Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes Mellitus

Streamlined Drug Class Review

March 7, 2024

Summary of CADTH FMEC Recommendation

Type 2 diabetes mellitus in patients who have a contraindication, intolerance, or inadequate glycemic control with metformin has several treatment options. The CADTH Formulary Management Expert Committee (FMEC) reviewed the best available evidence from a network meta-analysis and noted a consistent benefit of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists on all-cause death, cardiovascular death, nonfatal myocardial infarction, and health-related quality of life. SGLT2 inhibitors demonstrated a more favourable benefit for reductions of heart failure–related hospitalizations and end-stage renal disease. GLP-1 agonists demonstrated better reduction of nonfatal 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 any outcome benefits but were associated with higher risk of severe hypoglycemia and weight gain. 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 voted (7 to 1) in favour of the following reimbursement recommendations:

Recommendation 1

- SGLT2 inhibitors should be prioritized over sulfonylureas and dipeptidyl peptidase-4 (DPP-4) inhibitors in adults diagnosed with type 2 diabetes mellitus following inadequate control with metformin or a contraindication or intolerance to metformin.

Recommendation 2

- SGLT2 inhibitors and GLP-1 agonists both demonstrated clinical efficacy in the outcomes deemed important by FMEC. However, because of cost differences, SGLT2 inhibitors should be prioritized over GLP-1 agonists in adults diagnosed with type 2 diabetes mellitus following inadequate control with metformin or a contraindication or intolerance to metformin unless the drug plan cost per patient of a GLP-1 agonist is no more than the least costly SGLT2 inhibitor.

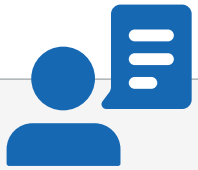
Therapeutic Landscape

What Is Type 2 Diabetes Mellitus?

Type 2 diabetes mellitus is caused by insulin resistance related to insulin deficiency or secretory defect and is associated with high mortality and complications, including myocardial infarction, stroke, and 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 some drugs within the class.



Persons With Lived Experience

Two people living with type 2 diabetes mellitus 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 with 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. The clinical experts consulted by CADTH noted the importance of aligning this review with the Diabetes Canada Clinical Practice Guidelines.

What Did We Hear From the Pharmaceutical Industry?

CADTH received input from 2 manufacturers on the project scope and feedback from 3 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 agonists 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 hemoglobin A1C) to support decision-making.

Refer to the Stakeholder Input section of the CADTH report.

Deliberative Summary

Table 1

Why Did FMEC Make This Recommendation?

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 of evaluating 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 hemoglobin A1C 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 hospitalizations related to heart failure and reduction in end-stage renal disease. However, GLP-1 agonists are more favourable in the reduction of nonfatal stroke. • SGLT2 inhibitors are associated with genital 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 that SGLT2 inhibitors demonstrated an improved efficacy compared to other antihyperglycemic drugs in the reduction of heart failure–related hospitalizations and end-stage renal disease, FMEC concluded these differences were marginal. • Dissenting opinion noted that GLP-1 agonists offer improved change in body weight and hemoglobin A1C compared to SGLT2 inhibitors. Additionally, it was noted that type 2 diabetes mellitus is a heterogeneous condition that requires individualized therapy according to a patient's clinical characteristics, risk profile, and/or personal preference. **SGLT2 Inhibitors vs. Sulfonylureas** • SGLT2 inhibitors offer 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 all-cause death and cardiorenal benefits, whereas DPP-4 inhibitors have not demonstrated these benefits. • DPP-4 inhibitors are considered weight neutral. **SGLT2 Inhibitors vs. Basal Insulins** • SGLT2 inhibitors offer 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.

Questions or considerations	Discussion points
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, nonfatal 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 over GLP-1 agonists, sulfonylureas, DPP-4 inhibitors, and basal insulins?	• FMEC noted that the annual costs of branded SGLT2 inhibitors are approximately 4 times higher than the 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 that 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, at list price. • 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 among SGLT2 inhibitors. There was dissenting opinion among FMEC, with some members highlighting that ertugliflozin has not demonstrated survival or cardiovascular benefits, as described in the CDEC review; however, ertugliflozin is not available in Canada. • FMEC also discussed the stakeholder feedback on potential intraclass differences among the GLP-1 agonists and highlighted that the NMA included several GLP-1 agonists that are not available in Canada. Two reanalyses were conducted that included semaglutide and dulaglutide together and semaglutide alone. The reanalyses revealed findings consistent with the original NMA results, which suggest there is a lack of intraclass variability.

CDEC = Canadian Drug Expert Committee; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; FMEC = Formulary Management Expert Committee; GLP-1 = glucagon-like peptide 1; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; HRQoL = health-related quality of life; NMA = network meta-analysis; OR = odds ratio; SGLT2 = sodium-glucose cotransporter-2; vs. = versus.

Decision Plane

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

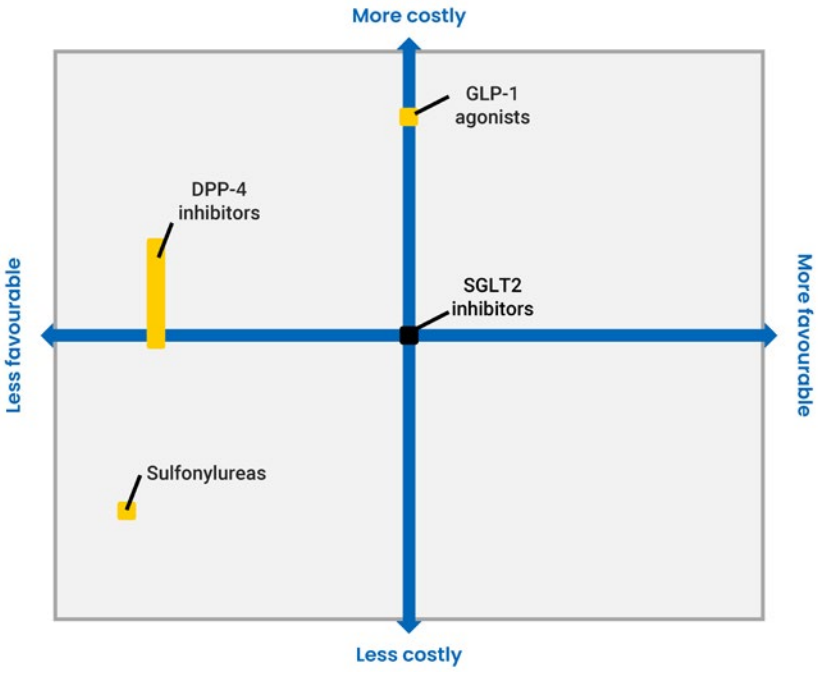
FMEC concluded that GLP-1 agonists and SGLT2 inhibitors have similar efficacy in the outcomes deemed most important by FMEC, recognizing that they both offer marginal benefits in different aspects. At list prices, GLP-1 agonists were more costly.

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 can cost more or less per patient than SGLT2 inhibitors, differing based on version (branded versus generic).

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

Figure 1

Decision Plane



DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium-glucose cotransporter-2.

Feedback on Draft Recommendation

CADTH received feedback on the draft recommendation from 2 clinician groups, 1 manufacturer, 1 patient group, and public drug plans. Although there was unanimous support from stakeholders on Recommendation 1, there were several questions raised related to Recommendation 2.

One clinician agreed with and had no objections to the draft recommendations, while the clinician group expressed some concerns with Recommendation 2. They argued that Recommendation 2 is inconsistent with the current standard of practice and does not consider the totality of comparative evidence given the heterogeneity of the condition. One manufacturer shared feedback that Recommendation 2 did not align with the evidence, patient values, or clinical practice guidelines. The patient group disagreed with Recommendation 2, emphasizing individualized care based on clinical scenarios (as outlined in their guidelines). They underscored the importance of considering quality of life, health outcomes, and administrative burdens to clinicians for this recommendation. Moreover, the public drug plans requested clarification to the wording of Recommendation 2 to account for conclusions by FMEC on the body of clinical evidence and differences between SGLT2 inhibitors and GLP-1 agonists.

FMEC concluded that SGLT2 inhibitors and GLP-1 agonists have similar efficacy in the outcomes deemed important and that prioritizing treatments based on cost differences is appropriate.

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)

Meeting date: November 30, 2023

Conflicts of interest: None

Special thanks: CADTH extends our special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience and from patient organizations (Diabetes Canada and Diabetes Action Canada), which included Laura Hoffe, Vikramjit Brar, Linxi Mytkoll, Al Martin, and Barb Duff.

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