SGLT-2 inhibitors as second-line therapy in type 2 diabetes

Despite the development of several pharmacological agents over the past decade, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium glucose cotransporter 2 (SGLT2) inhibitors, the management of hyperglycaemia in patients with type 2 diabetes remains challenging.

SGLT2 inhibitors are a new class of glucose-lowering agents that have a unique insulin-independent mechanism of action unlike sulfonylureas, GLP-1 receptor agonists, and DPP-4 inhibitors, which all have insulin-dependent action.1 SGLT2 inhibitors work primarily by increasing urinary glucose excretion, resulting in lowered blood glucose concentrations and improvements in peripheral insulin sensitivity and β-cell function.2 Currently, two SGLT2 inhibitors—dapagliflozin and canagliflozin—have marketing authorisation, and empagliflozin is likely to be approved soon because of the Committee for Medicinal Products for Human Use’s positive opinion.

The main advantages of SGLT2 inhibitors beyond glucose control include reduction in weight and blood pressure, and low risk of hypoglycaemia. Additionally, the insulin-independent mode of action suggests that these agents could be useful at any stage of the disease and in any combination with other antidiabetic agents. The main disadvantages of these agents are increased risk of genital infections and plasma volume depletion, and scarcity of long-term safety data.2 They are also less efficacious in people with renal impairment.

Although metformin is a well known first-line pharmacotherapy for type 2 diabetes, there is little consensus about the best second-line agent. This lack in consensus was shown in the latest position statement from the American Diabetes Association and European Association for the Study of Diabetes that suggested that either sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, or insulin can be used in combination with metformin when glycaemic targets are not met.3

To properly ascertain the place of SGLT2 inhibitors in the treatment algorithm of patients with type 2 diabetes, head-to-head trials of other glucose-lowering treatments are essential. SGLT2 inhibitors have a similar glucose lowering efficacy to metformin and DPP-4 inhibitors when used as monotherapy,4 and are licensed for use as first-line treatment when metformin cannot be used. Martin Ridderstråle and colleagues report in The Lancet Diabetes & Endocrinology a large (n=1549), 2-year, randomised, active-controlled trial of SGLT2 inhibitors as a second-line treatment. They compared the efficacy and safety of empagliflozin 25 mg once daily with glimepiride 1-4 mg once daily as an add-on to metformin monotherapy.5 Empagliflozin was non-inferior to glimepiride at 52 weeks (HbA1c difference vs glimepiride –0·07, 95% CI –0·15 to 0·01), whereas it was superior at 104 weeks (–0·11, –0·19 to –0·02). Although most of the patients did not attain the 4 mg dose in the glimepiride group, the non-inferiority of empagliflozin to glimepiride persisted irrespective of the glimepiride dose achieved during titration.

The percentages of adverse events were similar between groups but empagliflozin was associated with more genital infections and glimepiride with more hypoglycaemia. As expected, empagliflozin was associated with reductions in weight and blood pressure, whereas glimepiride resulted in weight gain. In a substudy, the weight reduction in the empagliflozin group was mostly due to reductions in fat mass (assessed with dual energy X-ray absorptiometry) and abdominal visceral and subcutaneous adipose tissue (assessed with MRI); these results are consistent with those noted with other SGLT2 inhibitors.6 The results of previous similar studies showed that dapagliflozin and canagliflozin at 100 mg/day were non-inferior to glipizide and glimepiride, respectively, as add-ons to metformin monotherapy at 52 weeks, whereas canagliflozin 300 mg/day was superior to glimepiride (least squares mean difference –0·12%, 95% CI –0·22 to –0·02).7,8 Although the difference in HbA1c in favour of the SGLT2 inhibitors is small in Ridderstråle and colleagues’ study, it occurred in the context of less hypoglycaemia and weight loss than in the glimepiride group. Additionally, this study is fairly long, suggesting that the glycaemic benefits of empagliflozin are more long-lasting compared with glimepiride.

Empagliflozin and canagliflozin have also been compared with sitagliptin as an add-on to metformin monotherapy.9,10 HbA1c reductions were similar between...
groups, but use of SGLT2 inhibitors was associated with greater weight loss and higher risk of genital infections after 12 weeks of treatment.\textsuperscript{9,10}

SGLT2 inhibitors seem to be a useful alternative to sulfonylureas because of greater and sustainable HbA\textsubscript{1c} reductions, a low risk of hypoglycaemia, increased weight loss, and a favourable effect on cardiovascular risk factors. However, sulfonylureas are cheaper, have long-term safety data, and have a positive effect on microvascular complications.\textsuperscript{1} Hence, with an increasing number of options, the choice of second-line treatment needs to be individualised according to factors including age, hypoglycaemia risk, renal function, weight, cardiovascular disease, and the use of concomitant treatments. The results from ongoing longer head-to-head trials of the sustainability of HbA\textsubscript{1c} reductions and the safety profile of SGLT2 inhibitors—specifically cardiovascular safety—will aid the choice of a second-line treatment.

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### The artificial pancreas: a digital-age treatment for diabetes

The artificial pancreas—the commonly accepted term for closed-loop glucose control—combines a continuous glucose monitor, insulin pump, and control algorithm into a system that automates insulin delivery. In The Lancet Diabetes & Endocrinology, Hood Thabit and colleagues\textsuperscript{11} multicentre, randomised crossover study assesses home-based use of overnight closed-loop insulin delivery for improvement of glucose control in 25 participants with type 1 diabetes. Extending previous work by the same group,\textsuperscript{2} the artificial pancreas system in the present study was automated, rather than manual, and was used by patients at home for 4 weeks. At-home use is a particularly notable aspect because in other outpatient trials the device was used in a controlled environment,\textsuperscript{1,4} and only one trial\textsuperscript{3} reported overnight closed-loop glucose control at home.

The primary outcome of Thabit and colleagues’ study—the proportion of time when overnight glucose was in the target range of 3.9–8.0 mmol/L between 0000 h and 0700 h—was significantly higher during the closed-loop period compared with during the control period (mean difference between groups 13.5% [95% CI 7.3–19.7; p<0.001]). Furthermore, closed-loop insulin delivery significantly lowered overnight mean glucose and time spent above target range; time spent below target was low and similar to during the control intervention. These results are in line with those reported by this group in adolescents.\textsuperscript{4} Additionally, glucose concentrations remained lower during the day—while the system was off—during closed-loop periods than during control periods, which could lead to reduced HbA\textsubscript{1c} concentrations and risk for diabetic complications.

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