Sodium-glucose cotransporter-2 inhibitors: A new era of kidney care

This review discusses clinical considerations and future use of sodium-glucose cotransporter-2 inhibitors in the context of kidney care.

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ABSTRACT

There is a significant and growing burden of chronic kidney disease in Canada. Sodium-glucose cotransporter-2 inhibitors, a class of glucose-lowering medications originally developed for patients with type 2 diabetes, have been found to be of benefit in modifying both kidney and cardiovascular disease trajectories, irrespective of diabetic status or hemoglobin A1c control. They work by multiple mechanisms, including pleiotropic effects on the kidney and reducing weight, blood pressure, and uric acid, and consistently demonstrate kidney and cardiovascular protection in patients with chronic kidney disease. To address the morbidity and mortality of individuals living with kidney disease, we need to translate this robust clinical trial evidence into clinical practice, a task that will partly fall on primary care physicians, who manage a large proportion of patients with chronic kidney disease. While this process will not be without challenges, uptake of this class of medications will unequivocally change the outcomes for patients living with chronic kidney disease across the entire spectrum of kidney disease for years to come.

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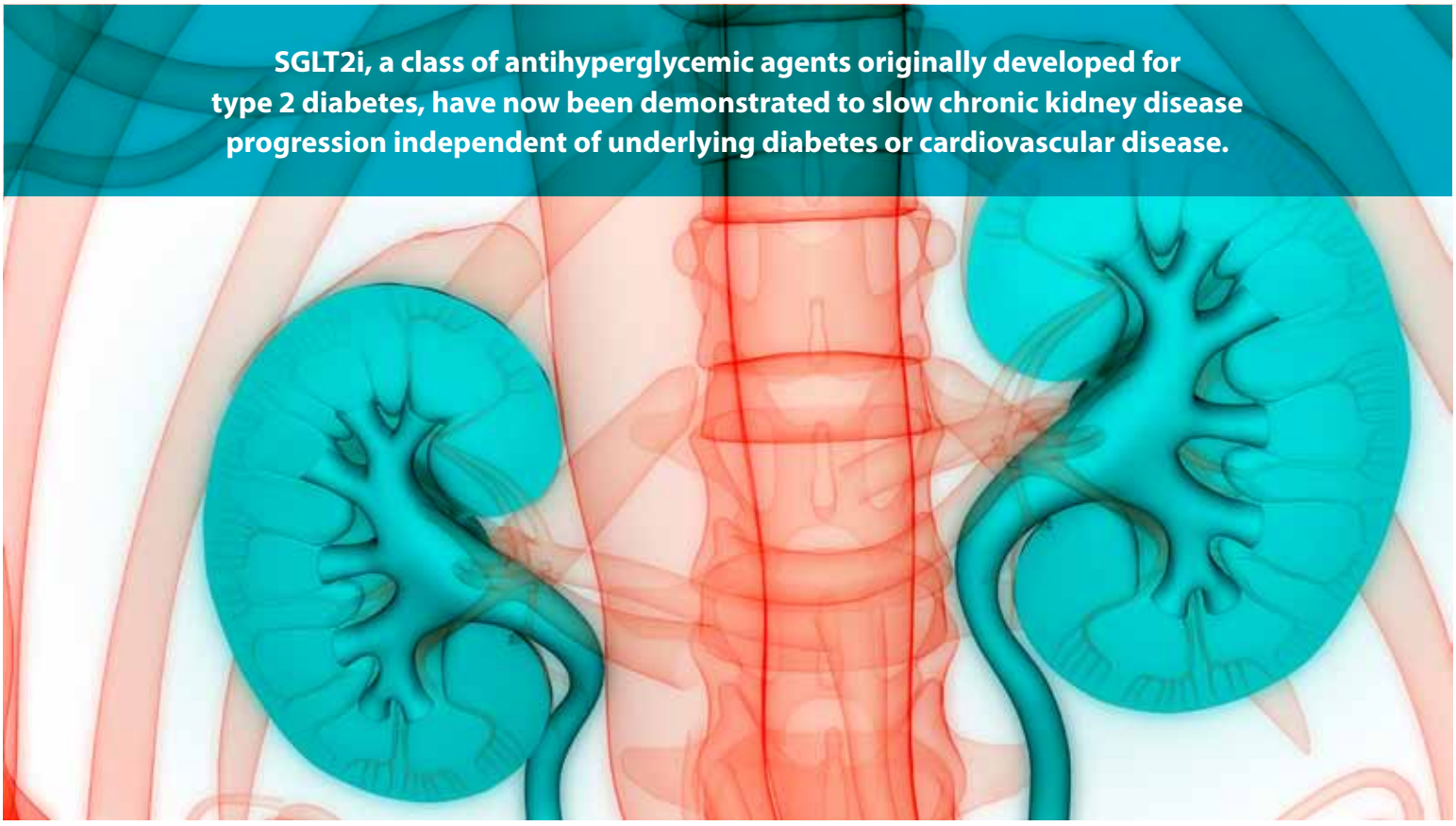
Background

Four million people currently live with chronic kidney disease in Canada, almost half of them under the age of 65.[1] Furthermore, the percentage of patients who progress to end-stage renal disease has grown by 35% since 2009.[1] Until recently, in addition to management of multimorbidities, the standard of care for patients with proteinuric kidney disease has been to initiate renin-angiotensin system inhibitor therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. This recommendation was based on considerable evidence from numerous clinical trials demonstrating a reduction in kidney disease progression, but not mortality, in patients who were on a renin-angiotensin system inhibitor, compared with those who were not.[2] However, since the first clinical trial demonstrating the renoprotective effects of renin-angiotensin system blockade in patients with diabetic kidney disease over 20 years ago, there has been a paucity of novel treatments to preserve renal function and modify the disease course of patients with chronic kidney disease,[3] until now. In a 2016 cardiovascular outcome trial of empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), in patients with type 2 diabetes, empagliflozin use was unexpectedly found to be associated with a slower progression of kidney disease.[4] More specifically, in patients with type 2 diabetes, empagliflozin reduced the risk of progression of albuminuria, doubling of serum creatinine, kidney failure, and death.[4] Since then, there have been numerous cardiovascular outcome trials and a handful of recent landmark clinical trials that have convincingly and consistently demonstrated the protective effects of SGLT2i on the kidney.[4-9] Although the benefits of SGLT2i are not unique to the kidney, this review aims to discuss clinical considerations and future use of SGLT2i in the context of kidney care.

Mechanisms of action

SGLT2i, also known as the "gliflozins," were originally developed for patients with type 2 diabetes.[10] They inhibit SGLT2, a low-affinity, high-capacity transport protein found in the proximal convoluted tubule of the nephron that is responsible for reabsorbing 90% of filtered glucose.[11-13] It was initially thought that by inhibiting reuptake of glucose and thus promoting glucosuria, SGLT2i could substantially lower blood glucose in hyperglycemic individuals independently of insulin and other glucose-lowering pathways.[11-13] While effective in those with preserved estimated glomerular filtration rate (eGFR), the glucose-lowering effects of SGLT2i are modest in patients with an eGFR of less than 45 mL/min/1.73 m^2.[12,14] Nonetheless, the protective effects of SGLT2i on the kidney are independent of whether patients have glycemic control or established cardiovascular disease.[15,16]

A full discussion of the proposed physiological mechanisms by which SGLT2i confer renoprotection is beyond the scope of this article. In brief, emerging evidence implicates SGLT2i across a spectrum of distinct renal pathophysiological processes. For instance, in individuals with diabetic kidney disease, SGLT2i may



attenuate nephron hyperfiltration, a known driver of intraglomerular hypertension and glomerular injury, by increasing sodium delivery to the macula densa, thereby restoring tubuloglomerular feedback.[17,18] SGLT2i also reduce cellular sodium and water reabsorption in the proximal tubule and promote paracellular sodium secretion through its actions on the sodium hydrogen exchanger, which is linked to SGLT2 by the membrane-associated protein MAP17.[19] Through reduction of sodium and glucose reabsorption in the proximal tubule, SGLT2i have been shown to shift tissue hypoxia in the cortical segment to the medullary segment of the nephron, which may increase production of erythropoietin, resulting in subsequent increases in red blood cell formation and oxygen-carrying capacity.[7,20] Finally, SGLT2i have been shown to attenuate vascular and renal reactive oxygen species, inflammation, and renal damage.[19]

In addition to these renal-specific benefits of SGLT2i, of which there are many others, the systemic effects of SGLT2i confer renoprotection as well. These include reductions in serum uric acid, body weight, and blood pressure, as well as benefits associated with reduced blood glucose levels and improved insulin sensitivity.[8]

Safety concerns in perspective

As with all medications, there are some safety concerns identified in the clinical trials reported to date. Importantly, these need to be weighed against the benefits of these medications, their true risks, and patient treatability. Although the absolute risk is low, patients on SGLT2i appear to be at increased risk of developing mycotic genital infections, which are typically not severe enough to warrant discontinuing SGLT2i therapy.[5,9,22] There have been suggestions that SGLT2i use may also increase the risk of urinary tract infections, lower limb amputations, and bone fractures, but recent meta-analyses have not supported this.[23,24] Patients with type 2 diabetes on SGLT2i may also be at increased risk of experiencing diabetic ketoacidosis with normal rather than elevated blood glucose levels, known as euglycemic diabetic ketoacidosis, so a higher index of suspicion is required in patients on SGLT2i.[25,26] In some earlier trials, there have also been rare reports of patients on SGLT2i developing necrotizing fasciitis of the perineum, also called Fournier gangrene.[9,27] However, it remains unclear whether gangrene development is associated with SGLT2i use.[28,29]

There have also been suggestions that SGLT2i therapy increases the risk of acute kidney injury in patients, but this has not been supported by evidence from large clinical trials.[4,5,27,30] In fact, a few meta-analyses have demonstrated a reduction in acute kidney injury risk for patients on SGLT2i.[23,24] A modest dip in GFR of approximately 5 mL/min/1.73 m^2 predictably occurs when starting SGLT2i.[4-6] While this may appear concerning, the GFR dip appears to be protective in the long term for patients with and without diabetic kidney disease.[5,6,31-33] However, as with other medications, such as renin-angiotensin system inhibitors and antihyperglycemic agents, it may be prudent to stop SGLT2i when acutely ill or hospitalized to reduce the risk of volume depletion.

SGLT2i are not currently recommended for patients with type 1 diabetes, patients who are pregnant or breastfeeding, patients with bilateral renal artery stenosis, and patients with severe liver disease.[21] Currently, they should also not be started in patients with an eGFR of under 25 mL/min/1.73 m^2, but a number of clinical trials that are examining starting these medications at a lower eGFR were being conducted at the time this article was written. Similarly, SGLT2i are not recommended for kidney transplant patients; however, there are a handful of published case series that have reported good effect of these medications on this patient population, and clinical trials are being planned to investigate this further.

Recommended guidelines for clinical use

The Kidney Disease: Improving Global Outcomes (KDIGO) working group and Diabetes Canada recommend that patients with type 2 diabetes, chronic kidney disease, and an eGFR greater than 30 mL/min/1.73 m^2 be treated with an SGLT2i in conjunction with metformin.[34,35] The choice of SGLT2i should consider patient factors such as patient comorbidities and side effect profiles as well as which SGLT2i have documented renal and cardiovascular benefits.[33,34] The KDIGO working group also recommends that once SGLT2i are initiated, they can be safely continued in patients whose eGFR drops below 30 mL/min/1.73 m^2, but as mentioned above, these medications should be withheld during bouts of prolonged fasting, surgeries, or critical medical illness.[34,35] At the time of writing, there are no other local or national guidelines regarding the use of SGLT2i for chronic kidney disease in nondiabetic patients. However, there is reasonable evidence to suggest that at least dapagliflozin is beneficial for chronic kidney disease patients irrespective of diabetic status.[6]

Clinical caveats

According to British Columbia guidelines, referral to nephrology by primary care is typically recommended when patients reach an eGFR of 30 mL/min/1.73 m^2.[36] This implies that, with respect to SGLT2i, primary care professionals will likely be tasked with identifying candidates most likely to benefit from SGLT2 inhibition, initiating SGLT2i therapy, and monitoring patients who are on them. Currently, as others have pointed out, considerable challenges remain in the translation of SGLT2i trial results into clinical practice.[12,21] First, there is likely to be resistance to SGLT2i uptake by medical professionals who are not comfortable managing patients on SGLT2i or who are not familiar with the clinical trial evidence. Therefore, patients who are candidates for SGLT2i therapy may go unrecognized. Second, identification of SGLT2i candidates requires detection of early signs of kidney disease through rigorous screening programs. There may, however, be less ability to implement such programs in rural and remote regions of BC where access to laboratory services and health care providers may be limited. Last, coverage of the cost of medication is a significant barrier for chronic kidney disease patients. In BC, both empagliflozin and dapagliflozin are covered by PharmaCare for patients with type 2 diabetes, but they are available only for patients who have failed two oral therapies.[37] Thus, for patients not meeting these criteria who face financial difficulties, prescribing SGLT2i such as dapagliflozin for chronic kidney disease may not be a suitable option. In the next 10 years, evidence will continue to emerge regarding the efficacy of SGLT2i for patients with chronic kidney disease and how to properly integrate SGLT2i into clinical practice.

SGLT2i may attenuate nephron hyperfiltration, a known driver of intraglomerular hypertension and glomerular injury, by increasing sodium delivery to the macula densa, thereby restoring tubuloglomerular feedback.

Conclusion

SGLT2i, a class of antihyperglycemic agents originally developed for type 2 diabetes, have now been demonstrated to slow chronic kidney disease progression independent of underlying diabetes or cardiovascular disease. The ability to slow progression of chronic kidney disease is of immense value given the large burden of illness that accrues with chronic kidney disease. This class of medications should be withheld during bouts of acute illness, as one holds angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and other medications to avoid untoward side effects. While there is still much that remains to be discovered about this class of medications, they should arguably be a cornerstone of chronic kidney disease treatment in the current era. We must be conscientious and diligent to ensure that uptake of SGLT2i is robust by increasing education and awareness about these medications, while ensuring that they are accessible to all. Given the socioeconomic disparities in those who develop chronic kidney disease and its impact on earning potential, there is a need to enable equitable access to these medications. Without attention to these important facts, we risk amplifying existing disparities.[38] SGLT2i are an exciting, safe, and effective therapeutic option for individuals with chronic kidney disease and are well poised to transform kidney care for years to come. ■

Competing interests

None declared.

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Considerable challenges remain in the translation of SGLT2i trial results into clinical practice.

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