Sodium-Glucose Co-Transport Inhibitors
Progress and Therapeutic Potential in Type 2 Diabetes Mellitus

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Abstract

The kidney plays a major role in glucose homeostasis because of its role in gluconeogenesis and the glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. Approximately 180 g of glucose is filtered daily in the glomeruli of a normal healthy adult. Typically, all of this glucose is reabsorbed with <1% being excreted in the urine. The transport of glucose from the tubule into the tubular epithelial cells is accomplished by sodium-glucose co-transporters (SGLTs). SGLTs encompass a family of membrane proteins that are responsible for the transport of glucose, amino acids, vitamins, ions and osmolytes across the brush-border membrane of proximal renal tubules as well as the intestinal epithelium. SGLT2 is a high-capacity, low-affinity transporter expressed chiefly in the kidney. It accounts for approximately 90% of glucose reabsorption in the kidney and has thus become the focus of a great deal of interest in the field of diabetes mellitus.

SGLT2 inhibitors block the reabsorption of filtered glucose leading to glucosuria. This mechanism of action holds potential promise for patients with type 2 diabetes mellitus (T2DM) in terms of improvements in glycaemic control. In addition, the glucosuria associated with SGLT2 inhibition is associated with caloric loss, thus providing a potential benefit of weight loss. Dapagliflozin is the SGLT2 inhibitor with the most clinical data available to date, with other SGLT2 inhibitors currently in the developmental pipeline. Dapagliflozin has demonstrated sustained, dose-dependent glucosuria over 24 hours with once-daily dosing in clinical trials. Although long-term safety data are lacking, studies to date have generally found dapagliflozin to be safe and well tolerated. Concerns related to SGLT2 inhibition include the fact that by their very nature they cause glucose elevation in the urine that can theoretically lead to urinary tract and genital infections, electrolyte imbalances and increased urinary frequency. Although studies to date have been promising in terms of these and other concerns, longer-term studies evaluating the usual safety and efficacy outcomes will need to be conducted. Similarly, head-to-head comparator trials are needed to determine the role of SGLT2 inhibitors in relation to the many other therapeutic options available for the treatment of T2DM. If significant reductions in haemoglobin A1c are associated with SGLT2 inhibitor therapy, and these agents are determined to be safe and well tolerated in the long term, they could become a major breakthrough in the T2DM treatment armamentarium.
Currently, over 23 million children and adults have diabetes mellitus in the US, a sum that equates to nearly 8% of the population.[1] Listed as the seventh leading cause of death in the US, diabetes increases the risk of heart disease and stroke by 2- to 4-fold.[2] Multiple studies have linked increased haemoglobin A1c (HbA1c) to an increased risk of diabetes-related complications, ischaemic heart disease and death.[3-5] Despite the clear need for ‘good’ glucose control, many patients are not able to achieve glycaemic goals set by the American Diabetes Association (ADA) and other professional organizations. Less than half of adults in the US with diabetes reach a target HbA1c level of <7%.[6-8] In the UKPDS (United Kingdom Prospective Diabetes Study), 18% of patients developed a diabetes-related complication within 6 years of a diagnosis of type 2 diabetes mellitus (T2DM).[9] Further complicating the matter, T2DM is a progressive disease, and treatment becomes more challenging as the disease progresses and β-cell function declines.[10] In fact, monotherapy is rarely successful in achieving glycaemic control in the long term. During the UKPDS, approximately 50% of patients required combination therapy within 3 years of diagnosis, with the percentage increasing to 75% by the ninth year of disease.[10] Given the need for combination therapy to meet glycaemic goals in most patients, the search for new therapeutic targets and novel mechanisms of drug action has yielded exciting findings with the potential to revolutionize the treatment of T2DM in the future.

Traditionally, pharmacotherapeutic interventions have been aimed at stimulating insulin secretion or addressing peripheral insulin resistance. One novel drug class currently under study, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, target another pathophysiological process present in people with T2DM. SGLT2 is a member of a large group of sodium substrate co-transporters for which there are genes expressed in various human tissues ranging from epithelial tissues to tissues within the CNS.[11] SGLT2 is a 672-amino acid transporter expressed within the S1 segment of the proximal tubule of the kidney and is believed to be responsible for the majority of renal glucose reabsorption.[12] Given the role of SGLT2 in glucose transport within the kidney, it has become an attractive therapeutic target in the treatment of T2DM.[13,14]

This review focuses on the role of the kidney in glucose homeostasis, the mechanism of action of SGLT2 inhibitors for the treatment of T2DM and early clinical data from investigational agents in this novel class of medications. Relevant literature was retrieved from a search of PubMed to January 2010 for English-language articles using the search terms ‘type 2 diabetes’ plus ‘dapagliflozin’, ‘canagliflozin’ and ‘SGLT2 inhibitor’. Bibliographies from retrieved articles were searched for additional relevant articles. Abstract books from recent endocrinology conferences (including annual meetings of the ADA and the European Association for the Study of Diabetes [EASD]) were also searched for recently published abstracts.

1. Role of the Kidney in Glucose Homeostasis

Although the kidney is not usually considered to be one of the major organs responsible for glucose homeostasis, a review of the data in support of such a position can only lead to the conclusion that this belief is erroneous. The kidney plays a major role in glucose homeostasis in two ways: (i) gluconeogenesis; and (ii) glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. Additionally, the kidney may not only play a significant role in normal glucose homeostasis, but may also play a role in diabetes and even in the management of hyperglycaemia.

1.1 Gluconeogenesis

Trials carried out over the past half decade, in animal models and in vitro, have demonstrated that the mammalian kidney can produce and release glucose under certain conditions.[13] It has been known for some time that the ability of the kidney to produce and release glucose during prolonged periods of fasting rivals that of the liver.[16] It has also been widely accepted for some
time that the kidney plays a significant role in glucose production during periods of acidosis, when hepatic gluconeogenesis is attenuated.\[17\] However, more recent studies have demonstrated that the kidney plays a significant role in glucose production during 'normal' physiological periods as well as during some pathological situations, with some studies indicating that renal glucose production accounts for approximately 25% of systemic glucose production.\[18\] The regulation of gluconeogenesis is complex and may be modulated (increased) by stimuli such as potassium depletion, experimental diabetes, parathyroid hormone, angiotensin II, catecholamines, glucocorticoids and thyroid hormone.

Glucose may be liberated into the systemic circulation via gluconeogenesis or glycogenolysis. Although glycogenolysis is a significant contributor, it is now believed that gluconeogenesis is responsible for approximately 55% of glucose released during the postabsorptive period.\[15\] Only two organs in the body possess the gluconeogenic enzyme and G-6-phosphatase enzyme activity sufficient to complete the final enzymatic step of gluconeogenesis: the liver and the kidney. Data suggest that renal glucose production accounts for approximately 20% of overall endogenous glucose release and is responsible for approximately 40% of all released glucose due to gluconeogenesis.\[15\]

The contribution of excessive gluconeogenesis to hyperglycaemia in patients with type 1 diabetes mellitus (T1DM) and T2DM is well documented. Additionally, an increase in renal gluconeogenesis has been demonstrated in animal models of diabetes and in some human studies.\[13\] In one study in patients with T2DM, it was reported that the increase in renal glucose release was about proportional to the increase observed in hepatic glucose release.\[19\] Therefore, it is reasonable to hypothesize that aberrations in renal glucose production and release may play a role in diabetes.

1.2 Glomerular Filtration and Reabsorption of Glucose

Approximately 180 g of glucose is filtered daily in the glomeruli of a normal healthy adult.\[20\] Typically, all of this glucose is reabsorbed with <1% being excreted in the urine.\[21\] The reabsorption of glucose from the tubules is very complex, involves multiple transport mechanisms, and includes transport of glucose out of the tubule and then across the basolateral membrane into the peritubular capillaries. Under normal conditions, when the tubular glucose load is approximately 120 mg/minute, no glucose is lost in the urine. However, when the glucose load exceeds the ‘glucose threshold’ and rises to a level >220 mg/minute, a small amount of glucose begins to appear in the urine.\[20\] There is a wide range of blood glucose levels required to provide a renal glucose load sufficient to exceed the ‘glucose threshold’. One study reported that these blood glucose levels ranged between 130 mg/100 mL and 300 mg/100 mL, and that there was a relationship between age and an increase in threshold levels.\[22\] As we age our glucose threshold increases. The ‘glucose threshold’ where some glucose is lost is reached before the transport maximum has been reached. This is because some nephrons excrete glucose before others have reached their transport maximum. The renal transport maximum is reached when all of the nephrons have reached their maximum capacity to reabsorb glucose.\[20\] The most common cause of glucosuria is diabetes and the average patient will not ‘spill’ glucose into their urine until their blood glucose concentration exceeds 180 mg/100 mL.

The transport of glucose through the basolateral membrane and back into the peritubular capillary is accomplished by glucose transporter proteins (GLUTs) and occurs by facilitated diffusion.\[23\] Thus, the exit of glucose across the basolateral membrane does not consume energy. This system utilizes GLUT2 transporters in the early proximal tubule and GLUT1 transporters in the late proximal tubule.\[23\]

The transport of glucose from the tubule into the tubular epithelial cells is accomplished by SGLTs. SGLTs encompass a family of membrane proteins that are responsible for the transport of glucose, amino acids, vitamins, ions and osmo-lytes across the brush-border membrane of proximal renal tubules as well as the intestinal epithelium.\[24\] SGLT1 is a low-capacity,
high-affinity sodium-glucose transporter found primarily in the gastrointestinal tract but is also found in the S3 segment of the proximal tubule.\(^{[24]}\) SGLT1 is primarily responsible for glucose absorption in the gastrointestinal tract and only accounts for approximately 10% of glucose reabsorption in the kidney. SGLT2 is a high-capacity, low-affinity transporter expressed chiefly in the kidney. SGLT3, while found widely throughout the body in skeletal muscle and the nervous system, is not a glucose transporter but is thought to be a glucose sensor.\(^{[25]}\) The function of other members of the SGLT family (SGLT4, 5 and 6) in humans is uncertain at this time.

The most salient SGLT transporter in the kidney is SGLT2. SGLT2 activity accounts for the majority of glucose reabsorption in the kidney and has thus become the focus of a great deal of interest in the field of diabetes. This transporter is located primarily in the brush-border membrane of the S1 (early) segment of the proximal tubule.\(^{[23,24]}\) SGLT2 binds with \(\text{Na}^+\) and glucose in the tubule fluid. The \(\text{Na}^+\) and glucose is translocated across the apical cell membrane. This process is driven by the electrochemical gradient for \(\text{Na}^+\) between the tubule and the cell, and because of this is termed ‘secondary active transport’.\(^{[24]}\)

Reduction of the activity of SGLT2 in the renal tubules has become an area of great interest in the past few years. The maximal reabsorptive capacity (\(T_m\)) of the renal tubules is variable but on average is 375 mg/minute.\(^{[26]}\) In non-diabetic individuals the filtered glucose load does not exceed 375 mg/minute, and all of the filtered glucose is reabsorbed and returned to the systemic circulation. In an individual with diabetes who experiences a filtered glucose load of >375 mg/minute, the reabsorptive capacity is exceeded and the excess glucose is eliminated via the urine. Methods to modify this pathway by reducing the reabsorptive capacity of the renal tubules so that excess glucose could be eliminated via the urine are being investigated. The two most likely methods for achieving this effect are by the administration of chemical inhibitors of SGLT2, to reduce the activity of present SGLT2 transporters, or by the use of SGLT2 oligonucleotides, to reduce the expression of SGLT2 transporters.\(^{[25]}\) Although both methods offer promise, the first method is much further along in development.

2. Sodium-Glucose Co-Transport (SGLT) Inhibitors

Given the relatively recent recognition of the importance of the kidney in normal glucose homeostasis, SGLT2 inhibitors have become a focus of developmental and clinical research in the field of diabetes.\(^{[27,28]}\) The first natural SGLT2 inhibitor, phlorizin, was isolated in 1835 from the root bark of the apple tree.\(^{[29]}\) When studied in animal models, phlorizin demonstrated the ability to lower both fasting and postprandial blood glucose levels without the occurrence of hypoglycaemia.\(^{[30]}\) Phlorizin studies in humans showed that oral administration caused renal glycosuria and weight loss.\(^{[31]}\) Upon characterization of SGLT2 in the 1990s, the mechanisms involved in phlorizin-induced glycosuria were realized, resulting in a therapeutic interest in phlorizin.\(^{[32]}\) Although it demonstrated potential clinical utility in animal and human models, phlorizin was ultimately not developed as a drug for the treatment of T2DM because of its rapid degradation by lactase-phlorizin hydrolase and poor absorption from the gastrointestinal tract.\(^{[29]}\) SGLT2 inhibitors have subsequently been developed – glycoside moieties derived from the basic phlorizin structure – that possess more favourable pharmacokinetic profiles. The mechanism of action of SGLT2 inhibitors is illustrated in figure 1.\(^{[33]}\) As noted in section 1.2, SGLT2 is responsible for the majority of the reabsorption of filtered glucose in the early proximal tubule of the nephron. By inhibiting SGLT2, its inhibitors block the reabsorption of filtered glucose, in turn leading to glycosuria. This mechanism of action holds potential promise for patients with T2DM in terms of improvements in blood glucose. In addition, the glycosuria associated with SGLT2 inhibition can result in a loss of approximately 200–300 kcal/day, thus providing a potential benefit of weight loss.\(^{[34]}\)
3. Dapagliflozin

As noted in the previous section, there are a number of SGLT2 inhibitors either previously studied or currently under study for the treatment of diabetes.[35] Dapagliflozin is an SGLT2 inhibitor currently in phase III studies. Of those SGLT2 inhibitors currently under study, dapagliflozin boasts the most published clinical data to date. The selectivity of dapagliflozin for SGLT2 allows for decreased renal reabsorption of glucose without a discernable effect on the function of SGLT1 in the small intestines; thus, gastrointestinal adverse events (AEs) are theoretically minimized with this agent.[36] The following discussion outlines clinical data available to date reporting the efficacy and safety of dapagliflozin.

3.1 Efficacy

Data from clinical studies involving healthy volunteers and patients with T2DM have been published. Single and multiple ascending-dose studies in healthy individuals involving dapagliflozin at dosages ranging from 2.5 to 500 mg/day have demonstrated sustained, dose-dependent glucosuria over 24 hours with once-daily dosing.[37] Dose-dependent glucosuria has likewise been demonstrated in studies involving patients with T2DM, such as in a monotherapy dose-ranging study in 389 participants with T2DM.[34] Participants were randomized to receive various doses of dapagliflozin ranging from 2.5 to 50 mg, metformin XR (extended release) or placebo for 12 weeks. Those receiving dapagliflozin experienced mean HbA1c changes from baseline of −0.55% to −0.90%, and mean changes in fasting plasma glucose from baseline of −16 to −31 mg/dL. Placebo-subtracted changes in weight from −1.3 to −2.0 kg were also achieved over 12 weeks of treatment in dapagliflozin-treated individuals. Similarly, another 14-day study in subjects with T2DM demonstrated statistically significant decreases in fasting serum glucose and improvements in oral glucose tolerance test results from baseline in dapagliflozin-treated subjects when compared with those randomized to placebo.[38]

Findings from a larger study in 546 patients with T2DM were recently reported at the 45th EASD Annual Meeting.[39] This randomized, double-blind, placebo-controlled trial enrolled patients aged 18–77 years. Participants were randomized to receive dapagliflozin 2.5 mg, 5 mg or 10 mg, or placebo, in addition to open-label metformin for 24 weeks. End of study changes in HbA1c from baseline were −0.67, −0.70, −0.84 and −0.30% in the dapagliflozin 2.5 mg, 5 mg, 10 mg and placebo groups, respectively (p < 0.05 for all dapagliflozin doses vs placebo). Beneficial changes in bodyweight were also seen after 24 weeks in all groups (−2.66%, −3.66%, −3.43% and −1.02%, respectively). The adjusted proportion of patients experiencing a ≥5% decrease from baseline in bodyweight was also calculated. The percentage (95% CI) of patients achieving ≥5% weight loss at 24 weeks was 24.0% (16.8, 31.2), 25.4% (18.1, 32.7), 28.0% (20.4, 35.5) and 5.9% (1.9, 9.8) in the four treatment groups, respectively. Based on these findings, the investigators concluded that once-daily dapagliflozin was associated with significant improvements in glycaemic control and clinically meaningful weight loss over 24 weeks of therapy when compared with placebo in T2DM patients inadequately controlled with metformin alone.

In addition to treatment-naive patients and those receiving metformin monotherapy, efficacy data for dapagliflozin as add-on therapy in T2DM patients poorly controlled on insulin plus oral antidiabetic drugs (OADs) was also recently
reported from a randomized, double-blind, placebo-controlled study. Participants (n = 71) were randomized to receive dapagliflozin 10 mg, dapagliflozin 20 mg or placebo, in addition to baseline OADs and 50% of their prestudy daily insulin dose for 12 weeks. Placebo-subtracted changes in HbA₁c (95% CI) from baseline for the dapagliflozin 10 mg and 20 mg groups were −0.70 (−1.1, −0.3) and −0.78 (−1.2, −0.4), respectively. In addition, in both dapagliflozin-treated groups 65.2% of patients achieved a ≥0.5% decline in HbA₁c from baseline versus 15.8% of placebo-treated patients. Weight loss was also achieved over 12 weeks in the dapagliflozin-treated patients. The placebo-subtracted changes in body-weight (95% CI) from baseline were −2.6 kg (−4.0, −1.2) and −2.4 kg (−3.8, −1.0) in the dapagliflozin 10 mg and 20 mg groups, respectively. Collectively, these findings suggest that dapagliflozin may be beneficial as add-on therapy in patients achieving inadequate glycaemic control with insulin plus an OAD combination therapy, and may help ameliorate the weight gain associated with insulin therapy in patients with T2DM. Additional clinical studies are currently underway with dapagliflozin. Clinical efficacy data involving dapagliflozin in combination with a variety of other antidiabetic agents are expected in the near future.

3.2 Adverse Events

Although long-term safety data are lacking, studies to date have generally found dapagliflozin to be safe and well tolerated. It is useful to note that genetic mutations involving SGLT2 cause isolated glucosuria similar to that achieved with SGLT2 inhibitors, with individuals affected not experiencing significant morbidity or a decreased life expectancy. Reported AEs in clinical trials were most often gastrointestinal in nature and appear to occur more commonly in patients receiving concomitant metformin therapy. SGLT2 inhibition is generally not associated with hypoglycaemia. Two episodes of hypoglycaemia, defined as symptomatic hypoglycaemia and/or a blood glucose level ≤50 mg/dL on multiple occasions, were reported in one phase II study in dapagliflozin-treated patients. Another phase II study reported hypoglycaemia in 6–10% of dapagliflozin-treated patients, compared with 4% in the placebo group and 9% in those receiving metformin. When used as add-on therapy in patients inadequately controlled with metformin monotherapy, hypoglycaemia was reported in 2.2–3.7% of patients receiving dapagliflozin, compared with 2.9% of placebo-treated patients over 24 weeks of treatment. In contrast, the incidence of hypoglycaemia appears to be increased when dapagliflozin is used as add-on therapy to insulin plus OAD therapy, with 25.0–29.2% of dapagliflozin-treated patients reporting hypoglycaemia compared with 13.0% of those receiving placebo.

Given the mechanism of SGLT2 inhibitors, renal monitoring has been performed in clinical trials to identify any potential changes in renal function resulting from therapy. Short-term trials with dapagliflozin have not identified any clinically significant changes in renal function or electrolyte levels to date. Fourteen days of treatment showed no clinically meaningful changes in estimated glomerular filtration rate or in 24-hour urine excretion of electrolytes. Dapagliflozin has demonstrated a diuretic effect in clinical trials as evidenced by an increased 24-hour urinary output volume ranging from 107 to 470 mL above baseline in dapagliflozin-treated patients. The diuretic effect of dapagliflozin has been associated with an observed mean decrease in systolic blood pressure ranging from −2.6 to −6.4 mmHg in one study. Although this could be a theoretical benefit in patients with T2DM, hypotension is a potential concern, with up to 2% of dapagliflozin-treated patients reporting a hypotensive event. However, it is important to note that in this study 2% and 4% of placebo- and metformin-treated individuals, respectively, experienced a hypotensive event. Increased magnesium and decreased uric acid levels have also been reported with treatment. Safety data from long-term clinical trials are needed to further determine the safety of SGLT2 inhibition in terms of renal function.

Other potential AEs associated with SGLT2 inhibition are urinary tract infections (UTIs) and
genital infections secondary to increased glucosuria. In the study conducted by List and colleagues,\[34\] 5–12% of dapagliflozin-treated patients reported a UTI, compared with 6% of placebo-treated and 9% of metformin-treated patients. Genital infections occurred in 2–7% of those in the dapagliflozin group, with no infections reported in placebo-treated participants and 2% of those receiving metformin reporting such an event. In a 24-week study, UTI rates were similar in dapagliflozin-treated patients (4.4–8.1%) when compared with those receiving placebo (8.0%).\[39\] However, genital infections occurred more frequently in those receiving dapagliflozin versus placebo (8–13.1% vs 5.1%, respectively). The relationship between SGLT2 inhibitors and such infections warrants further study in long-term trials to determine the risk of UTI and genital infections with prolonged therapy.

4. Other Select SGLT2 Inhibitors in Development

Several SGLT2 inhibitors in addition to dapagliflozin have been studied in phase II and III trials. Sergliflozin, remogliflozin and canagliflozin are three other notable agents that have been studied in this drug class. Sergliflozin and remogliflozin, developed by GlaxoSmithKline, have both been halted from further development because of the evaluation of "circumstances including the development status of SGLT2 inhibitors by competitors".\[43,44\] Canagliflozin, under development by Johnson & Johnson, is currently in phase III study,\[41\] with no published clinical data available to date. A number of other SGLT2 inhibitors that have been recently described in clinical development for the treatment of T2DM are currently in preclinical, and phase I and II studies.\[35,41\]

5. Discussion and Conclusions

Elevated plasma glucose levels are impacted by numerous physiological mechanisms. In T1DM, the main cause of hyperglycaemia is the lack of insulin production and release from the β cells of the pancreas. Similarly, patients with T1DM have an absolute deficiency in amylin secretion. In T2DM patients, blood glucose is elevated because of insulin insensitivity, lack of first-phase insulin release, progressive β-cell dysfunction, excess levels of glucagon and low levels of glucagon-like peptide-1 (GLP-1). The more we learn about glucose homeostasis, the more we realize that we still have much more to learn. With our current knowledge of the physiology and pathophysiology of glucose, it seems unlikely that many other pathways will be discovered that impact blood glucose levels. Yet, new unique treatments to lower blood glucose are being, or have been, developed in recent years. The approval of new drug categories for the management of T2DM, such as the dipeptidyl-peptidase-4 inhibitors sitagliptin, saxagliptin and vildagliptin, the bile acid sequestrant colesevelam and dopamine agonist bromocriptine, have opened new avenues for clinicians to address hyperglycaemia in patients who are refractory to other treatment approaches. Similarily, SGLT2 inhibitors, if approved, will provide clinicians with yet another therapeutic tool to treat T2DM patients.

SGLT2 inhibitors have the potential to have a significant impact on the treatment of patients with T2DM, which may also prove to be true for those with T1DM. This novel class of medications addresses hyperglycaemia with a unique mechanism of action that has been shown in preclinical models to lower blood glucose independently of insulin.\[45-48\] Early phase I and II studies have suggested SGLT2 inhibitors to be not only effective but also tolerable and safe. Pharmaceutical manufacturers are aggressively trying to develop drugs in this class, with a number of agents currently in the developmental pipeline. There exists a great deal of positive anticipation in lieu of results from phase III clinical trials to better elucidate the efficacy and safety of this class of medications across various patient populations and clinical scenarios.

Concerns related to SGLT2 inhibitor use include the fact that by their very nature they cause glucose to be elevated in the urine and excreted through the ureters, bladder and urethra. Will long-term studies give cause for concern regarding the incidence of UTIs and genital infections?
Will detrimental electrolyte imbalances result due to loss of potassium or magnesium with long-term therapy? Will issues arise regarding urinary frequency or urgency? Will monitoring of these drugs require urine glucose tests to be used again? Of course, longer-term studies evaluating the usual safety and efficacy outcomes will need to be conducted. Likewise, head-to-head comparator trials are needed to determine the role of SGLT2 inhibitors in relation to the many other therapeutic options available for the treatment of T2DM. The cost of this therapy will also be a determinant of its use in the current economic environment.

The initial response to this new method to possibly treat diabetes patients is positive and potentially exciting. The fact that weight loss is an outcome will stimulate many patients and clinicians alike towards the use of SGLT2 inhibitors. Of additional benefit, SGLT2 inhibitor therapy is expected to be associated with a low risk of hypoglycaemia because there is no interference with the normal counter-regulatory mechanisms of glucose homeostasis. Mechanistically, SGLT2 inhibitors could be used as monotherapy or as a component of combination therapy at any stage of disease. If significant reductions in HbA1c are associated with SGLT2 inhibitor therapy, and these agents are determined to be safe and well tolerated in the long term, they could become a major breakthrough in the treatment armamentarium for patients with diabetes.

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