Management & prevention of type 2 diabetes

Incretin-based therapies: A wealth of studies but not much evidence beyond glucose lowering

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The first of the incretin therapies – glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors – became available around 10 years ago. In the UK, we now have five GLP-1 analogues and five DPP-4 inhibitors available. A large number of individual randomised controlled trials of these agents have been published.

Systematic reviews and meta-analyses of randomised trials provide high-quality evidence to inform patient care decisions, implement healthcare policies and develop clinical practice guidelines. The systematic review is regarded as the highest level of evidence. There is now almost an "industry" of systematic reviewers, working in many countries of the world, publishing this level of "high-quality" evidence.

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In the paper summarised alongside, Gamble and colleagues have reviewed the systematic reviews of incretin-based therapies that have been published. In total, their search strategy found 84 such articles! They assessed the quality of these using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. DPP-4 inhibitors were evaluated in 64 reviews and GLP-1 analogues in 51. Almost half of the reviews did not report a funding source. Only 6% received an AMSTAR score indicating high quality, and nearly half (46%) had a score indicating low quality.

This review of systematic reviews confirmed that incretin-based therapies were consistently associated with a pooled weighted mean reduction in HbA_{1c} of more than 5 mmol/mol (0.5%). They were not associated with a clinical risk of hypoglycaemia. GLP-1 receptor agonists were associated with an increased risk of nausea, vomiting and diarrhoea.

The authors conclude that there is as yet no definitive evidence of benefits of incretin-based medications beyond lowering glucose. They also say that, despite the vast number of systematic reviews that have been published, there is still a dearth of evidence regarding important outcomes for patients treated with these therapies.

So, although many systematic reviews on incretin-based therapies have been published, nearly half of them were of low quality, and they have not yet taken us much further than the fact that these therapies lower glucose levels without causing hypoglycaemia. ■

Diabetes Obes Metab

Systematic reviews reviewed: Incretin therapies

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 These authors synthesised the findings of 84 systematic reviews of the effects of glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors in people with T2D. The Assessment of Multiple Systematic Reviews (AMSTAR) checklist was used to assess the quality of the reviews.

2 Only five reviews were of high quality (AMSTAR score ≥9 out of a possible 11), and almost half (n=39) were of low quality (AMSTAR score ≤4).

3 Both GLP-1 analogues and DPP-4 inhibitors were found to result in significant reductions in HbA_{1c} compared with both placebo and metformin (pooled weighted mean reductions of >5 mmol/mol [>0.5%]), but not compared with sulphonylureas, thiazolidinediones or insulin.

4 There was some evidence that the agents had positive effects on macrovascular complications, but the results were non-significant in the majority of reviews. Similarly, the effects on cardiovascular outcomes were non-significant, and no comparisons were made for microvascular complications.

5 The agents were associated with a reduced risk of hypoglycaemia and weight gain compared with drugs that are known to have these side-effects. Compared to metformin and placebo, there was no significant difference.

6 Compared with DPP-4 inhibitors, GLP-1 analogues tended to produce greater HbA_{1c} reductions but had more gastrointestinal side effects, such as nausea, vomiting and diarrhoea.

Gamble JM, Clarke A, Myers KJ et al (2015) Incretin-based medications for type 2 diabetes: an overview of reviews. *Diabetes Obes Metab* **17**: 649–58

Diabetes Obes Metab

Canagliflozin in older people with T2D: 2-year outcomes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 This phase III randomised controlled trial was conducted to assess the effects of canagliflozin 100 mg or 300 mg in people aged 55–80 years with T2D and an HbA_{1c} of 53–86 mmol/mol (7–10%) on their current treatment regimen.

2 A total of 714 people (mean age, 64 years; mean HbA_{1c}, 61 mmol/mol [7.7%]) were randomised in a 1:1:1 ratio to receive canagliflozin 100 mg, 300 mg or placebo, in addition to their ongoing diabetes therapy.

3 At the 2-year follow-up, 36%, 42% and 20% of participants in the 100 mg, 300 mg and placebo groups, respectively, had achieved an HbA_{1c} of <53 mmol/mol (7.0%), and 13%, 24% and 5% achieved an HbA_{1c} of <48 mmol/mol (6.5%).

4 HbA_{1c} reduced significantly in both canagliflozin groups compared with placebo (least-squares mean difference, –0.49% and –0.60% with 100 mg and 300 mg, respectively).

5 Mean body weight decreased by 2.7 kg (3.0%) and 3.5 kg (3.8%) from baseline in the two canagliflozin groups, and canagliflozin recipients were significantly more likely to lose ≥5% of body weight compared with placebo (28% and 33% vs 10.5%).

6 Adverse events occurred in around 90% of participants in all three groups and were mostly mild to moderate in severity. Urinary tract infections (14.5% and 16.5% vs 10.1% of participants) and events related to diuresis (9.1% and 12.3% vs 5.5%) were more common in the canagliflozin groups than the placebo group.

Bode B, Stenlöf K, Harris S et al (2015) Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55–80 years with type 2 diabetes. *Diabetes Obes Metab* **17**: 294–303

Diabetes Res Clin Pract

Sulphonylurea use and risk of falls in older people

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 In this retrospective study from the US, the risk of falls in 12 327 nursing home residents who began treatment with biguanides and/or sulphonylureas was evaluated.

2 Between 2008 and 2010, a total of 5060 falls occurred in 41% of the cohort, and 497 (10%) of these resulted in a fracture.

3 Regardless of age or frailty (defined by the individuals' ability to perform activities of daily living), sulphonylurea use was associated with an excess rate of severe hypoglycaemia; however, for the most part, sulphonylureas were not associated with falls or fractures.

4 The exception to this was in moderately frail people, in whom sulphonylurea use was associated with an excess risk of falls (adjusted hazard ratio, 1.13; 95% confidence interval, 1.00–1.26).

Lapane KL, Jesdale BM, Dubé CE et al (2015) Sulfonylureas and risk of falls and fractures among nursing home residents with type 2 diabetes mellitus. *Diabetes Res Clin Pract* **109**: 411–9

Diabetes Res Clin Pract

Risk factors for heart failure in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 This systematic review and meta-analysis was performed to determine the most significant risk factors for heart failure (HF) in people with T2D.

2 In 31 studies with a total of 507 637 participants with T2D (mean age, 62 years), the mean cumulative incidence of HF was 10.7% over 4.8 years of follow-up.

3 After adjustment for confounders, the most significant risk factors were coronary heart disease (hazard ratio [HR], 1.77), HbA_{1c} ≥86 mmol/mol (≥10%; HR, 1.66), insulin use (HR, 1.43), HbA_{1c} 75–86 mmol/mol (9.0–10.0%; HR, 1.31), fasting blood glucose (HR, 1.27 per standard deviation) and each 5-year increase in age (HR, 1.26).

4 These findings may help clinicians to make decisions about screening for HF in people with diabetes.

Wang Y, Negishi T, Negishi K, Marwick TH (2015) Prediction of heart failure in patients with type 2 diabetes mellitus – a systematic review and meta-analysis. *Diabetes Res Clin Pract* **108**: 55–66

Diabetes Metab Res Rev

Effects of T2D on memory and executive function

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 T2D is known to increase the risk of cognitive impairment and subsequent dementia.

2 The aim of this systematic review and meta-analysis was to evaluate whether T2D has effects on specific cognitive subdomains. Cohen's *d* values were used to determine effect sizes.

3 Fifteen articles comparing 2370 people with T2D and 21 426 controls were analysed.

4 People with T2D had decrements in episodic memory (d=0.51), logical memory (d=0.24) and processing speed (d=0.22). Within the subdomains of executive function, phonemic fluency (d=0.35) and cognitive flexibility (d=0.52) were also affected.

5 Verbal short-term memory and working memory were unaffected.

6 Hippocampal changes in the pre-diabetes state and accelerated cognitive ageing in T2D were proposed as possible causes of these changes.

Sadanand S, Balachandar R, Bharath S (2015) Memory and executive functions in persons with type 2 diabetes: a meta-analysis. *Diabetes Metab Res Rev* 10 May [Epub ahead of print]

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