Management & prevention of type 2 diabetes

SGLT2 inhibitors: The third published systematic review and meta-analysis

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a new class of glucose-lowering agents. Two drugs in this new class are currently available in the UK (dapagliflozin and canagliflozin), the first of which was launched around 18 months ago. A number of other SGLT2 inhibitors are in development.

Systematic review and meta-analysis of relevant randomised controlled trials (RCTs) are regarded in evidence-based medicine to be the highest level of evidence. It used to be several years after the launch of a new drug class before a systematic review and meta-analysis of their effects were published. The glitazones, for example, were launched around 2000; the systematic review and meta-analysis that reported on the possible cardiovascular risk of rosiglitazone (Nissen and Wolski) was published in 2007.

Since then, this process significantly sped up. The SGLT2 inhibitors had been available in the UK for just over 12 months when this paper by Monami et al, summarised alongside, became the third systematic review and meta-analysis to be published. It contains more trials than previous reviews (25 in this paper) and includes published studies on four agents (eight studies of canagliflozin, 14 studies on dapagliflozin, one study on empagliflozin and two studies on ipragliflozin). The included RCTs of Monami et al's systematic review and meta-analysis studied 7524 participants on SGLT2 inhibitor agents and 3628 in comparator groups. The mean trial duration was 30 weeks; the mean age of individuals at participant recruitment was 56.3 years; the mean duration of diabetes was 6.1 years; the mean HbA_{1c} was 65 mmol/mol (8.1%); and the mean BMI was 31.6 kg/m^2. All of these figures could be considered to be representative of real world people living with type 2 diabetes in the UK.

The main outcome measure of the majority of the individual RCTs was a reduction in HbA_{1c} versus placebo at 12 or 24 weeks. Several trials had data at 52 weeks. The RCTs showed significant reductions in HbA_{1c} at all time points compared with placebo. At 24 weeks the change in HbA_{1c} was –6.5 mmol/mol (–0.6%). The results of active comparator trials indicate that SGLT2 inhibitors had a similar efficacy to metformin and sitagliptin.

Other measurable outcomes were also investigated in this meta-analysis by Monami et al. In placebo-controlled trials, weight loss was recorded in the first 24 weeks and maintained up to 52 weeks, and, in head-to-head trials with the sulphonylurea glipizide, BMI was reduced by 1.1 kg/m^2 at 24 and 52 weeks. SGLT2 inhibitors were also associated with a modest but statistically significant increase in HDL-cholesterol with no effect on total- and LDL-cholesterol, and systolic and diastolic blood pressure were reduced by 1.2 and 1.9 mmHg, respectively, compared to placebo.

The most commonly reported adverse effect in the trials was genital infections, which increased four-fold both versus placebo and versus active comparator. An increase in lower urinary tract infections was also described. There were no increases in serious adverse events and no signal for increases in mortality, adverse cardiovascular disease outcomes, malignancies, renal failure and bone fractures.

The authors concludes that "SGLT-2 inhibitors, orally administered once daily, are effective in the treatment of type 2 diabetes, providing additional benefits beyond glucose lowering, such as weight loss, reduction of blood pressure and increase in HDL cholesterol. Apart from genital and, to a lesser extent, urinary tract infections, which are rather frequent but usually mild, SGLT-2 inhibitors appear to be well tolerated. Further studies are granted to confirm their long-term safety."

In my opinion the SGLT2 inhibitors are a very interesting and useful new class of oral glucose-lowering agent. ■

Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Eng J Med* **356**: 2457–71

Diabetes Obes Metab

SGLT2 inhibitors: Systematic review and meta-analysis

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

1 A systematic review and meta-analysis were conducted to assess the overall efficacy and safety of sodium–glucose cotransporter 2 (SGLT2) inhibitor agents for the treatment of T2D in adults.

2 Searches of the Cochrane, EMBASE and MEDLINE databases and clinicaltrials.gov were carried out up until May 2013 for randomised controlled trials of ≥12 weeks' duration that treated individuals either with an SGLT2 inhibitor or with placebo or another drug. From 316 results, 25 articles were eligible for inclusion in the meta-analysis.

3 The primary measurable outcome was the effect of SGLT2 inhibitors on HbA_{1c} at 12, 24 and 52 weeks. The safety events investigated were hypoglycaemia, urinary tract infections and genital tract infections.

4 At all time points in placebo-controlled trials, SGLT2 inhibitors produced a significant reduction in HbA_{1c}.

5 In placebo-controlled trials, SGLT2 inhibitors caused weight loss during the first 24 weeks, which was maintained up to 52 weeks.

6 SGLT2 inhibitors were associated with a similar hypoglycaemic risk to that of metformin and dipeptidyl peptidase-4 inhibitors.

7 Additional benefits of SGLT2 inhibitors included decreased blood pressure and increased HDL-cholesterol levels.

Monami M, Nardini C, Mannucci E (2013) Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 5 Dec [Epub ahead of print]

Diabetes Care

Hypoglycaemia and arrhythmia risk among people with T2D and CVD

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

1 The aim of this observational study was to investigate the relationship between glycaemic variability, caused by different treatment strategies for T2D, and increased risk of cardiac arrhythmias as a result of hypoglycaemia.

2 In total, 30 people with T2D and documented cardiovascular disease (CVD) treated with insulin and/or sulphonylureas were compared against 12 age-matched people with T2D and CVD who were treated with metformin and/or dipeptidyl peptidase-4 inhibitors; the latter served as the control group.

3 All participants underwent 5 days of continuous glucose monitoring and electrocardiogram recording for monitoring ventricular arrhythmias and were instructed to notice symptoms of hypoglycaemia and arrhythmias.

4 There was a high incidence of asymptomatic severe episodes of hypoglycaemia (<3.1 mmol/L) in participants treated with insulin and/or sulphonylureas, particularly at bedtime; there were no episodes of severe hypoglycaemia in the control group.

5 People who experienced severe hypoglycaemia (n=12) had a higher number of severe ventricular arrhythmias (e.g. ventricular couplets or ventricular tachycardia).

6 Severe episodes of hypoglycaemia are associated with an increased risk of severe ventricular episodes in people with T2D with recorded CVD being treated with insulin and/or sulphonylureas.

Stahn A, Pistrosch F, Ganz X et al (2014) Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases. *Diabetes Care* **37**: 516–20

J Clin Endocrinol Metab

Improved survival of complicated T2D

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

1 This longitudinal follow-up study used all-cause and cause-specific mortality data from 2002 to 2010 to estimate the time trend in mortality among 5844 Danish people with complicated T2D from the Steno Diabetes Center.

2 In total, there were 1341 deaths during 32 913 person-years of follow-up.

3 Total mortality among people with complicated T2D had decreased per year in men by 5.5% (95% confidence interval [CI], 2.9–8.0%) and in women by 3.3% (95% CI, 0.0–6.4%).

4 The decline in the mortality of men was significantly steeper than the reduction in mortality in the Danish background population. The decline in mortality was attributed to a decline in cardiovascular mortality.

Færch K, Carstensen B, Almdal TP, Jørgensen ME (2014) Improved survival among patients with complicated type 2 diabetes in Denmark. *J Clin Endocrinol Metab* 31 Jan [Epub ahead of print]

Diabetes Care

Hypoglycaemia and cognitive decline

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

1 The association between episodes of severe hypoglycaemia and cognitive decline was investigate using data collected from older participants of the Edinburgh Type 2 diabetes Study. Participants were aged 60–75 years and lived independently.

2 Cognitive function was measured from baseline to 4 years and seven neuropsychological tests were combined into a standard ability factor.

3 A history of hypoglycaemia at baseline and incident hypoglycaemia throughout the 4 years were associated with a greater cognitive decline during follow-up.

4 Lower cognitive ability at baseline was associated with a two-fold higher incidence of severe hypoglycaemia over 4 years.

Feinkohl I, Aung PP, Keller M et al (2014) Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care* **37**: 507–15

New Engl J Med

BMI and mortality association: Adults with incident T2D

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

1 The association between BMI and mortality is complex with some research finding that there is decreased mortality among obese or overweight people compared to normal weight people.

2 The BMIs of 11 427 people with incident T2D (8970 from the Nurses' Health Study and 2457 from the Health Professionals Follow-up Study) were included and hazard ratios were calculated for mortality.

3 In total, 3083 deaths occurred over a mean period of 15.8 years of follow-up.

4 A J-shaped association was found between BMI immediately before diagnosis of T2D and mortality among all participants. No evidence was found of lower mortality among participants with T2D who were overweight or obese at diagnosis or of an "obesity paradox".

5 The lowest risk of all-cause mortality was for participants with a BMI between 22.5 and 24.9 kg/m^2 at the time of T2D diagnosis.

Tobias DK, Pan A, Jackson CL et al (2014) Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med* **370**: 233–44

"Lower cognitive ability at baseline was associated with a two-fold higher incidence of severe hypoglycaemia over a 4-year period."