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.

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 HbA1c 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.


Roger Gadsby
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Canagliflozin in older people with T2D: 2-year outcomes

Diabetes Obes Metab

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.

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

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.

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).


Sulphonylurea use and risk of falls in older people

Diabetes Res Clin Pract

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), HbA1c ≥86 mmol/mol (≥10%; HR, 1.66), insulin use (HR, 1.43), HbA1c 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.


Risk factors for heart failure in T2D

Diabetes Res Clin Pract

1 Diabetes 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.


Effects of T2D on memory and executive function

Diabetes Metab Res Rev

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Incidence of HF was 10.7% over 4.8 years of follow-up.

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