Journal club: New kids on the block – friend or foe?

Tirzepatide has just received its NICE Technology Appraisal and will need to be made available for suitable patients over the next few months (NICE, 2023). Horizon scanning also suggests that several once-weekly insulins are likely to be launched within the next 12 months.

What does the evidence indicate? Let's start with tirzepatide. Tirzepatide is a novel dual GIP and GLP-1 receptor agonist. In the UK, it has been approved for the management of type 2 diabetes if triple therapy with metformin and two other oral glucose-lowering medications has been ineffective, not tolerated or contraindicated, and if:

- BMI is ≥35 kg/m^2 and there are specific psychological or other medical issues associated with obesity,
  or
- BMI is <35 kg/m^2 and insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related complications.

BMI thresholds can be reduced by 2.5 kg/m^2 for South Asian, Black and certain other minority ethnic groups. So a very broad range of patients with type 2 diabetes.

The fact that tirzepatide 15 mg once weekly is superior to even semaglutide 1 mg once weekly when it comes to weight loss (–5.5 kg; P<0.001) and improvement in HbA_{1c} (–0.45%; P<0.001) is clear (Frías et al, 2021). These results were over a 40-week period; however, the effect of tirzepatide on the long-term risk of developing type 2 diabetes in people with obesity is unknown. In a *post hoc* analysis of the SURMOUNT-1 study, a model based on the Cardiometabolic Disease Staging Score was used to predict the risk of type 2 diabetes in those with obesity (Hankosky et al, 2023). Essentially, tirzepatide 15 mg once weekly reduced the 10-year relative risk of type 2 diabetes by around 69%, compared to 11% with placebo. As the predicted risk was 22.9%–24.3% at baseline and 14.7% at 72 weeks' follow-up, the number needed to treat to prevent a single case of type 2 diabetes was only around 10.

Karakasis et al (2023) have published a meta-analysis on the safety and efficacy of once-weekly basal insulins, including insulin icodec and insulin efsitora alfa. The once-weekly analogues resulted in greater reductions in HbA_{1c} than daily long-acting analogues such as glargine, which did not quite reach significance (mean difference –0.13%; P=0.08). Time in range was greater with the once-weekly analogues, without an increase in hypoglycaemic events. These agents may have specific indications, such as ease of use in patients that require external agency for insulin administration or those with severe needle phobia. They may also be just generally more convenient for most people with diabetes who require insulin.

A reminder, as we finish, to continue with our focus on the tried and tested recent kids on the block. I have always wondered whether the SGLT2 inhibitors are equally efficacious across the full range of BMI in people with type 2 diabetes. The study by Yu et al (2023) appears to show that, in the case of canagliflozin, they are. In the CANVAS and CREDENCE programmes, a total of 14 520 participants were included. Canagliflozin reduced the risk of major adverse cardiovascular events by 17% across the full range of BMI, with no heterogeneity of effect. Similarly, the risk of renal outcomes was reduced by 25% across the BMI sub-groups. So SGLT2 inhibitors are effective regardless

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Citation: Patel V (2023) Journal club: New kids on the block – friend or foe? *Journal of Diabetes Nursing* **[Early view publication]**

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of the BMI – in case you needed convincing.

I think we may have an innate therapeutic inertia gene, often triggered by frailer patients. We should take note of the study by Kutz et al (2023) that even frail patients have better outcomes with the newer glucose-lowering agents. Compared with DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists were associated with a lower rate of cardiovascular events and mortality. There was also evidence of comparable safety among older people with type 2 diabetes with these agents, irrespective of frailty status.

Of course, until now I have been overlooking a major concern. These agents will not be cheap. To have a place in therapy, new treatments such as tirzepatide and weekly insulins will need to be clearly better in several differing domains. This would include reducing hospital admissions, reducing costs in the healthcare system and patient preference. The evidence to date is compelling and favours a place for these two new medications in our clinical armamentarium. Early engagement with the clear intent of improving patient outcomes in a patient-centred, cost-efficient programme of clinical care will be needed. ■

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