Canada's Drug and Health Technology Agency

CADTH Reimbursement Recommendation

Sodium-Glucose Cotransporter 2 Inhibitors in Type 2 Diabetes Mellitus

Streamlined Drug Class Review

DRAFT for Stakeholder Feedback

November 30, 2023

Summary of CADTH FMEC Recommendation

The treatment of type 2 diabetes mellitus (T2DM) in patients who have a contraindication, intolerance, or inadequate glycemic control with metformin offers a choice from several available treatment options. The CADTH Formulary Management Expert Committee (FMEC) reviewed the best available evidence from a network meta-analysis (NMA). FMEC noted a consistent benefit of both the sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists on all-cause death, cardiovascular death, non-fatal myocardial infarction and health-related quality of life (HRQoL). SGLT2 inhibitors demonstrated a more favourable benefit in terms of reductions of heart failure related hospitalization and end-stage renal disease. GLP-1 agonists demonstrated better reduction of non-fatal stroke. SGLT2 inhibitors were associated with genital infection, amputation, and ketoacidosis, whereas GLP-1 agonists were associated with severe gastrointestinal events. Sulfonylureas and basal insulins did not demonstrate benefits in all-cause death or cardiorenal outcomes but were associated with higher risk of severe hypoglycemia and weight gain. Overall, the annual cost of the least costly SGLT2 inhibitor was lower than the annual cost of any GLP-1 agonist, at list price.

Based on the overall evidence on efficacy, safety, and costs, FMEC concluded, with a vote of 7-1 in favour of the following reimbursement recommendations:

Recommendation 1

- SGLT2 inhibitors should be prioritized over sulfonylureas and DPP-4 inhibitors in adult patients diagnosed with type 2 diabetes mellitus following inadequate control with metformin or a contraindication/intolerance to metformin.

Recommendation 2

- SGLT2 inhibitors should be prioritized over GLP-1 agonists in adult patients diagnosed with type 2 diabetes mellitus following inadequate control with metformin or a contraindication/intolerance to metformin unless the drug plan cost per patient of a GLP-1 agonist is no more than the least costly SGLT2 inhibitor.

Therapeutic Landscape

What Is Type 2 Diabetes Mellitus?

Diabetes mellitus is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action, or both. Type 2 diabetes mellitus is caused by insulin resistance related to insulin deficiency or secretory defect. Type 2 diabetes mellitus is associated with high mortality and complications which include myocardial infarction, stroke, end-stage renal disease, as well as microvascular complications such as retinopathy and nephropathy.

Why Did CADTH Conduct This Review?

Publicly funded drug plans requested this Streamlined Drug Class Review of SGLT2 inhibitors given the emergence of new evidence in cardiorenal benefits and the loss of exclusivity of drugs within the class.

Persons with Lived Experience

Two people living with type 2 diabetes spoke directly to the committee on their experiences and distinctive challenges living with the condition and with SGLT2s and GLP-1 treatments. One person highlighted different obstacles affecting their employment as a truck driver, including the frequent need to check blood sugar levels, managing side effects, and the inconvenience of subcutaneous injections. The other person highlighted minimal side effects from their treatments but underscored the supply chain issues of GLP-1s as having a profound impact.

Both individuals expressed concerns for the financial strain of medications. People living in rural areas may have additional costs and challenges to access specialist care and resources. They also stressed the significance of the impact of diet and flexibility of treatment options on their quality of life.

Living long enough to watch their children grow up was a primary factor when discussing treatment options.

Stakeholder Feedback

What Did We Hear From Patients?

CADTH consulted with Diabetes Canada throughout the project. CADTH also considered insights from the Living with Type 2 Diabetes collaborative review. Patients living with type 2 diabetes want less invasive treatment options to reduce the burden of medication administration. There is a desire to increase access to and affordability of treatments. People living with type 2 diabetes also want medications with few or no adverse effects, especially hypoglycemia, weight gain, and gastrointestinal and urogenital side effects.

What Did We Hear From Clinicians?

CADTH did not receive input from clinician groups during the open call for stakeholder feedback. Clinical experts consulted by CADTH noted the importance of aligning this review with Diabetes Canada's Clinical Practice Guidelines.

What Did We Hear From the Pharmaceutical Industry?

CADTH received input from two manufacturers on the project scope and feedback from three manufacturers on the summary report. Questions were posed related to the procedures and alignment of study objectives and research questions. One manufacturer raised concerns with the lack of discussion about combination use of GLP-1 agonist and insulin. Another manufacturer disagreed with the assumption of no intraclass differences within the GLP-1 agonist drug class, citing an unblinded phase IV study. Some manufacturers suggested incorporating additional studies. One manufacturer suggested that the CADTH review should align with the Diabetes Canada Clinical Practice Guidelines.

What Did We Hear From Public Drug Programs?

Feedback from public drug programs included the request for additional comparators (i.e., basal insulins) and outcomes (e.g., change in HbA1c) to support decision making.

Refer to Stakeholder Input section of the CADTH report

Deliberative Summary

Table 1: Why Did FMEC Make This Recommendation?

Questions or considerations	Discussion Points
Is there sufficient evidence to support the added clinical benefit of SGLT2 inhibitors compared to GLP-1 agonists, sulfonylureas, DPP-4 inhibitors, and basal insulins?	FMEC noted the importance to evaluate clinically relevant outcomes such as all-cause death and cardiorenal benefits (e.g., reduction in cardiovascular events or end-stage renal disease). Surrogate outcomes (e.g., change in HbA1C or body weight) for the treatment of type 2 diabetes mellitus were also considered by FMEC. **SGLT2 inhibitors vs. GLP-1 agonists** • SGLT2 inhibitors and GLP-1 agonists have comparable efficacy based on all-cause death, cardiovascular benefits, and HRQoL. In addition, SGLT2 inhibitors are more favourable in the reduction of hospitalization related to heart failure and the reduction in end-stage renal disease. However, GLP-1 agonists are more favourable in the reduction of non-fatal stroke. • SGLT2 inhibitors are associated with mycotic infections (OR 3.30, 95% CI 2.88 to 3.78), amputation (OR 1.27, 95% CI 1.01 to 1.61), and ketoacidosis (OR 2.07, 95% CI 1.44 to 2.98); whereas GLP-1 agonists are associated with severe gastrointestinal events (OR 1.97, 95% CI 1.39 to 2.80). • FMEC deliberated on the evidence and agreed that SGLT2 inhibitors and GLP-1 agonists are overall comparable in mortality and important cardiorenal benefits. FMEC also acknowledged the difference in stroke reduction for GLP-1 agonists, with a detailed review of absolute difference in event rates. Given SGLT2 inhibitors also benefit in the reduction of heart failure related hospitalization and end-stage renal disease, FMEC concluded these differences were marginal. • Dissenting opinion noted the GLP-1 agonists offer improved change in body weight and HbA1C compared to SGLT2 inhibitors. Additionally, it was noted that type 2 diabetes mellitus is a heterogeneous condition that requires individualization of therapy according to a

Questions or considerations	Discussion Points
	patient's clinical characteristics, risk profile, and/or personal preference. **SGLT2 inhibitors vs. Sulfonylureas** • SGLT2 inhibitors offer benefits in all-cause death and cardiorenal benefits, whereas sulfonylureas have not demonstrated these benefits. • Sulfonylureas are associated with a higher risk of severe hypoglycemia and weight gain. **SGLT2 inhibitors vs. DPP-4 Inhibitors** • SGLT2 inhibitors offer benefits in all-cause death and cardiorenal benefits, whereas DPP-4 inhibitors have not demonstrated these benefits. **SGLT2 inhibitors vs. Basal Insulins** • SGLT2 inhibitors offer benefits in all-cause death and cardiorenal benefits, whereas basal insulins have not demonstrated these benefits. • Basal insulins are associated with higher risk of severe hypoglycemia and weight gain. • FMEC discussed that exogenous insulin plays a different role in the management of type 2 diabetes mellitus compared to oral antihyperglycemics and may always be a treatment option over the course of the disease.
Is there a high level of confidence in the NMA to support differences between SGLT2 inhibitors and GLP-1 agonists, sulfonylureas, DPP-4 inhibitors, and basal insulins?	• FMEC noted that the NMA selected for the class review was of rigorous methodology. All outcomes have been rated for the certainty of evidence following the GRADE approach and the review followed the established protocol described in the publication. • Both SGLT2 inhibitors and GLP-1 agonists are more favourable than standard treatments for the following outcomes (rated with high to moderate certainty): all-cause death, cardiovascular death, non-fatal myocardial infarction, and HRQoL. Note that standard treatments include standard care (e.g., lifestyle modification) and standard drug treatments (e.g., metformin and/or sulfonylureas) other than the drug under investigation.
Is there an economic benefit of prioritizing SGLT2 inhibitors	• FMEC noted that the annual costs of branded SGLT2 inhibitors are approximately four times higher than the

Questions or considerations	Discussion Points
compared to GLP-1 agonists, sulfonylureas, DPP-4 inhibitors, and basal insulins?	generic SGLT2 inhibitors. Dapagliflozin has generic versions currently available; several generic versions for canagliflozin and empagliflozin are currently under review by Health Canada. • FMEC noted the annual cost of a generic version of dapagliflozin is approximately 10 times lower than the annual cost of semaglutide at list prices. The annual costs of branded SGLT2 inhibitors are less than the annual costs of all GLP-1 agonists. • The annual costs of generic SGLT2 inhibitors are less than the annual costs of branded DPP-4 inhibitors. The annual costs of generic SGLT2 inhibitors are comparable or less than the generic DPP-4 inhibitors. • The annual costs of generic SGLT2 inhibitors are higher than the annual costs of sulfonylureas. • The annual costs of basal insulins cannot be determined given the variability of insulin doses and types.
Is there an intraclass difference to be considered?	• FMEC agreed with the NMA authors that there should be no significant intraclass differences among the drugs under review (i.e., SGLT2 inhibitors, GLP-1 agonists, DPP-4 inhibitors, and sulfonylureas). • FMEC discussed a potential for intraclass differences amongst SGLT2 inhibitors. There was dissenting opinion that CDEC concluded that ertugliflozin has not demonstrated survival or cardiovascular benefit, however, ertugliflozin is not available in Canada. • FMEC also discussed the stakeholder feedback on potential intraclass differences among the GLP-1 agonists and highlighted the NMA included several GLP-1 agonists that are not available in Canada. Two re-analyses were conducted including semaglutide and dulaglutide together and semaglutide alone. Both re-analyses revealed consistent findings compared to the original NMA results. These findings suggest there is a lack of intraclass variability.

105 **SU: sulfonylureas; SGLT2 = sodium-glucose cotransporter-2; GLP-1 = glucagon like peptide; DPP-4 = dipeptidyl peptidase-4;**
106 **HRQoL = health related quality of life**

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Decision Plane

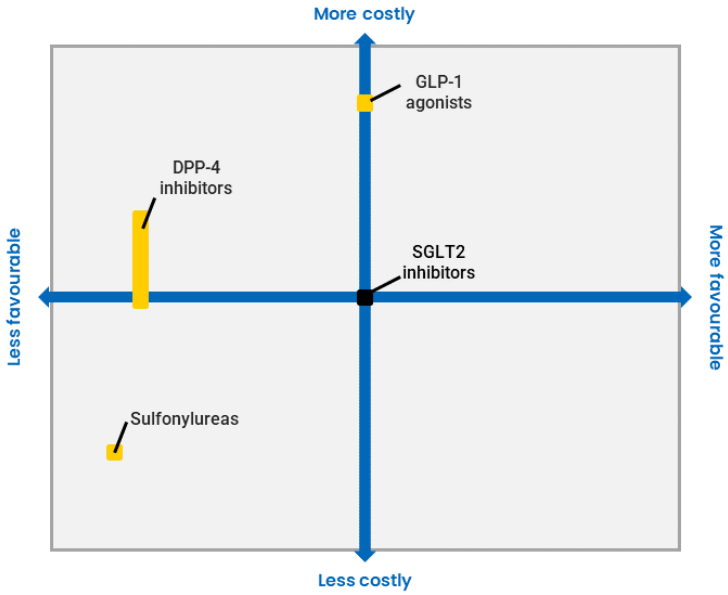
A decision plane was used during the deliberation to assess the classes of SGLT2 inhibitors within two domains: cost and favourability (as defined by the totality of evidence on efficacy and safety). With SGLT2 inhibitors at the origin, FMEC deliberated on the relative location of sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 agonists, and basal insulins on the decision plane.

FMEC concluded that GLP-1 agonists and SGLT2 inhibitors have similar efficacy in outcomes deemed most important by FMEC, recognizing they both offer marginal benefits in different aspects. GLP-1 agonists were also more costly.

Sulfonylureas were less favourable compared to SGLT2 inhibitors, despite having lower costs. DPP-4 inhibitors were less favourable compared to SGLT2 inhibitors. DPP-4 inhibitors cost more or less per patient than SGLT2 inhibitors, which differs based on version (branded vs generic).

Given the role basal insulins play in the management of type 2 diabetes and the uncertainty in cost associated with its use, the committee was unable to determine the location of basal insulins on the decision plane.

Figure 1:
Decision Plane



Drug classes are represented by squares plotted on the decision plane. The area of the squares aims to illustrate potential variability for cost and clinical favourability within the class. Squares crossing over the horizonal or vertical axes demonstrate variability in cost and clinical favourability in comparison to the drug class at the origin.

Feedback on Draft Recommendation

<to be updated after the stakeholder feedback period>

FMEC Information

Members of the Committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, Dr. Zaina Albalawi (guest specialist), Dr. Parmjit Sohal (guest specialist)

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Conflicts of interest: None

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