



SGLT2 Inhibitors: A Multi-Pronged Tool Against Type 2 Diabetes

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Introduction

The 2013 Canadian Diabetes Association guidelines for diabetes management reinforce the need for patients to achieve evidence-based treatment targets for blood glucose, blood pressure and LDL-C. With respect to glycemic control, the CDA advocates that antihyperglycemic agents be selected according to individual needs and preferences, and with complementary mechanisms of action. In addition to the familiar therapies described in the guidelines, a novel class of oral medications known as sodium glucose cotransporter-2 (SGLT2) inhibitors will soon be available in Canada. These medications improve glucose control by reducing the kidney's ability to resorb filtered glucose. In addition to glucose lowering, these agents can also reduce body weight and blood pressure. Potential adverse effects include an increase in urinary tract and mycotic genital tract infections. Preliminary data from large studies of their cardiovascular safety profile are reassuring, and more definitive trials are underway. This paper will introduce clinicians to this new class of oral antihyperglycemic agents.

Diabetes in Canada

The prevalence of type 2 diabetes in Canada and worldwide, and our foreknowledge of an expanding epidemic with potentially devastating morbidity and mortality, are cause for sober reflection by clinicians. More than 350 million people worldwide, including 2.4 million Canadians (nearly 7% of the population), have diabetes. At current incidence rates, the number

will be 3.7 million, or nearly one in 10 Canadians, by 2020 (Public Health Agency of Canada, 2011).

Many recent clinical trials highlight the microvascular (nephropathy, neuropathy, retinopathy) benefits accruing from glycemic control, and the cardiovascular benefits of vascular protection strategies in people with diabetes. Over the last decade or so, there has been intensive dissemination of management guidelines based on these strategies. An ever-wider range of therapies targeting hyperglycemia, hypertension and dyslipidemia are available. Nevertheless, a stubbornly small proportion of patients achieve the recommended treatment targets of A1C $\leq 7\%$, blood pressure (BP) $< 130/80$ mmHg and low-density lipoprotein cholesterol (LDL-C) ≤ 2 mmol/L. In the recent Diabetes Mellitus Status in Canada survey, for example, only 50% of patients met the glycemic goal, 57% the LDL-C target, and 36% had optimal BP (Leiter L et al. *Can J Diabetes* 2013;37(2):82-9). The challenges of diabetes management and strategies to address gaps in care must remain key points of focus for health practitioner education.

Updated guidelines for disease prevention and management were published in 2013 by the Canadian Diabetes Association (<http://guidelines.diabetes.ca/>; *Can J Diabetes* 2013;37(suppl 1):S1-S212). Changes from the 2008 guidelines include the use of A1C $\geq 6.5\%$ as a new criterion for making the diagnosis of type 2 diabetes; a glucose control pharmacologic treatment algorithm that emphasizes individualization of both modes and goals of therapy according to patient need and preferences; and the recommendation to initiate medical therapy immediately and relatively aggressively in most patients with A1C $\geq 8.5\%$ at diagnosis.

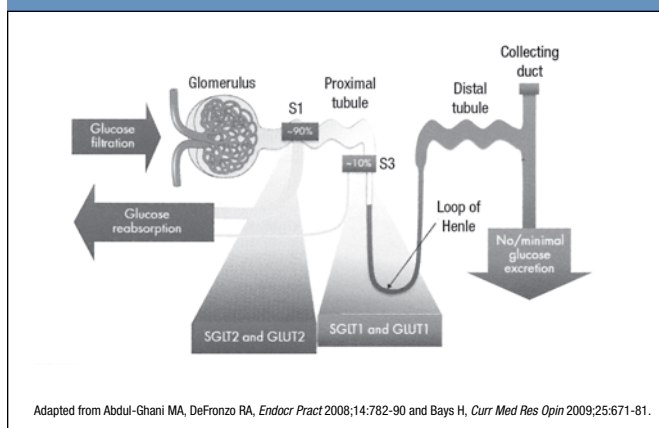
New Agents with a Novel Mechanism

Against this background, there continues to be room for novel therapies that help people with diabetes reach their treatment goals. A unique class of oral medications, sodium glucose cotransporter-2 (SGLT2) inhibitors, are now being used in the US, Europe and Australia, and Health Canada

approval of one or more of these agents is anticipated. The most extensive data available emanate from clinical studies of canagliflozin, dapagliflozin and empagliflozin.

At the glomerulus, glucose is freely filtered from the blood into the urinary filtrate (Figure 1). The body has developed mechanisms to defend against the calorie loss related to losing filtering glucose, and these systems are designed to efficiently reclaim all of the filtered glucose under normal circumstances. The sodium glucose co-transporters (SGLTs) are present on the surface of the proximal convoluted tubular cells, and face towards the urinary filtrate. The SGLTs resorb filtered glucose back into the proximal convoluted tubular cells. The resorbed glucose then returns to the circulation through the glucose transporter 2 (GLUT 2) system. Importantly, these are referred to as co-transporters, as glucose is resorbed along with sodium. These co-transporters ensure maximal resorption of these nutrients and their return to the bloodstream. There are multiple members of the SGLT family. In the kidneys, about 90% of glucose is resorbed via SGLT2 and about 10% via SGLT1. The latter are more prominent in glucose resorption in the small intestine. These co-transporters have been described respectively as the ‘bulldozers’ and ‘brooms’ of glucose resorption in the kidney. Their function is vital to humans with a low-calorie diet because they minimize energy loss; however, given the abundant daily food intake of most North American individuals, the importance of fully protecting against calorie loss in the urine is declining. Assuming a glomerular filtration rate (GFR) of 180 L per day, and an average blood glucose concentration of 5 mmol/L, the kidneys resorb about 900 mmol of glucose (162 g), equivalent to 648 calories.

Figure 1. Mechanism of Renal Glucose Reabsorption



The SGLT system has a maximum capacity: glucose is fully resorbed as long as the blood level does not exceed

about 12 mmol/L; any amount of sugar beyond this threshold is allowed to spill into the urine. Following administration of an SGLT2 inhibitor, about 30 to 50% of the filtered glucose is lost in the urine, resulting in glucosuria of about 60 to 80 g/day, or about 240 to 320 calories. Osmotic diuresis leads to increased urinary output (100-500 mL/day), and a mild decrease in plasma volume and increase in hematocrit of 2% to 3%. The glucosuria and ensuing reduction in blood glucose is independent from insulin secretion mechanisms.

Efficacy of SGLT2 Inhibitors: A1C, Body Weight and BP Effects

Lowers A1C

In studies of people with diabetes and normal renal function, SGLT2 inhibitors consistently produced a dose-dependent decrease in A1C of between 0.6 and 1.1%. Similar results were achieved whether the drug was given as monotherapy, in combination with metformin, a sulfonylurea, a thiazolidinedione or insulin, or even in triple therapy, suggesting that this insulin-independent mechanism is complementary to the mechanism of action of other classes of drugs. A1C lowering with SGLT2 inhibitors is similar or better than that achieved with a DPP-4 inhibitor, and appears to be superior to sulfonylureas. In a recent 2-year study, canagliflozin 300 mg was associated with greater A1C lowering than glimepiride (Leiter L et al. CDA annual meeting, Montreal 2013, abstract 70). Similarly, dapagliflozin 10 mg was found to be more efficacious than glipizide over 2 years even though its initial effect on A1C was not as dramatic (Nauck M et al. ADA Annual Meeting, San Diego 2011, abstract 40LB). Because urinary glucose excretion is proportional to plasma glucose, a more potent effect of medications on A1C can be expected in patients with a higher initial value. In an open-label study of empagliflozin in which patients had an initial mean A1C of 11.5%, the mean decrease was 3.7% (Roden M et al. *Lancet Diabetes Endocrinol* 2013;1:208-19.)

Because the total amount of glucose filtered at the glomerulus falls as the GFR falls, the potency of SGLT2 inhibitors is lower in patients with chronic kidney disease. When the GFR is approximately 45-60 mL/min, the expected decrease in A1C is about half that observed in patients with normal kidney function. It may therefore be prudent to restrict the use of these agents to patients with GFR above this threshold.

Lowers Body Weight

The loss of glucose and calories in the urine promotes weight loss. Studies suggest an average weight loss of 2 to 4 kg over a period of 6 months. This result is likely similar to that achievable with GLP-1 receptor agonists, although no head-to-head trial has been performed. About 80-90% of patients lose some weight, with 20 to 33% of patients losing over 5% of their body weight. Two-thirds of the weight reduction is attributable to fat loss rather than reduction in lean body mass. After 6 months, the patients' weight appears to stabilize despite persistent glucosuria. The reason(s) for this plateau have not yet been elucidated.

Lowers Blood Pressure

Patients taking an SGLT2 inhibitor experience a fall in systolic BP (SBP) of 4 to 6 mmHg. The decrease is most impressive in patients with baseline SBP higher than 140 mmHg; diastolic BP falls by about 2 mmHg. BP reduction is observed even in patients with compromised kidney function. While it is tempting to attribute the fall in BP to intravascular volume contraction, this appears to be a transient phenomenon, while the reduction in BP is persistent. The exact mechanism for the fall in BP with these medications remains unclear, but only about 30-40% of the reduction can be attributed to weight loss.

Safety, Renal Function Effect, and Impact on Hypoglycemia

Among the potential consequences of the 'sweetened' urine produced with SGLT2 inhibition is an increase in urinary and genital tract infections. These are most likely in the first six months of treatment and are generally mild to moderate. Reports to date indicate an approximate 30% increase in cystitis, especially in women; but no increase in pyelonephritis. Mycotic infections are also three to four times more frequent with these medications versus placebo; again, women are most affected. These infections respond to usual treatments and have not usually required withdrawal of therapy.

With respect to volume depletion effects, in studies to date the incidence of orthostatic hypotension, dizziness or dehydration has been low, although individuals age ≥ 65 , and those on loop diuretics, ACEi or ARBs may be at greater risk. In patients at risk for volume depletion effects, a lower initial dose of

the SGLT2 inhibitor or an adjustment to the dose of diuretics may be required.

In patients exposed to an SGLT2 inhibitor, there is a transient and mild decrease in GFR of 4-5 mL/min shortly after initiation. This phenomenon is related to a mildly contracted intravascular volume and intrarenal hemodynamic changes. Within a few weeks the decline in GFR returns to baseline due to renal compensatory mechanisms. In patients with moderate CKD, there can be a more persistent decline in GFR, but a washout study of empagliflozin demonstrated reversibility of this effect, indicating no permanent adverse effect on renal function with SGLT2 inhibition. Further studies will help to establish the long-term impact of SGLT2 inhibition on renal function, but preliminary data suggests a possible nephroprotective effect.

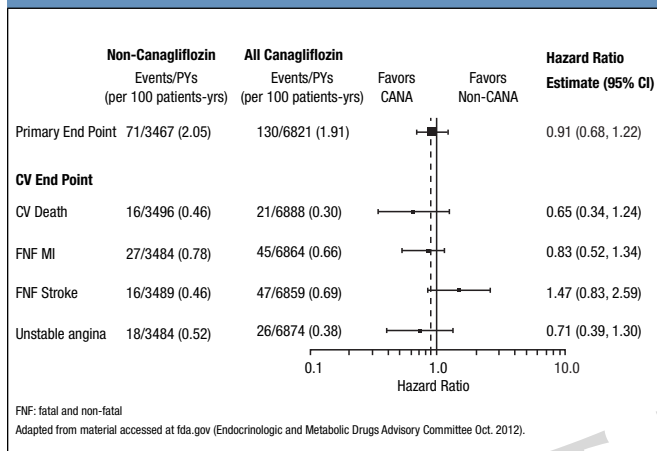
SGLT2 mediated glucose excretion is proportional to plasma glucose, limiting the risk of hypoglycemia. As mentioned earlier, the mechanism of action of SGLT2 inhibitors is insulin-independent, and counter-regulatory mechanisms remain intact. Insulin levels fall when plasma glucose is low. Studies to date provide reassurance that when used as monotherapy or in combination with metformin or another agent with a low potential to induce hypoglycemia, SGLT2 inhibitors do not increase the risk of hypoglycemia. Hypoglycemic episodes do become somewhat more likely when these agents are combined with a background therapy known to increase the risk of hypoglycemia such as sulfonylureas or insulin, and the dose of these medications may need to be reduced when an SGLT2 inhibitor is added.

Cardiovascular Safety Considerations

Loss of body weight/fat mass and a decrease in A1C and BP can reasonably be expected to have positive effects on cardiovascular (CV) outcomes. SGLT2 inhibition is associated with changes in the lipid profile. Pooled study data suggest HDL-C and triglyceride (TG) levels improve by 0.02 to 0.07 and 0.06 to 0.2 mmol/L respectively. However, LDL-C increases by 0.1 to 0.2 mmol/L or 2% to 8%. The clinical relevance of the small rise in LDL-C is uncertain. Cardiovascular safety information from the initial Phase III trials is reassuring, however, the results of ongoing dedicated CV safety studies of SGLT2 inhibitors are eagerly awaited. Data released from CANVAS, an ongoing study of canagliflozin in more than 4000 patients at high CV risk (Veracruz F et al. *Am Heart J* 2013;166(2):217-23), indicate that to date, there is no statistical difference between the safety of this

agent and placebo. A slight but nonsignificant increase in stroke observed in the treatment arm has a very wide confidence interval, suggesting it may be due to chance (Figure 2).

Figure 2. Canagliflozin: Incidence and HR for Adjudicated CV Events

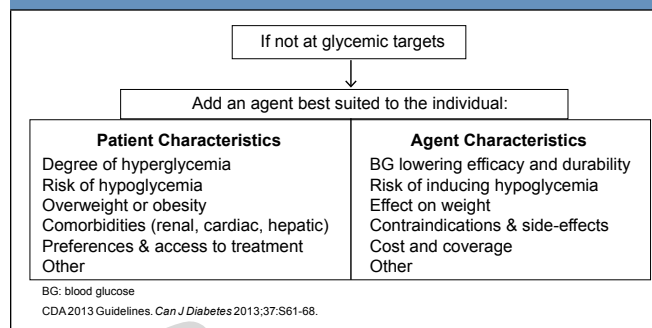


Another Option for Individualized Therapy

The latest CDA practice guidelines emphasize the need for people with diabetes to achieve targets for A1C, optimize vascular health and ensure renal protection in order to improve their long-term outcomes. In addition to advocating for positive lifestyle changes, the CDA gives guidance on the use of antihyperglycemic pharmacotherapy (Figure 3). Metformin remains the agent of choice for first-line therapy. Additional treatment to lower blood glucose levels will ideally involve medications with synergistic or complementary mechanisms to address all causes of hyperglycemia in type 2 diabetes. Selection of additional agents should take into consideration the needs and preferences of the patient, including comorbidities, health concerns such as obesity, the

risks of hypoglycemia and other adverse effects, and costs/drug coverage. Convenience of the drug regimen should also be a factor. Studies have demonstrated that oral regimens that reduce pill burden can be helpful (Dailey GE. *Managed Care* 2004;February:41-9).

Figure 3. Individualizing Antihyperglycemic Therapy



Summary

While the role of SGLT2 inhibitors in the management of people with diabetes in Canada remains to be determined, the members of this class have many desirable characteristics. These medications have a unique mechanism of action that will complement metformin and other antihyperglycemic agents. With their positive impact on A1C, weight and blood pressure, and a low risk of inducing hypoglycemia, they have the potential to help safely control glycemia and aid vascular protection. Their multiple effects may reduce the treatment burden for some individuals. Their benefits must, of course, be balanced against potential inconveniences or adverse effects such as a higher incidence of urinary and genital tract infections, and the potential for effects related to volume depletion. Their cardiovascular safety profile has yet to be confirmed but preliminary signals from large studies are reassuring, and more definitive trials are underway. Overall, their advent is welcome news in the ongoing and challenging battle against the epidemic of type 2 diabetes. □

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