the COVID-19 pandemic and at least one fifth of participants tested positive. Of the 160 serious adverse events identified during the trial, 20% were deemed to be related to COVID-19, as were nearly one third of the 11 deaths (which were evenly distributed between the placebo and tirzepatide groups).

Treatment efficacy was assessed in two ways:

- "Treatment regimen" estimand, which included all those who were randomised, irrespective of whether they continued treatment (these are the results discussed here).
- "Efficacy" estimand, which reported average efficacy in those who continued on treatment as intended.

A body-weight reduction of 5% or more is considered clinically meaningful. Older drugs currently licensed by the FDA or EMEA for treatment of obesity achieve average placebo-subtracted weight loss of 3–8.6%, and bariatric surgery can achieve weight reduction of 25–30% over 1–2 years. Once-weekly semaglutide 2.4 mg, licensed in the UK for obesity treatment alongside lifestyle measures, and awaiting publication of its final NICE technology appraisal, achieved average placebo-adjusted weight reduction of 12.4%, with almost one third of participants achieving weight reduction of at least 20%. Direct comparison between different trials with different drugs is not appropriate due to differing participants and trial designs.

Writing in an accompanying editorial, Rosen and Ingelfinger (2022) suggest that these results could have major ramifications for people with obesity, and that people with obesity now have additional options to lose weight and maintain normoglycaemia. They highlighted important unanswered questions, including whether the mechanisms of weight loss differ between tirzepatide and GLP-1 RAs, whether major cardiovascular disease events will be reduced, whether gastrointestinal side effects will reduce with time, whether intermittent use of tirzepatide might be possible and, as with all new drugs, whether unforeseen concerns will be identified with longer-term use in larger numbers.

To access the full paper, click here.

SURPASS-4 and chronic kidney disease

The open-label, phase 3 SURPASS-4 trial had previously demonstrated that tirzepatide improved glycaemic control compared with insulin glargine in people with type 2 diabetes inadequately controlled on oral medications (including SGLT2 inhibitors) and high cardiovascular risk (Del Prato et al, 2021). This pre-specified analysis evaluated the effects of tirzepatide on renal outcomes (primary outcome: a composite of ≥40% eGFR decline, new-onset macroalbuminuria, renal death or progression to end-stage renal disease [ESRD]).

A total of 1995 participants were enrolled and followed for up to 104 weeks (median, 85 weeks). At study end, the risk of the primary endpoint was significantly reduced in tirzepatide versus insulin recipients (hazard ratio [HR], 0.58; 95% CI, 0.43–0.80). However, this was largely driven by a reduction in new-onset macroalbuminuria (HR, 0.41), as the risk of 40% eGFR decline was not significantly reduced (although eGFR decline over time was slowed) and there were no renal deaths and only five people progressed to ESRD (all in the insulin group). These effects were consistent across high-risk population subgroups and background SGLT2 inhibitor use.

Presenting the findings, Dr Hiddo Heerspink (University Medical Center Groningen, the Netherlands) concluded that a renoprotective effect of tirzepatide was possible (rather than a deleterious effect of insulin glargine), and that the agent should be evaluated further.

Artificial intelligence-led precision nutrition advice results in type 2 diabetes remission

This randomised controlled trial offers a glimpse into the future of using data to provide precision nutritional and lifestyle advice to improve health outcomes. The Twin Precision Nutrition programme uses artificial intelligence to analyse daily data collected from continuous glucose monitors, sensor watches, blood pressure meters, smart scales and detailed patient food intake information to provide an individual with daily precision health guidance, including nutrition, exercise, sleep and breathing recommendations, delivered by an app and by health coaches.

Interim data on 262 individuals with type 2 diabetes who had participated in the trial for 180 days (199 randomised to the intervention and 63 to standard care) were available for analysis. At baseline, mean age was 45 years, diabetes duration 3.9 years and HbA_{1c} 75 mmol/mol (9.0%). After 180 days, 94.9% of participants in the intervention group had achieved an HbA_{1c} <48 mmol/mol (6.5%), including 83.9% who achieved this without taking metformin. Mean HbA_{1c} fell by 36 mmol/mol in the intervention group, compared with 4 mmol/mol in the standard care group.

The study is ongoing, and the authors acknowledged that further, longer-term study will be required.

Dulaglutide in paediatric type 2 diabetes

The once-weekly GLP-1 RA dulaglutide was shown to be a safe and effective treatment for paediatric type 2 diabetes in findings presented at the Sessions and published simultaneously in the *New England Journal of Medicine*.

In a double-blind randomised controlled trial, 154 young people with type 2 diabetes (age 10 to <18 years with a BMI over the 85th percentile), treated with diet and

lifestyle and/or metformin, with or without basal insulin, were assigned to placebo or dulaglutide 0.75 mg or 1.5 mg.

After 26 weeks of treatment, compared with an increase of 6.6 mmol/mol in the placebo group, mean HbA_{1c} decreased by 6.6 and 9.8 mmol/mol in the dulaglutide 0.75 mg and 1.5 mg groups, respectively (P<0.001 for both comparisons). Overall, 51% of dulaglutide recipients (either dose) achieved an HbA_{1c} of <53 mmol/mol, compared with 14% of placebo recipients. There were no significant differences in BMI between the groups.

The overall safety profile of dulaglutide matched that in adults, with gastrointestinal symptoms (mostly mild) among the most common adverse events.

These findings could extend the list of treatment options for type 2 diabetes in young people, at a time when incidence is rising rapidly.

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Del Prato S, Kahn SE, Pavo I et al; SURPASS-4 investigators (2021) Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* **398**: 1811–24

Jastreboff AM, Aronne LJ, Ahmad NN et al; the SURMOUNT-1 Investigators (2022) Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 4 Jun (Epub ahead of print)

Rosen CJ, Ingelfinger JR (2022) Shifting tides offer new hope for obesity. *N Engl J Med* 4 Jun (Epub ahead of print)

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