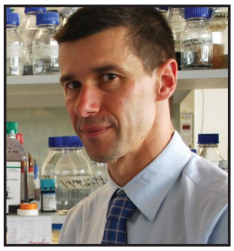
# SGLT-2 INHIBITORS – AT THE LIMITS

## A novel strategy to improve type 2 diabetes, cardiovascular and renal outcomes



***Professor John Wilding***
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**Professor John Wilding described the clinical benefits that are emerging from the use of highly selective SGLT-2 inhibitors in type 2 diabetes and pointed out that this would probably lead to an exploration of their usefulness in other cardiovascular conditions, such as heart failure.**

**We are not yet at the limit of determining the usefulness of these agents in diabetes, cardiovascular and renal disease, he noted.**

## Mechanism of action

The SGLT-2 inhibitors limit the SGLT-2 glucose transporter function, which is mainly responsible for the reabsorption of glucose from the proximal kidney tubule into the circulation. In diabetes with accompanying hyperglycaemia, there is upregulation of the SGLT-2 transporter activity; this results in more glucose being returned to the circulation and contributing further to hyperglycaemia. The SGLT-2 inhibitors that are now available are highly selective.

By removing glucose, glucose levels are directly lowered and therefore so is $HbA_{1c}$. Calories are also lost, which is very important in type 2 diabetes, and the sodium load is reduced; this leads to a resetting of sodium balance and a drop in blood pressure (Table 1).

It is important also to note that these agents have a very low risk of hypoglycaemia as insulin release is not stimulated.

***The SGLT-2 inhibitors, in principle, have a very simple mode of action and can perhaps be described as very smart diuretic agents.***

**Table 1. Advantages of SGLT-2 inhibitors**

| |
|---|
| • Glucose-lowering at all stages of diabetes |
| • Potential for combination therapy with a wide range of oral glucose-lowering drugs, including insulin |
| • Weight loss |
| • Blood pressure-lowering |
| • Low risk of hypoglycaemia |

## Initial concerns

"When these agents were first released, I was more concerned about genital fungal infections, less so about bacterial urinary tract infections", Professor Wilding commented.

There was also a concern that SGLT-2 inhibitors would cause massive diuresis; this, in fact, does not occur and the increased diuresis of 200-300 ml does not result in either severe volume depletion or electrolyte imbalance.

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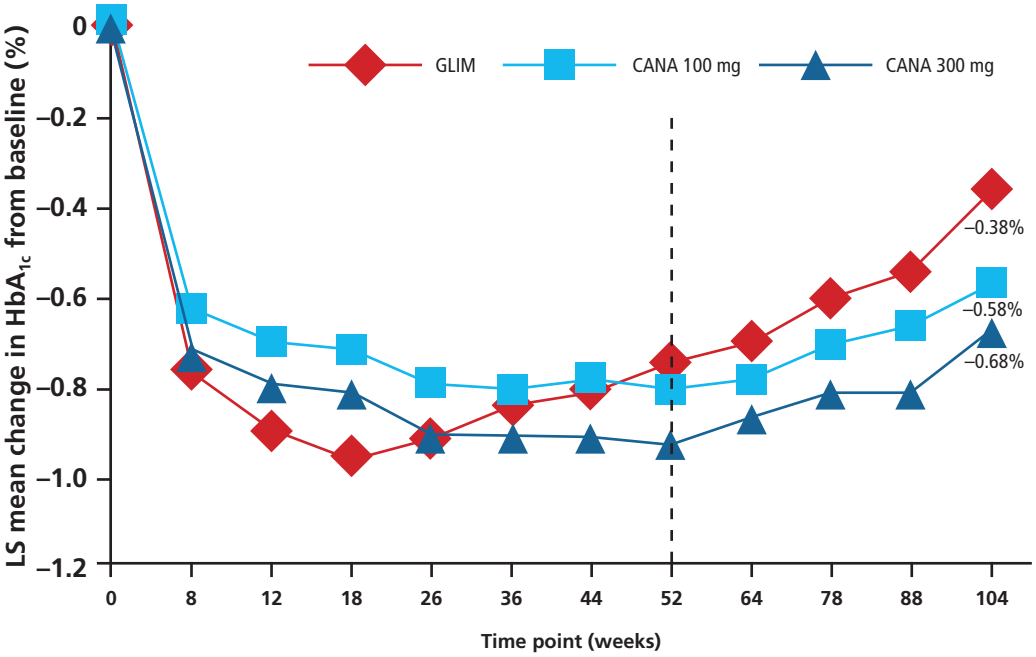
# Clinical effectiveness in diabetes

A number of pivotal clinical trials have shown the effectiveness of these agents.

## SGLT-2 inhibitors versus glimepiride

In this randomised, double-blind study,[1] 1 450 type 2 diabetes patients were given canagliflozin 100 mg or 300 mg, or glimepiride (titrated up to 6-8 mg/day). The sulphonylurea caused an initial steeper drop in $HbA_{1c}$, but both doses of canagliflozin showed greater sustained $HbA_{1c}$ lowering as compared to glimepiride (Figure 1).[1] The incidence of genital mycotic infections and urinary tract infections was higher with canagliflozin, but these infections were generally mild to moderate and led to few discontinuations.




Both CANA doses showed a reduction in $HbA_{1c}$ vs GLIM at 104 weeks when assessed using MMRM[a,b]
The coefficient of durability (rate of $HbA_{1c}$ rise from week 26 to week 104) was lower with canagliflozin 100 mg and 300 mg vs glimepiride (0.16%, 0.16% and 0.37% respectively)[c]

Vertical bars represent standard error.
[a] Difference in LS mean change vs GLIM: –0.20%; 95% CI –0.34, –0.06.
[b] Difference in LS mean change vs GLIM: –0.30%; 95% CI –0.44, –0.16.
[c] Difference for CANA 100 mg and 300 mg vs GLIM were –0.21% (–0.29, –0.13) and –0.21% (–0.30, –0.13), respectively.
GLIM, glimepiride; MMRM, mixed-model repeated measures.

**Figure 1. Canagliflozin: change in $HbA_{1c}$ (MMRM) vs glimepiride as add-on to metformin over 104 weeks**

Fewer patients had hypoglycaemic episodes with canagliflozin than glimepiride. A clinically significant 4% reduction in body weight was achieved with canagliflozin. A modest drop in blood pressure also occurred in canagliflozin-treated patients (a drop of 2-3 mmHg), which was sustained over the two-year period.

## SGLT-2 inhibitors' efficacy across the spectrum of diabetes severity[2-7]

In an illustrative review of the evidence for a single SGLT-2 inhibitor (dapagliflozin), Professor Wilding pointed to the very consistent reduction in $HbA_{1c}$ when SGLT-2 inhibitors are used as monotherapy or in combination with other oral agents or insulin. A consistent weight loss is also seen across this spectrum of diabetes severity (1.8-3 kg).

Real-world experience is very similar to that seen in clinical trials in primary care, using, for example, the General Practice Research Database as a UK primary care data resource.[8]

## Cardiovascular safety outcomes

A number of cardiovascular trials have been initiated to show the cardiovascular safety of SGLT-2 inhibitors (Table 2). The first was the EMPA-REG OUTCOME trial with empagliflozin.[9]

**Table 2. SGLT-2 inhibitor outcome trials in type 2 diabetes**

| Trial Name | Target Enrollment | Timing |
|---|---|---|
| CANVAS (canagliflozin) | *n* = 4 330 | Began 2009; Ending 2017 |
| CANVAS-R (canagliflozin) | *n* = 5 700 | Began 2013; Ending 2017 |
| CREDENCE (canagliflozin) | *n* = 3 700 | Began 2014; Ending 2019 |
| EMPA-REG OUTCOME (empagliflozin) | *n* = 7 000 | Began 2010; Reported Sept 2015 |
| DECLARE (dapagliflozin) | *n* = 17 150 | Began 2013; Ending 2019 |
| VERTIS (ertugliflozin) | *n* = 8 000 | Began 2013; Ending 2019 |

It is important to look at the EMPA-REG OUTCOME study design, in which more than 11 000 patients at high cardiovascular risk were screened, with 7 020 being randomised to treatment with placebo or two doses of empagliflozin (10-25 mg), which were later pooled due to similar outcomes. The study was double-blind and was set to continue until at least 691 patients experienced an adjudicated primary outcome event.[9]

The primary outcome (three-point MACE) of death from cardiovascular causes, non-fatal myocardial infarction (MI) or stroke was significantly reduced, driven by a significant reduction in cardiovascular death, a non-significant reduction in non-fatal MI and a non-significant rise in stroke. The four-point MACE (primary outcomes plus hospitalisation for unstable angina) did not quite reach clinical significance.

An important effect seen in the secondary analysis was a significant decrease in hospitalisation for heart failure, Professor Wilding pointed out.

## Is the cardiovascular benefit an individual drug or dose effect?

A meta-analysis of all available data for SGLT-2 inhibitors from both published trials and regulatory submissions suggested there was no heterogeneity in drug action.[10] This view was largely driven by the EMPA-REG OUTCOME trial data (80% of events included), and it is therefore very difficult to draw a final conclusion at this stage, observed Professor Wilding.

### The CVD-REAL study

This CVD-REAL study, conducted in the USA and Europe, identified 154 000 patients initiated on SGLT-2 inhibitors, who were then very closely matched to one million type 2 diabetes patients who were new users of other oral glucose-lowering agents. Thirteen percent had prior cardiovascular disease in both cohorts and 44% were women. Patients were on similar treatment (80% on blood pressure-lowering agents, 67% on a statin and 78% on metformin). In the primary analysis, there was a 39% reduction in heart failure hospitalisation and a 51% all-cause death reduction in patients on any SGLT-2 inhibitor; these findings were consistent with those of EMPA-REG OUTCOME.

### What is the basis of the SGLT-2 inhibitors' cardiovascular benefit?

The basis of the reduction in heart failure hospitalisation and all-cause mortality is not driven by glucose-lowering (only a 0.3% difference in $HbA_{1c}$ in the EMPA-REG study). Possible mechanisms include raised ketone levels, which increase insulin sensitivity and provide a fuel for myocardial metabolism at times of ischaemia. Reduction in body weight could also play a role, but the renal effects may also favour cardiovascular risk reduction (Figure 2).

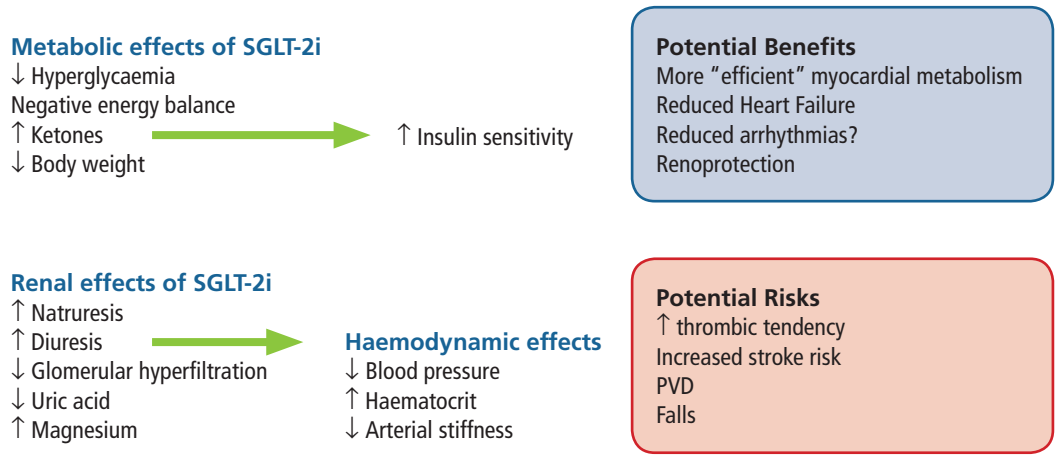



**Figure 2. Why might SGLT-2 inhibitors influence cardiovascular events/heart failure/mortality**

## Reno-protective effects of SGLT-2 inhibitors

There are some data to suggest that SGLT-2 inhibitors stabilise eGFR in patients as there is less reduction in eGFR over time on these agents compared to glimepiride, for example, Professor Wilding noted.

In the evaluation of secondary renal effects in the EMPA-REG OUTCOME trial, there was a 39% relative risk reduction (RRR) in incidence or worsening nephropathy and a 46% RRR in the composite renal markers (doubling of serum creatinine, renal replacement therapy and renal death).

The hypothesis for renal benefit is based on changes in glomerular feedback and a drop in intraglomerular pressure (Figure 3).

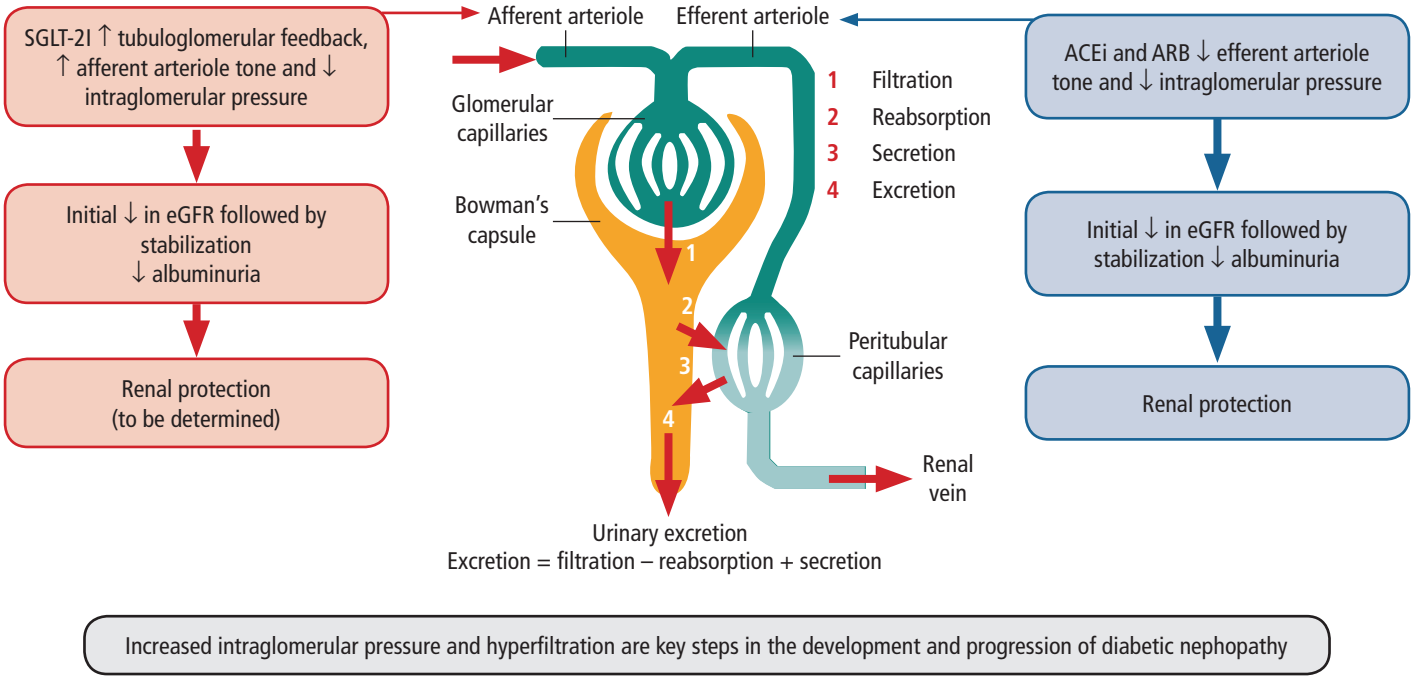



**Figure 3. SGLT-2 inhibition and ACEi/ARB reduce intraglomerular pressure: Possible mechanism for renal protection**

*It is important to balance the positive data on this class of agent with an understanding of potential adverse effects.*

## Adverse events

There is an increase in genital infections with SGLT-2 inhibitors – 10% of women and 4% of men are expected to experience at least one event while on treatment. Bacterial urinary tract infections occur, but they are not severe and respond to antibiotic therapy. Volume depletion must be considered in the elderly, those on loop diuretics and those with concomitant illness. Hypoglycaemia is not a problem and the increase in LDL-cholesterol in the light of the EMPA-REG OUTCOME trial may not be a clinical problem. The bone fracture risk may be due to falls or hypotension. Keto-acidosis is very rare, but does occur.

In conclusion, this class of glucose-lowering medication is now included in many type 2 diabetes guidelines and may offer the clinician an important opportunity to lower cardiovascular and renal risk in type 2 diabetes.

## References


1. Leiter La, Yoon KH, Arias P, *et al*. Canagliflozin provides durable glycaemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind phase 3 study. *Diabetes Care* 2015; **38**(3): 355-364.
2. Ferrannini E, Ramos SJ, Salsali A, *et al*. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomised, double-blind, placebo-controlled phase 3 trial. *Diabetes Care* 2010; **33**(10): 2217-2224.
3. Bailey CJ, Gross JL, Pieters H, *et al*. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; **375**(9733): 2223-2233.
4. Strojek K, Yoon KH, Hruba V, *et al*. Effect of dapagliflozin glycaemic control with glimepiride: a randomised 24-week, double-blind, placebo-controlled trail. *Diabetes Obes Metab* 2011; **13**(10): 928-938.
5. Mathieu C, Ranetti AE, Lid D, *et al*. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care* 2015; **38**(11): 2009-2017.
6. Wilding JP, Woo V, Soler NG, *et al*. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; **156**(6): 405-415.
7. Matthaei S, Rohwedder K, Grohl A, *et al*. Dapagliflozin improves glycaemic control and reduces body weight as add on therapy to metformin plus sulphonylureas. Poster presented at the 49th EASD Conference, Barcelona, Spain; 23-27 Sept 2013. Abstract 937-P.
8. Williams T, van Staa T, Puri S, *et al*. Recent advances in the utility and use of General Practice Research Database as an example of a UK primary care data resource. *Ther Adv Drug Safety* 2012; **3**(2): 89-99.
9. Zinman B, Inzucchi DE, Lachin JM, *et al*. Rationale, design and baseline characteristics of a randomised, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetology* 2014; **13**: 102.
10. Wu JH, Foote C, Blomster J, *et al*. Effects of sodium-glucose contransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2016; **4**(5): 411-419.





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