Commentary

Policies, Guidelines and Consensus Statements: Pharmacologic Management of Type 2 Diabetes—2015 Interim Update

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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The process of the development of the Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada included provisions to update individual chapters prior to the planned published revision in 2018 (1). An updated literature search that focused on new evidence published since the development of the 2013 guidelines yielded 1787 citations. After review of these citations, the chapter authors advised the steering and executive committees that there were no significant changes in evidence to warrant the formulation of any new recommendations or the revision of any current recommendations. As such, it was recommended that a full update of the chapter be deferred until the planned revision of the entire Clinical Practice Guidelines in 2018.

However, the steering committee decided it was warranted to publish an interim commentary addressing the approval, in Canada, of a new class of antihyperglycemic agents—sodium-glucose linked transporter 2 (SGLT2) inhibitors—for the pharmacologic management of diabetes. Two agents from this class have received notice of compliance by Health Canada since the publication of the 2013 guidelines: canagliflozin and dapagliflozin (2). This update was deemed necessary by the steering committee because the addition of a new class of pharmacologic therapy represents a significant change in the management options for diabetes, yet the next complete update of the guidelines is still 3 years away.

SGLT2 inhibitors block glucose transport in the proximal renal tubule, which results in the urinary excretion of glucose, thereby lowering blood glucose and body weight (3,4). Network meta-analyses show that, when added to metformin, SGLT2 inhibitors generally have similar or slightly better efficacy in lowering glycated hemoglobin levels than do other antihyperglycemic agents (5,6). The incidence of hypoglycemia with SGLT2 inhibitors is rare unless they are used in combination with insulin or sulfonylureas (3). Because of the glycosuria resulting from the use of these agents, there is an increased risk for urinary tract infections, genital mycotic infections and hypotension caused by osmotic diuresis (3). Although SGLT2 inhibitors lower blood pressure (3) and raise high-density lipoprotein cholesterol, they elevate low-density lipoprotein cholesterol modestly (7,8), and their cardiovascular safety remains unknown and awaits long-term clinical trials. An imbalance in bladder cancer was noted with dapagliflozin in early clinical trials; however, many of the subjects with bladder cancer had pre-existing hematuria (9). There have been reported cases of diabetic ketoacidosis, without the usual elevated blood glucose, in patients with type 2 diabetes being treated with SGLT2 inhibitors (10–13). These cases are rare and further details await ongoing reviews. Patients on an SGLT2 inhibitor with symptoms of breathing difficulty, nausea, vomiting, abdominal pain, confusion or fatigue, even in the absence of high blood glucose, should be evaluated for ketoacidosis. If the ketoacidosis is confirmed, appropriate measures should be undertaken to correct the acidosis. The SGLT2 inhibitor therapy should be interrupted and its subsequent long term use should be reassessed (10,13). Use of SGLT2 inhibitors is not currently approved for type 1 diabetes. Figure 1 summarizes the therapeutic considerations for SGLT2 inhibitor therapy in the management of type 2 diabetes mellitus. The efficacy of SGLT2 inhibitors with respect to glucose lowering is
Figure 1. Management of hyperglycemia in type 2 diabetes. A1C, glycated hemoglobin; BG, blood glucose; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; SGLT2, sodium glucose linked transporter 2; TZD, thiazolidinedione; UTI, urinary tract infection.
dependent on their effects on urinary glucose excretion, which is attenuated in patients with renal dysfunction (14). Figure 2 summarizes the contraindications to use of SGLT2 inhibitors in patients with declining renal function based on product monographs.

In the pharmacologic management of type 2 diabetes, metformin remains the first agent of choice (15). SGLT2 inhibitors are a new class of antihyperglycemic agents available for the treatment of diabetes in Canada, and their use can be considered in management plans individualized to meet patients’ characteristics, as outlined in Figure 1.

References