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CADTH Reimbursement Review

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

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Key Messages

What Is the Issue?

- Since the last CADTH therapeutic review on type 2 diabetes in 2018, new evidence on the impact of sodium-glucose cotransporter-2 (SGLT2) inhibitors on clinically important outcomes such as all-cause death, cardiovascular outcomes, renal outcomes, and patient-important outcomes (e.g., safety) has emerged.
- According to the Canadian Institutes for Health Information (CIHI), diabetes drugs accounted for the most growth in spending by public drug programs in 2021.
- According to the 2023 CADTH Health Technology Review titled *Living With Type 2 Diabetes*, people living with type 2 diabetes want treatment options that are less invasive and more affordable, and cause few or no adverse effects, especially hypoglycemia, weight gain, and gastrointestinal and urogenital side effects.
- The new therapeutic landscape of SGLT2 inhibitors in Canada (emergence of new evidence on clinically important outcomes and the introduction of SGLT2 inhibitor generics) since CADTH last conducted a Reimbursement Review highlights the opportunity to review the place in therapy of SGLT2 inhibitors for type 2 diabetes.

What Did We Do?

- At the request of public drug programs, CADTH conducted a Streamlined Drug Class Review to provide an appraisal of the evidence available to address the place in therapy of SGLT2 inhibitors compared to other antihyperglycemic agents for the treatment of type 2 diabetes mellitus. CADTH Streamlined Drug Class Reviews leverage the most comprehensive and rigorously conducted systematic reviews (SRs) and network meta-analyses (NMAs) to address timely policy questions. A literature search of published SRs with NMAs identified a recent study by Shi et al.¹ that compared the efficacy and harms of drug treatments for type 2 diabetes.
- CADTH also underwent stakeholder engagement to seek feedback on the project scope, receiving input from patient organizations, clinician organizations, drug plans, and industry. CADTH contacted Canadian patient and clinician associations with a likely interest in this drug class review and companies who hold a Canadian licence for branded versions of the drugs included in the class.



Key Messages

- A utilization analysis of antihyperglycemic agents from 2019 to 2022 was conducted, assessing utilization patterns across drug classes and public drug programs using CIHI data.

What Did We Find?

- SGLT2 inhibitors offer additional clinical benefits compared to standard treatments including improvement in all-cause death, cardiovascular death, and nonfatal myocardial infarctions. In addition, SGLT2 inhibitors reduce hospitalization for heart failure and end-stage renal disease.
 - Other benefits of SGLT2 inhibitors include weight loss, lower risk for severe hypoglycemia, and improvement in health-related quality of life.
 - Safety concerns include genital infections, ketoacidosis, and amputation.
- Glucagon-like peptide-1 (GLP-1) agonists offer additional clinical benefits compared to standard treatments including all-cause death, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
 - Other benefits include a reduction in end-stage renal disease, lower risk of severe hypoglycemia, improvement in health-related quality of life, and greater weight loss compared to other type 2 diabetes treatments.
 - Main safety concerns include severe gastrointestinal events.
- Other antihyperglycemics – including dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, and basal insulins – do not improve all-cause death or cardiorenal outcomes.
 - Sulfonylureas may increase all-cause death, although evidence is of low certainty.
 - Sulfonylureas and basal insulins can increase the risk of severe hypoglycemia and weight gain.
- From 2019 to 2022, there was notable growth in the utilization and expenditures of antihyperglycemic therapies.
 - GLP-1 agonists, particularly semaglutide, and SGLT2 inhibitors, especially empagliflozin, showed notable growth in both claimants and expenditures.
 - GLP-1 agonists also exhibited the highest average annual cost of utilization per beneficiary.



Key Messages

What Does This Mean?

- Compared to other antihyperglycemic drugs, SGLT2 inhibitors and GLP-1 agonists show benefits on clinically important outcomes beyond glycemia, such as all-cause death and cardiovascular, renal, and patient-important outcomes (e.g., safety).
- As SGLT2 inhibitors approach the end of exclusivity in Canada, the availability of generics could provide cost-saving opportunities for public drug programs while having a benefit on clinically important outcomes.
- Given significant public drug program expenditures on antihyperglycemic drugs, coupled with the desire to improve overall survival and other important patient-related outcomes, there is a need to re-evaluate the current reimbursement criteria of SGLT2 inhibitors in type 2 diabetes.



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Abbreviations

AMSTAR2	A MeaSurement Tool to Assess Systematic Reviews 2
CI	confidence interval
CIHI	Canadian Institutes for Health Information
DPP-4	dipeptidyl peptidase-4
FMEC	Formulary Management Expert Committee
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRIPP2	Guidance for Reporting Involvement of Patients and the Public 2
NMA	network meta-analysis
NPDUIS	National Prescription Drug Utilization Information System
OR	odds ratio
pCPA	pan-Canadian Pharmaceutical Alliance
RCT	randomized controlled trial
SGLT2	sodium-glucose cotransporter-2
SMD	standardized mean difference
SR	systematic review

Background

Type 2 Diabetes Mellitus

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.² In type 2 diabetes mellitus, the body is unable to use the insulin properly, which can lead to high levels of blood sugar if left untreated.

According to Diabetes Canada, the prevalence of diabetes in 2022 was approximately 10% among people living in Canada. This estimate includes both diagnosed type 1 and type 2 diabetes, with type 2 diabetes accounting for approximately 90% to 95% of all cases. However, when accounting for undiagnosed type 2 diabetes, the prevalence is estimated to be 14%.³ In Canada, diabetes is estimated to reduce life span by 5 to 15 years⁴ and all-cause mortality is estimated to be twice as high for individuals with diabetes than those without diabetes.⁵

In addition to hyperglycemia, the clinical manifestations of diabetes include polydipsia, polyuria, blurred vision, and fatigue. If left untreated, diabetes mellitus carries increased risk of cardiovascular disease, renal failure, blindness, and premature death. In Canada, it is estimated that diabetes contributes to 30% of strokes, 40% of heart attacks, 50% of kidney failure requiring dialysis, 70% of all nontraumatic leg and foot amputations, and is the leading cause of blindness.^{3,6} Furthermore, 90% of people with type 2 diabetes have obesity, so it is essential to utilize treatment options that impact health outcomes and target prevalent risk factors to promote weight loss.⁷

Diabetes is diagnosed based on pre-established diagnostic criteria with venous samples and laboratory methods: “fasting plasma glucose ≥ 7.0 mmol/L or, glycated hemoglobin (A1C) $\geq 6.5\%$ or, 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥ 11.1 mmol/L or, random plasma glucose ≥ 11.1 mmol/L.”⁸

Note that if a single test result meets the diagnostic criteria in the absence of symptomatic hyperglycemia, a repeat confirmatory laboratory test result is required to be done on another day.⁸

Type 2 diabetes is preventable and caused by a combination of individual, social, environmental, and genetic factors. Among these, the modifiable risk factors for type 2 diabetes include overweight and obesity, prediabetes, physical inactivity, unhealthy eating, high blood pressure, and high cholesterol.⁸

Treatments

Type 2 diabetes mellitus is a metabolic disease with no current definitive cure, and often requires multiple therapies as the disease progresses with time. In general, management of type 2 diabetes mellitus encompass a combination of nutritional therapy, physical activity, and pharmacological therapy. Among these modalities, pharmacological therapy continues to be an important mainstay treatment strategy. First-line pharmacological therapy continues to be metformin, or with insulin if metabolic decompensation is present.⁸ New clinical practice guidelines place emphasis on adding on or substituting for a drug with demonstrated cardiorenal benefit, and indicate that therapies should be individualized based on evolving evidence and patient-specific factors.⁹

In Canada, subsequent treatment options include SGLT2 inhibitors, GLP-1 agonists, DPP-4 inhibitors, insulin secretagogues, thiazolidinediones, and insulin therapy. These treatment options differ in their ability to lower hemoglobin A1C (glycated hemoglobin), cost, risk of hypoglycemia, and impact on weight gain or weight loss.⁸ In addition, recent evidence also indicates that certain treatment options also offer additional survival and cardiorenal benefits.¹

In addition to improving glycemic control in patients with type 2 diabetes, individuals may also require other therapies to minimize diabetes-related complications (such as lipid-lowering drugs, angiotensin-converting enzyme [ACE] inhibitors, and antiplatelets), to reduce the risk of cardiovascular disease or diabetes-related nephropathy and other complications.⁸

Rationale and Policy Issues

According to CIHI, diabetes drugs contributed the most to growth in public drug program spending in 2021.¹⁰ Specifically, SGLT2 inhibitors were the fifth-largest contributors to growth in spending (increasing by 6.15%), whereas GLP-1 agonists were the largest contributor to growth in spending (increasing by 11.7%). Expenditures for these 2 drug classes grew by \$200 million between 2020 and 2021, accumulating to roughly \$620 million. It is thought that this growth is a result of increasing prevalence of diabetes in Canada^{11,12} as well as changes in prescribing guidelines¹³ to encourage earlier use of SGLT2 inhibitors and GLP-1 agonists.

According to the 2023 CADTH Health Technology Review titled [Living With Type 2 Diabetes](#),¹⁴ people living with type 2 diabetes want treatment options that are less invasive and can reduce the burden of medication administration. In addition, there is a desire to increase access to and affordability of type 2 diabetes treatments in Canada. People living with type 2 diabetes also want medications that cause few or no adverse effects, especially hypoglycemia, weight gain, and gastrointestinal and urogenital side effects. [Table 1](#) lists the currently available drugs in Canada for the treatment of type 2 diabetes.

Since the last CADTH [Therapeutic Review on Type 2 Diabetes](#) in 2018,¹⁵ new evidence on the use of SGLT2 inhibitors has emerged. For example, several NMAs^{1,16} have been published to inform the comparative benefits and harms of drug treatment in type 2 diabetes, including SGLT2 inhibitors. Specifically, more evidence is now available to offer information on clinically important outcomes such as all-cause mortality,¹ cardiovascular outcomes,¹ renal outcomes, and patient-important outcomes (e.g., safety).¹ With the imminent loss of exclusivity and introduction of SGLT2 inhibitor generics, this important class of drugs may offer additional value and cost-savings opportunities in formulary management in Canada. [Table 2](#) lists the status of data protection and patent expiry for SGLT2 inhibitors.¹

The new therapeutic landscape of SGLT2 inhibitors in Canada (i.e., the emergence of new evidence on clinically important outcomes and the introduction of SGLT2 inhibitor generics) since CADTH last conducted a Reimbursement Review highlights the opportunity to review the place in therapy of SGLT2 inhibitors in type 2 diabetes. As the public funding of SGLT2 inhibitors currently ranges from restricted coverage in some jurisdictions to open benefits in others, there is national interest from public drug programs to conduct this Streamlined Drug Class Review. This review can serve as a platform to support harmonization of funding

criteria and to inform decision-makers on their formulary management. This Streamlined Drug Class Review will review the comparative efficacy and harms of SGLT2 inhibitors among adult patients with type 2 diabetes following first-line use of or intolerance to metformin.

Table 1: Products Available in Canada

Generic name (brand name)	Route	Manufacturer
SGLT2 inhibitors		
Canagliflozin (Invokana) Canagliflozin-metformin (Invokamet)	Oral Oral Oral	Janssen Inc.
Empagliflozin (Jardiance) Empagliflozin-metformin (Synjardy)	Oral Oral Oral	Boehringer Ingelheim (Canada) Ltd.
Dapagliflozin (Forxiga) Dapagliflozin-metformin (XigDuo)	Oral Oral	AstraZeneca Canada Inc.
GLP-1 agonists		
Semaglutide (Ozempic) Semaglutide (Rybelsus) Insulin degludec-liraglutide (Xultophy) Liraglutide (Victoza)	Subcutaneous Oral Subcutaneous Subcutaneous	Novo Nordisk Canada
Lixisenatide (Adlyxine) Lixisenatide-insulin glargine (Soliqua)	Subcutaneous Subcutaneous	Sanofi-Aventis Canada Inc.
Exenatide (Byetta) Dulaglutide (Trulicity)	Subcutaneous Subcutaneous	Eli Lilly Canada Inc.
DPP-4 inhibitors		
Alogliptin (Nesina) Alogliptin-metformin (Kazano)	Oral Oral	Takeda Canada Inc.
Linagliptin (Trajenta) Linagliptin-metformin (Jentadueto)	Oral Oral	Boehringer Ingelheim (Canada) Ltd.
Saxagliptin (Onglyza) Saxagliptin-metformin (Komboglyze)	Oral Oral	AstraZeneca Canada and generics
Sitagliptin (Januvia) Sitagliptin-metformin (Janumet) Sitagliptin-metformin XR (Janumet XR)	Oral Oral Oral	Merck Canada Inc. and generics
Sulfonylurea		
Gliclazide, gliclazide modified-release, glimepiride, glyburide	Oral	Generics

Generic name (brand name)	Route	Manufacturer
Basal insulins		
Insulin detemir (Levemir) Insulin degludec (Tresiba) Isophane insulin (Novolin GE NPH)	Subcutaneous Subcutaneous Subcutaneous	Novo Nordisk Canada
Insulin glargine (Basaglar) NPH insulin (Humulin N)	Subcutaneous Subcutaneous	Eli Lilly Canada Inc.
Insulin glargine 200 units/mL (Lantus) Insulin glargine 300 units/mL (Toujeo)	Subcutaneous Subcutaneous	Sanofi-Aventis Canada

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; SGLT2 = sodium-glucose cotransporter-2; XR = extended release.

Table 2: Status of Data Protection and Patent Expiry for SGLT2 Inhibitors

Generic name	Brand name	Data protection expiry date	Pediatric extension	Data protection ended (yes or no)	Patent end date (for longest filed)	Patent expired (yes or no)
Dapagliflozin	Forxiga	December 12, 2022	NA	Yes	March 21, 2028	No
Dapagliflozin plus metformin	XigDuo	December 12, 2022	NA	Yes	November 12, 2030	No
Canagliflozin	Invokana	May 23, 2022	NA	Yes	May 11, 2031	No
Canagliflozin plus metformin	Invokamet	May 23, 2022	NA	Yes	July 7, 2030	No
	Invokamet XR	May 23, 2022	NA	Yes	May 11, 2031	No
Empagliflozin	Jardiance	July 23, 2023	NA	Yes	April 16, 2034	No
Empagliflozin plus metformin	Synjardy	July 23, 2023	NA	Yes	April 3, 2034	No

NA = not applicable; SGLT2 = sodium-glucose cotransporter-2; XR = extended release.

Objectives

The objective of this report is to summarize and critically appraise (if applicable):

- the best available evidence regarding the efficacy and harms of SGLT2 inhibitors compared to other antihyperglycemics available in Canada for the treatment of adult patients with type 2 diabetes mellitus
- stakeholder feedback received from patient, health care practitioner, and manufacturer perspectives on the need for therapies in type 2 diabetes mellitus and the scope of the drug class review
- economic considerations that compare costs of antihyperglycemics used to treat type 2 diabetes mellitus, based on product monograph dosing and real-world utilization.

In addition, this summary report will be used by the CADTH Formulary Management Expert Committee (FMEC) during the deliberation of the Streamlined Drug Class Review. For more information, refer to [Procedures for CADTH Streamlined Drug Class Reviews](#).

Policy Question

Does current evidence support the improved efficacy (mortality and cardiorenal outcomes) and safety of SGLT2 inhibitors, compared to other antihyperglycemics (i.e., GLP-1 agonists, sulfonylureas, DPP-4 inhibitors) and basal insulins for the treatment of adult patients with type 2 diabetes after first-line use of or intolerance to metformin?

Research Questions

1. What is the clinical efficacy (mortality and cardiorenal outcomes) of SGLT2 inhibitors compared to other antihyperglycemics (i.e., GLP-1 agonists, DPP-4 inhibitors, sulfonylureas, basal insulins) in adult patients with type 2 diabetes mellitus?
2. What are the harms associated with SGLT2 inhibitors compared to other antihyperglycemics (i.e., GLP-1 agonists, DPP-4 inhibitors, sulfonylureas, basal insulins) in adult patients with type 2 diabetes?
3. How do costs compare across SGLT2 inhibitors and other antihyperglycemics (i.e., GLP-1 agonists, DPP-4 inhibitors, sulfonylureas, basal insulins) for the treatment of adult patients with type 2 diabetes after first-line treatment with or intolerance to metformin?

Stakeholder Engagement

Overview

CADTH involves clinicians, patients, associations, and industry to improve the quality and significance of our work. It also allows those affected by our reviews to have an opportunity to learn about and contribute to them. On the International Association for Public Participation Federation's Spectrum for Public Participation, our engagement activities can be described as being at the "Involve" level, as we interact with stakeholders multiple times during our process to ensure concerns and aspirations are consistently understood and considered. We aim for all stakeholders to find engaging with CADTH to be a productive and worthwhile experience. For more information, refer to [Procedures for CADTH Streamlined Drug Class Reviews](#).

Note that an honorarium was offered for the person with lived experience's time and expertise as a gesture of appreciation for their contributions. Additionally, association participants and the person with lived experience were thanked by name in the acknowledgements section of the report.

Reflections

Use of the Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2) Short Form reporting checklist outlines the process of engagement, and where and how stakeholders' contributions were used in the review.

Table 3: Stakeholder Involvement in SGLT2 Inhibitors for Type 2 Diabetes Mellitus

Topic	Item	Section(s)
Aim	CADTH involves clinicians, patients, associations, and industry to improve the quality and significance of our work.	—
Methods	Diabetes Canada and 4 pharmaceutical companies were involved in the review. Two clinical experts, an endocrinologist and family physician specializing in diabetes care, provided peer review, answered questions of the CADTH team and will be involved in the deliberation and voting of the Formulary Management Expert Committee on November 30, 2023.	—
Engagement results	<p>Past patient and clinician input – including the Health Technology Review titled <i>Living With Type 2 Diabetes</i> – emphasized the need for medications that cause few or no adverse effects, emphasizing hypoglycemia, weight gain, and gastrointestinal and urogenital side effects as particularly undesirable treatment outcomes. CADTH heard the emotional impact of affordability of medications, especially for systematically disadvantaged groups.</p> <p>Stakeholders asked CADTH to:</p> <ul style="list-style-type: none"> • consider the appropriateness of the study by Shi et al., for a Canadian context • consider the adverse events that may impact patients receiving SGLT2 or DPP-4 treatments • consider aligning this review with Diabetes Canada's clinical practice guidelines • consider cardiovascular outcomes, renal outcomes, and hospitalization for heart failure, in addition to glycemic parameters and adverse event outcomes • consider including urinary tract infections as a safety outcome. 	Project Scope, Table 2 Summary Report
Discussion and conclusions	Dialogue between CADTH and the associations helped build trust and greater understanding of each other's goals. The engagement method, which was reliant on technology, may have excluded certain populations, potentially limiting diverse perspectives on the challenges faced by people in Canada living with type 2 diabetes mellitus.	—
Reflections and critical perspective	The <i>Living With Type 2 Diabetes</i> Health Technology Review offered a fresh approach for CADTH to use patient input and avoid repetitive requests to associations for input. However, there remains a gap in capturing the perspectives of individuals outside patient or clinician associations, or those not included in the published literature. Engaging with a greater number of people with lived experience would have enabled greater diversity and provided differing perspectives on the challenges and experiences facing those living with type 2 diabetes mellitus.	—

Note: CADTH provided 10 business days for stakeholders to provide feedback at the following stages:

- proposed project scope (September 2023)
- draft summary report (available October 19, 2023)
- draft recommendations (available December 2023).

Feedback opportunities are communicated through the CADTH Weekly Summary emails to subscribers.

Summary of Patient and Clinician Association Input

CADTH received interest from multiple patient groups and met with Diabetes Canada to answer questions related to the review, to identify important perspectives from past patient and clinician input most relevant to this class review, and to support a person living with type 2 diabetes to speak with the expert committee. CADTH received positive feedback from Diabetes Canada on the scope of the project.

In addition, CADTH conducted a Health Technology Review titled [Living With Type 2 Diabetes](#).¹⁴ The report highlights important treatment considerations for individuals with type 2 diabetes mellitus, such as improving accessibility and affordability of medications, respectful and effective communication in therapeutic relationships, the necessary knowledge to support medication-related decisions, and the value of individualized treatment plans offering diverse choices.

CADTH heard from a patient group that many people without medical insurance cannot afford SGLT2 inhibitors or GLP-1 agonists. Sulfonylureas and metformin are used first-line as a pathway to access, or because they are more affordable than other options. The issue of affordability was also reflected in CADTH's *Living With Type 2 Diabetes* Health Technology Review, which outlined disparities in access to type 2 diabetes mellitus treatment as well as the need for increased access to and affordability of medications. The report outlines how disparities in accessing type 2 diabetes mellitus treatment can be intensified for equity-deserving groups due to geographic limitations, systemic racism, unemployment risks, inadequate insurance, and socioeconomic challenges, which may require interventions to address and prevent further disparities in type 2 diabetes mellitus outcomes among these groups.

A patient group highlighted the need to consider the harms and adverse effects of available treatments.

Stakeholders emphasized the importance of aligning this review with Diabetes Canada's *2022 Clinical Practice Guidelines*, recognizing that the effectiveness of a patient's treatment depends not only on the potential effectiveness of a specific drug class or medication, but also on individual patient factors. The clinical experts consulted by CADTH agreed with the clinical outcomes included in the research protocol, including mortality, cardiovascular and renal outcomes, hospitalization for heart failure, and adverse event outcomes. In addition, the clinical experts requested to include 1 additional outcome, hemoglobin A1C.

Summary of Industry Input

Industry stakeholders provided feedback on the NMA informing this Streamlined Drug Class Review and made suggestions of supplementary publications that CADTH may wish to consider.

Industry stakeholders also proposed alternative data sources such as IQVIA for cost analysis. Given that the focus of the cost analysis is on public drug programs, for which the use of CIHI data is reasonable, this was not pursued.

Industry stakeholders emphasized the importance of maintaining consistency in evidence thresholds for reimbursement recommendations, especially when differences in efficacy and harms exist among medications, and emphasized the need for cost-utility analyses.

Summary of Drug Program Input

CADTH has received input from public drug programs, including feedback on the research protocol and a draft of the summary report. Public drug programs noted that confidential product listing agreements currently exist for drugs included in this review that may not be reflective of list prices.

Clinical Review

NMAs allow the use of both direct and indirect evidence to determine the relative efficacy and harms of different treatment options, and help fill the gap in evidence arising from a lack of key treatment comparisons that are needed to inform practice. The approach chosen for this Streamlined Drug Class Review was guided by the need to provide a timely appraisal of the evidence regarding comparative efficacy and harms of SGLT2 inhibitors relative to other antihyperglycemic agents available in Canada for type 2 diabetes in this rapidly changing treatment landscape. The approach taken is a “best evidence summary,” in which the aim is to identify and leverage 1 or more existing evidence syntheses (e.g., SRs with meta-analyses and/or NMAs) of high methodological quality that comprehensively address the research question of the Streamlined Drug Class Review. The selected evidence syntheses are summarized and critically appraised to inform the policy question.

Search Methods

An information specialist performed the literature search, using a peer-reviewed search strategy in accordance with CADTH’s [PRESS Peer Review of Electronic Search Strategies](#) checklist.¹⁷

The initial search was completed on August 31, 2023, and limited to English-language documents published since January 1, 2016. The search time frame was determined based on the emergence of relevant evidence on cardiovascular outcomes since 2016 identified during project scoping.¹⁸ Regular alerts updated the search until project completion.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH’s [Grey Matters: A Practical Tool For Searching Health-Related Grey Literature](#). Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for the detailed search strategy.

Selection Criteria and Process

One reviewer screened the titles and abstracts of the search results for relevance to the clinical research question. Records were excluded if they were in languages other than English and did not meet the selection criteria outlined in [Table 4](#). A second reviewer reviewed the included records to confirm agreement, and both reviewers identified the most recent and relevant SRs for inclusion based on the selection criteria. Potentially relevant records were retrieved, and their abstract or full text was examined by 1 reviewer.

To avoid overlap of primary studies that could introduce bias if outcome data from the same studies were included multiple times, the most recent and comprehensive systematic review with NMA that included all intervention and comparator drugs, as well as outcomes of interest, would be selected to inform the Streamlined Drug Class Review. Further, the selection criteria and methodology from the publication were also examined by a single reviewer. The publication date, population, drug class of interest, and outcomes were reviewed to identify potential overlap. Criteria for the selection of the systematic review were based on a balance of comprehensiveness, relevance, recency, and methodological quality.¹⁹ If all of the outcomes of interest outlined in the research protocol were not found in a single NMA, additional supplemental evidence from other NMAs was considered.

The quality of the included NMAs was assessed using A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR2)²⁰ and the International Society for Pharmacoeconomics and Outcomes Research (IPSOR) checklist.²¹

Table 4: Systematic Review Selection Criteria

Criteria	Description
Population	Adult patients with type 2 diabetes
Interventions	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)
Comparators	Antihyperglycemics including the following (any dosage with route of administration, as per Table 1): <ul style="list-style-type: none"> • GLP-1 agonists <ul style="list-style-type: none"> ◦ short-acting: exenatide, lixisenatide ◦ longer-acting: dulaglutide, exenatide extended release, liraglutide, semaglutide • sulfonylureas (gliclazide, gliclazide MR, glimepiride, glyburide) • DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin) • basal insulins (insulin detemir, insulin degludec, insulin glargine, NPH insulin, isophane insulin)
Outcomes	Efficacy: <ul style="list-style-type: none"> • all-cause death • cardiovascular death • nonfatal myocardial infarction • nonfatal stroke • admission to hospital for heart failure • end-stage kidney disease • health-related quality of life score • body weight change

Criteria	Description
	<ul style="list-style-type: none"> • change in hemoglobin A1C Safety: <ul style="list-style-type: none"> • genital infection • amputation • ketoacidosis • severe gastrointestinal events • severe hypoglycemia
Study design	Published SRs of RCTs with meta-analyses and/or network meta-analyses
Report dates	2016 up to 2023

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MR = modified release; NPH = neutral protamine hagedron; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter-2; SR = systematic review.

Summary of Evidence

Included SRs

The literature search identified 1,110 records. Of these, 993 records were excluded due to irrelevant populations, comparators, or study designs; 177 records of potentially relevant articles (e.g., NMAs) were included for scrutiny. Of these, 80 records were excluded because they did not contain NMAs. The remaining 37 relevant SRs with NMAs were reviewed for second-level screening based on systematic review selection criteria as outlined in [Table 4](#). Full-text articles were retrieved if information was not available from a title and abstract. Appendix 1 presents the flow chart of the study selection.

Two SRs with NMAs (Shi et al. [2023] and Palmer et al. [2021])^{1,16} were selected to inform this Streamlined Drug Class Review. Excluded studies with exclusion reasons are listed in Appendix 3. Reasons for exclusion included inappropriate patient populations (e.g., non-type 2 diabetes population), fewer drug classes than required per our eligibility criteria (e.g., SGLT2 inhibitors versus 1 to 2 other drug classes), and inappropriate or few outcomes (e.g., renal outcomes only).

The NMA by Shi et al. was included as it represents the most recent and comprehensive evidence reporting the outcomes of interest for this review. However, as this NMA did not include change in glycated hemoglobin A1C, an outcome of interest to this review, another NMA (Palmer et al. [2021]) was included to supplement the evidence.

Methods of the Included NMAs

The NMA by Shi et al. (2023)¹ compared the benefits and harms of drug treatments for adults with type 2 diabetes. The predefined protocol for the SR was registered in PROSPERO (International Prospective Register of Systematic Reviews) (CRD42022325948).

Shi et al., 2023

Search Methods and Study Eligibility Criteria

The authors searched Ovid MEDLINE, Embase, and Cochrane Central up to October 14, 2022, and included randomized controlled trials (RCTs) that compared drugs used to treat adults with type 2 diabetes with a follow-up of at least 24 weeks. The authors considered the following drug classes: SGLT2 inhibitors, GLP-1 agonists, DPP-4 inhibitors, thiazolidinediones, sulfonylureas, metformin, alpha-glucosidase inhibitors, meglitinides, insulins, dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 agonists, and nonsteroidal mineralocorticoid receptor antagonists. The following outcomes were included: all-cause death, cardiovascular death, nonfatal stroke, end-stage kidney disease, amputation, nonfatal myocardial infarction, admission to hospital for heart failure, body weight change, health-related quality of life, severe hypoglycemia, severe gastrointestinal events, genital infection, ketoacidosis due to diabetes, and hyperkalemia leading to admission to hospital. These outcomes were defined as follows in the study:

- All-cause death was defined as “the number of patients who died due to any reason within follow-ups.”¹
- Cardiovascular death was defined as “the number of patients who died due to acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, and any other determined cardiovascular cause within follow-ups.”¹
- Non-fatal myocardial infarction was defined as “the number of patients who suffered an acute myocardial infarction but not died within follow-ups.”¹
- Non-fatal stroke was defined as “the number of patients who suffered a stroke but not died within follow-ups.”¹
- Hospitalization for heart failure was defined as “the number of patients who are admitted to the hospital because of the worsening heart failure, with documented new or worsening symptoms of heart failure on presentation, physical examination and laboratory tests supporting the worsening of heart failure, and they stay in hospital for at least 12 hours (or a change in calendar date if the hospital admission and discharge times are unavailable) to receive initiation or intensification of treatment specifically for heart failure.”¹
- End-stage kidney disease was defined as “the number of patients who were with a long-term dialysis, kidney transplantation, a sustained eGFR < 15 mL per minute per 1.73 m², a sustained percent decline in eGFR of at least 40% or a doubling of serum creatinine, or kidney-related death.”¹
- Health-related quality of life was defined as “a change of health-related life score from baseline to follow-up end measured by several questionnaires.”¹
- Severe hypoglycemia was defined as “the number of patients who suffered at least 1 hypoglycemia event which led to a medical assistance. The study prioritizes the definition above but adopted any other study-reported definition if unavailable.”¹
- Severe gastrointestinal events were defined as “the number of patients who suffered at least 1 severe gastrointestinal event or gastrointestinal event leading to discontinuation. The study prioritizes the definition above but adopted any other study-reported definition if unavailable.”¹

- Genital infection was defined as “the number of patients who suffered at least 1 genital infection event.”¹
- Amputation was defined as “the number of patients who suffered at least 1 amputation event.”¹
- Ketoacidosis due to diabetes was defined as “the number of patients who suffered at least 1 ketoacidosis event due to diabetes.”¹
- Hyperkalemia leading to hospitalization was defined as “the number of patients who suffered at least 1 hyperkalemia leading to hospitalization.”¹
- Body weight change was defined as “the change of absolute body weight in kilogram from baseline to follow-up end.”¹

Data Synthesis

The authors conducted a random-effect NMA using a frequentist graph theoretic approach with the weighted least square estimator and Moore-Penrose pseudoinverse.²² The authors started with the assumption that the relative effects were similar across drugs among the same class unless evidence supported otherwise. The network nodes were grouped into drug classes based on their mechanisms of action. There was 1 exception; based on the evidence,²³ the impact of GLP-1 agonists on body weight change was not similar across drug classes. The authors used the continuity correction to account for a zero event by adding 0.5 to all cells of groups for RCTs with at least 1 zero event in the analysis.

The authors evaluated the global heterogeneity with generalized methods of moments estimate of variance between RCTs. They also tested by the design based decomposition of Cochran’s Q statistics.²⁴ Indirect estimates from the network were calculated by node splitting and back calculation methods.²⁵

The author judged the local incoherence by considering the clinical and statistical significance of the ratio of direct and indirect estimates for each network loop. They also used comparison adjusted funnel plots to evaluate global small study effects that could reflect publication bias.

The intransitivity was evaluated based on distribution comparisons of potential effect modifiers (i.e., baseline age, sex, body mass index, hemoglobin A1C, proportion of patients with cardiovascular disease, and duration of diabetes) for each direct comparison and outcome. Metaregressions were also done on these parameters with treatment effects for each drug outcome.

Sensitivity Analyses

Sensitivity analyses were performed with the following scenarios:

- a Bayesian NMA adjusted by trial duration
- a Mantel-Haenszel fixed-effect NMA for rare events
- a meta-analysis excluding trials with high risks for bias
- a meta-analysis for end-stage kidney disease that restricted the definition to a composite of long-term dialysis, kidney transplant, and death from kidney failure
- a meta-analysis pooling study-reported hazard ratios for the trials with at least 2 years of follow-up.

Metaregression

The following four metaregressions were performed for trial characteristics and aggregated patient characteristics with continuous variables:

- proportion of patients with established cardiovascular disease (hypothesizing a larger relative effect in reducing death and cardiovascular and kidney outcomes in trials with a higher proportion of patients with cardiovascular disease)
- mean patient eGFR at baseline (hypothesizing a larger relative effect in reducing death and cardiovascular and kidney outcomes in patients with lower eGFR)
- mean patient body mass index at baseline (hypothesizing a larger relative effect in reducing death and cardiovascular and kidney outcomes in patients with higher body mass index)
- trial follow-up length (hypothesizing a larger relative effect in reducing death and cardiovascular and kidney outcomes in studies with longer follow-up).

The authors used the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN) tool to rate the credibility of any apparent subgroup effect (the regression coefficient's credible interval excludes null effect). The authors assumed the relative effects across populations would be constant if no credible subgroup effect was indicated.

Assessment of Risk of Bias

Pairs of reviewers assessed the risk of bias of individual RCTs independently. The Cochrane risk-of-bias tool,²⁶ modified by the CLARITY group (McMaster University, Hamilton, Canada), was used to inform the risk-of-bias assessments for the following domains: random sequence generation, allocation concealment, blinding to allocated interventions, missing outcome data, selective outcome reporting, and other concerns. Responses for each item were: definitely yes (for low risk of bias), probably yes, probably no, and no (for high risk of bias).

Assessment of the Certainty of the Evidence

The certainty of evidence at the level of the comparison outcome was assessed following Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance.²⁷ Evidence from direct comparisons started as high-certainty evidence and could be rated down (to moderate, low, or very low) for risk of bias, inconsistency of effects, indirectness, or publication bias. Indirect comparisons could be rated down for intransitivity. Using the random walk approach,²⁸ a contribution matrix quantified the proportional contribution of each direct comparison with each indirect and network comparison. The final certainty for network evidence was rated down for incoherence and imprecision.²⁹ Imprecision was rated following the GRADE guidance.³⁰

Minimally important differences (i.e., thresholds of clinical importance) were established by a previous guideline panel.³¹ When the point estimate was less than the threshold, the authors rated their certainty in little-to-no effect. Otherwise, the authors rated their certainty in a nonzero effect (using the null as the threshold). The certainty was rated down for imprecision by 2 levels when the 95% confidence interval (CI) crossed more than 1 threshold of importance.

Palmer et al., 2021

Search Methods and Study Eligibility Criteria

The authors searched Ovid MEDLINE, Embase, and Cochrane Central up to August 11, 2020. They evaluated SGLT2 inhibitors and GLP-1 agonists in patients with type 2 diabetes at varying cardiovascular and renal risk. The predefined protocol for the SR was registered in PROSPERO (CRD201915380).

RCTs comparing SGLT2 inhibitors or GLP-1 agonists to placebo, standard care, or other glucose-lowering treatments in adults with type 2 diabetes, with follow-up periods of 24 weeks or longer, were included. Studies were screened independently by 2 reviewers for eligibility, extracted data, and assessed risk of bias.

Data Synthesis

A frequentist pairwise meta-analysis was conducted for each direct comparison of 2 treatments using a restricted maximum likelihood estimation. A common heterogeneity estimate was assumed within the network. Agreement between direct and indirect estimates were assessed in every closed loop of evidence using node-splitting approaches, and for the entire network using a design-by-treatment interaction.

Assessment of Risk of Bias

Using the Cochrane tool for assessing risk of bias in randomized trials, 2 reviewers assessed risk of bias, with adjudication by a third reviewer. The domains included random sequence generation, allocation concealment, blinding, missing outcome data, and selective reporting of outcomes. The authors reported low levels of blinding for participants, investigators, and outcome assessors. Overall, 40.2% of trials were at low risk of bias in random sequence generation and 69.2% were at low risk of bias in allocation concealment. In addition, 60.5% reported blinding for participants and investigators and 13.7% reported blinding for outcome assessment, while 42.9% were adjudicated as being at low risk of attrition bias and 46.5% were at low risk of bias from selective outcome reporting.

Assessment of Certainty of Evidence

The authors used the GRADE approach to report the certainty of evidence and provided estimated absolute risks of cardiovascular and kidney disease. The authors identified the heterogeneity of clinical settings in the included trials as a limitation. However, the authors also pointed out that the consistency of the results across studies diminished this concern. Some outcomes had imprecise estimates of effects and low-certainty evidence.

Summary of Results

Description of Included Studies

The NMA included 816 RCTs with 471,038 participants. Across RCTs, the mean age was 57.7 years (95% CI, 57.4 to 58.1), and 56.6% (95% CI, 55.8% to 57.5%) of patients were male. The mean body mass index at baseline was 29.5 kg/m² (95% CI, 29.3 to 29.8). The mean hemoglobin A1C at baseline was 8.1% (95% CI, 8.1% to 8.2%). Across RCTs, a mean of 58.6% (95% CI, 40.9% to 74.9%) of patients had confirmed cardiovascular disease at baseline, and the mean duration of diabetes was 7.4 years (95% CI, 5.2 to 10.1). The median follow-up across RCTs was 6 months (interquartile range, 5.5 to 12.0).

Risk of Bias in Included Studies

Among the 816 RCTs, 223 (27%) were judged to be at high risk of bias for at least 1 of the 6 domains, mostly due to lack of blinding (62%), missing outcome data (26%), or inadequate allocation concealment (25%).

[Table 5](#) provides a summary of overall risk of bias according to drug classes across all 6 domains. As highlighted in the table, a higher percentage of study arms for some drug classes – such as basal insulins (52.7%) and sulfonylureas (27.3%) – had a high risk of bias.

Table 5: Summary of Overall Risk of Bias According to Drug Classes

Drug class	Total number of arms with high risk of bias across 6 domains	Total number of arms	Arms with high risk of bias, %
Basal insulins	29	55	52.7
DPP-4 inhibitors	50	324	15.4
GLP-1 agonists	41	239	14.2
SGLT2 inhibitors	39	252	15.5
Standard treatments	55	522	10.5
Sulfonylureas	41	150	27.3

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

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Description of Findings

The following sections provide a summary of results from the NMA comparing SGLT2 inhibitors with other drug treatments in type 2 diabetes. The comparisons of each drug treatment are also presented with comparisons to standard treatments, as these are often important considerations in clinical practice. Standard treatment was defined as the treatment regimens that patients received before adding a new drug. Standard treatments include standard care (such as healthy behaviour interventions) and standard drug treatments such as metformin and / or sulfonylurea other than the drug of interest in the randomized trial.

Efficacy

For the outcome of nonfatal stroke by risk strata, the estimated absolute effects are reported in the [Supplemental Materials](#) for this report, in Appendix 7, Table 10.

All-Cause Death

In the analysis of all-cause death, there were 257 contributing RCTs with 342,237 participants and 15,371 events.

Compared to standard treatments, both SGLT2 inhibitors (odds ratio [OR] = 0.88; 95% CI, 0.83 to 0.94; high certainty) and GLP-1 agonists (OR = 0.88; 95% CI, 0.82 to 0.93; high certainty) reduce all-cause death. Metformin may reduce all-cause death (OR = 0.84; 95% CI, 0.67 to 1.04; low certainty). Sulfonylureas may possibly increase all-cause death (OR = 1.10; 95% CI, 0.97 to 1.26; low certainty). For DPP-4 inhibitors (OR =

1.01; 95% CI, 0.95 to 1.08; low certainty) and basal insulins (OR = 0.79; 95% CI, 0.19 to 3.32; low certainty), it is uncertain whether they have an impact on all-cause death.

In comparison to SGLT2 inhibitors for the outcome of all-cause death, the ORs for each intervention were as follows: for GLP-1 agonists, the OR was 1.01 (95% CI, 0.88 to 1.16; very low certainty); for DPP-4 inhibitors, the OR was 0.87 (95% CI, 0.79 to 0.96; moderate certainty); for sulfonylureas, the OR was 0.80 (95% CI, 0.69 to 0.93; moderate certainty), and for basal insulins, the OR was 0.81 (95% CI, 0.59 to 1.10; very low certainty).

Note that the authors presented outcome data by risk strata; this information is provided at the [DiabetesNMA website](#) and is also available from the [original publication](#).

Cardiovascular Death

For the analysis on cardiovascular death, there were 144 contributing RCTs, including 275,679 patients and 9,120 events.

Compared to standard treatments, SGLT2 inhibitors and GLP-1 agonists reduced cardiovascular death; for SGLT2 inhibitors, the OR was 0.86 (95% CI, 0.83 to 0.94; high certainty) and for GLP-1 receptors, the OR was 0.87 (95% CI, 0.81 to 0.94; high certainty). Other interventions including metformin, sulfonylureas, DPP-4 inhibitors, and basal insulins, had little effect, no effect, or an uncertain effect on the outcome of cardiovascular death.

In comparison to SGLT2 inhibitors for the outcome of cardiovascular death, the ORs for each intervention were as follows: for GLP-1 agonists, the OR was 0.99 (95% CI, 0.88 to 1.11; low certainty); for DPP-4 inhibitors, the OR was 0.86 (95% CI, 0.77 to 0.97; moderate certainty); for sulfonylureas, the OR was 0.86 (95% CI, 0.69 to 1.06; low certainty); and for basal insulins, the OR was 0.39 (95% CI, 0.04 to 3.85; low certainty).

Table 6: Efficacy Outcomes and HRQoL With Drug Treatments for Type 2 Diabetes Compared to Standard Treatments

Intervention	All-cause death OR (95% CI)	Cardiovascular death OR (95% CI)	Nonfatal myocardial infarction OR (95% CI)	Nonfatal stroke OR (95% CI)	Admission to hospital for heart failure OR (95% CI)	End-stage kidney disease OR (95% CI)	HRQoL score OR (95% CI)
SGLT2 inhibitors	0.88 (0.83 to 0.94)	0.86 (0.80 to 0.94)	0.90 (0.82 to 0.98)	0.99 (0.88 to 1.11)	0.66 (0.60 to 0.73)	0.61 (0.55 to 0.67)	0.30 (0.10 to 0.49)
GLP-1 agonists	0.88 (0.82 to 0.93)	0.87 (0.81 to 0.94)	0.91 (0.85 to 0.98)	0.85 (0.77 to 0.94)	0.91 (0.83 to 0.99)	0.83 (0.75 to 0.92)	0.17 (0.07 to 0.27)
Metformin	0.84 (0.67 to 1.04)	0.95 (0.48 to 1.88)	0.86 (0.68 to 1.09)	0.97 (0.71 to 1.33)	1.45 (0.28 to 7.36)	1.61 (0.36 to 7.24)	0.04 (-0.25 to 0.33)
DPP-4 inhibitors	1.01 (0.95 to 1.08)	1.00 (0.92 to 1.09)	1.01 (0.92 to 1.11)	0.91 (0.80 to 1.03)	1.05 (0.95 to 1.16)	1.04 (0.93 to 1.16)	0.03 (-0.12 to 0.17)
Sulfonylureas	1.10 (0.97 to 1.26)	1.01 (0.83 to 1.23)	1.00 (0.83 to 1.22)	1.05 (0.84 to 1.32)	0.99 (0.79 to 1.23)	0.68 (0.37 to 1.24)	0.23 (-0.19 to 0.64)
Basal insulins	1.10 (0.81 to 1.49)	1.28 (0.83 to 1.99)	0.98 (0.47 to 2.06)	0.76 (0.33 to 1.77)	0.94 (0.62 to 1.43)	1.20 (0.62 to 2.30)	0.00 (-0.25 to 0.24)
Standard treatments	Reference	Reference	Reference	Reference	Reference	Reference	Reference

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HRQoL = health related quality of life; OR = odds ratio; SGLT2 = sodium-glucose cotransporter-2.

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Nonfatal Myocardial Infarction

The analysis on nonfatal myocardial infarction included 209 RCTs with 293,042 patients and 8,906 events.

Compared to standard treatments, SGLT2 inhibitors reduced nonfatal myocardial infarction, with an OR of 0.90 (95% CI, 0.82 to 0.98; high certainty). GLP-1 agonists also reduced nonfatal myocardial infarction, with an OR of 0.91 (95% CI, 0.85 to 0.98; moderate certainty). Metformin may also reduce nonfatal myocardial infarction, with an OR of 0.86 (95% CI, 0.69 to 1.09; low certainty).

In comparison to SGLT2 inhibitors for the outcome of nonfatal myocardial infarction, the ORs for each intervention were as follows: for GLP-1 agonists, the OR was 0.98 (95% CI, 0.88 to 1.10; low certainty); for DPP-4 inhibitors, the OR was 0.88 (95% CI, 0.78 to 1.01; low certainty); for sulfonylureas, the OR was 0.89 (95% CI, 0.72 to 1.10; very low certainty); and for basal insulins, the OR was 0.92 (95% CI, 0.43 to 1.92; very low certainty).

Nonfatal Stroke

For the analysis of nonfatal stroke, the analysis included 178 RCTs with 283,728 patients and 4,878 events.

Compared to standard treatments, GLP-1 agonists demonstrated the ability to reduce nonfatal stroke with high certainty (OR = 0.85; 95% CI, 0.77 to 0.94; high certainty), while SGLT2 inhibitors had low certainty in demonstrating a reduction in this outcome (OR = 0.99; 95% CI, 0.88 to 1.11; low certainty). Metformin, sulfonylureas, DPP-4 inhibitors, and basal insulins had little, no, or uncertain effects on nonfatal stroke. For metformin, the OR was 0.97 (95% CI, 0.71 to 1.33; low certainty). For sulfonylureas, the OR was 1.05 (95% CI, 0.84 to 1.32; low certainty). For DPP-4 inhibitors, the OR was 0.91 (95% CI, 0.80 to 1.03; low certainty) and for basal insulins, the OR was 0.76 (95% CI, 0.33 to 1.77; low certainty).

In comparison to SGLT2 inhibitors for the outcome of nonfatal stroke, the ORs for each intervention were as follows: for GLP-1 agonists, the OR was 1.16 (95% CI, 1.00 to 1.35; low certainty); for DPP-4 inhibitors, the OR was 1.10 (95% CI, 0.93 to 1.30; low certainty); for sulfonylureas, the OR was 0.94 (95% CI, 0.73 to 1.20; very low certainty); and for basal insulins, the OR was 1.30 (95% CI, 0.56 to 3.03; very low certainty).

When SGLT2 inhibitors were compared to GLP-1 agonists, the relative effect had an OR of 1.16 (95% CI, 1.00 to 1.35; low certainty). This translates to the following anticipated absolute effects:

- For adults with 3 or fewer cardiovascular risk factors, the baseline (5-year) risk for nonfatal stroke was 26 per 1,000 persons. The anticipated absolute effect (over the course of 5 years) is 4 more nonfatal strokes (range, 0 to 9) per 1,000 persons (moderate certainty).
- For adults with more than 3 cardiovascular risk factors, the baseline (5-year) risk for nonfatal stroke was 50 per 1,000 persons. The anticipated absolute effect (over the course of 5 years) is 8 more nonfatal strokes (range, 0 to 16) per 1,000 persons (low certainty).
- For adults with cardiovascular disease only (no chronic kidney disease), the baseline (5-year) risk for nonfatal stroke was 93 per 1,000 persons. The anticipated absolute effect (over the course of 5 years) is 14 more nonfatal strokes (range, 0 to 29) per 1,000 persons (moderate certainty).

- For adults with chronic kidney disease only (no cardiovascular disease), the baseline (5-year) risk for nonfatal stroke was 104 per 1,000 persons. The anticipated absolute effect (over the course of 5 years) is 15 more nonfatal strokes (range, 0 to 32) per 1,000 persons (moderate certainty).
- For adults with established cardiovascular disease and chronic kidney disease, the baseline (5-year) risk for nonfatal stroke is 166 per 1,000 persons. The anticipated absolute effect (over the course of 5 years) is 22 more nonfatal strokes (range, 0 to 46) per 1,000 persons (moderate certainty).

Note that for the outcome of nonfatal stroke, the estimated absolute effects are reported in the [Supplemental Materials](#) for this report (Appendix 7, Table 10).

Admission to Hospital for Heart Failure

The analysis for this outcome included 142 RCTs with 252,055 participants and 6,681 events.

Compared to standard treatments, SGLT2 inhibitors reduced admission to hospital for heart failure, with an OR of 0.66 (95% CI, 0.60 to 0.73; high certainty). GLP-1 agonists may reduce admission to hospital for heart failure, with an OR of 0.91 (95% CI, 0.83 to 0.99; moderate certainty). Metformin (OR = 1.45; 95% CI, 0.28 to 7.36; low certainty), sulfonylureas (OR = 0.99; 95% CI, 0.79 to 1.23; low certainty), DPP-4 inhibitors (OR = 1.05; 95% CI, 0.95 to 1.16; low certainty), and basal insulins (OR = 0.94; 95% CI, 0.62 to 1.43; low certainty) had little, no, or uncertain effects on this outcome.

In comparison to SGLT2 inhibitors for the outcome of admission to hospital for heart failure, the ORs for each intervention were as follows: for GLP-1 agonists, the OR was 0.73 (95% CI, 0.64 to 0.83; moderate certainty); for DPP-4 inhibitors, the OR was 0.63 (95% CI, 0.55 to 0.72; moderate certainty); for sulfonylureas, the OR was 0.67 (95% CI, 0.53 to 0.85; moderate certainty); and for basal insulins, the OR was 0.70 (95% CI, 0.46 to 1.09; low certainty).

End-Stage Kidney Disease

For this outcome, the analysis included 54 RCTs with 209,754 patients and 6,972 events.

The authors concluded that, compared to standard treatments, SGLT2 inhibitors (OR = 0.61; 95% CI, 0.55 to 0.67; high certainty) and GLP-1 agonists (OR = 0.83; 95% CI, 0.75 to 0.92; moderate certainty) probably reduce end-stage kidney disease. The certainty of evidence has been rated down by the authors given its indirectness. The composite outcome of end-stage kidney disease was driven by variation in the reporting of kidney outcomes among trials. The authors stated that SGLT2 inhibitors are possibly superior to GLP-1 agonists. Other drugs, including metformin, sulfonylureas, DPP-4 inhibitors, and basal insulins, have little or uncertain effects on this outcome.

In comparison to SGLT2 inhibitors for end-stage kidney disease, the ORs for each intervention are as follows: for GLP-1 agonists, the OR was 0.73 (95% CI, 0.63 to 0.84; low certainty); for DPP-4 inhibitors, the OR was 0.58 (95% CI, 0.50 to 0.68; low certainty); for sulfonylureas the OR was 0.89 (95% CI, 0.48 to 1.64; very low certainty); and for basal insulins, the OR was 0.51 (95% CI, 0.26 to 0.98; low certainty).

Body Weight Change

Mean difference in body weight was used as the effect measure. For this outcome, there were 531 RCTs, with 279,118 patients for the analysis.

Among the interventions of interest in this review, the GLP-1 agonists had varying effects on body weight change, with semaglutide (subcutaneous) being associated with the greatest changes in body weight, followed by semaglutide (oral), liraglutide, dulaglutide, and lixisenatide.

As a drug class effect, SGLT2 inhibitors were associated with a mean body weight change of -1.98 kg (95% CI, -2.18 to -1.78 ; moderate certainty). The mean body weight change associated with metformin was -0.83 kg (95% CI, -1.40 to -0.26 ; moderate certainty). Basal insulins were associated with a mean body weight change of 2.15 kg (95% CI, 1.74 to 2.56 ; high certainty). Sulfonylureas were associated with a mean body weight change of 1.78 kg (95% CI, 1.50 to 2.06 ; moderate certainty).

As noted by the Diabetes Canada Clinical Practice Guidelines, a sustained weight loss of at least 5% of initial body weight can improve glycemic control and cardiovascular risk factors.⁸ Hence, body weight change can have an impact on important outcomes in type 2 diabetes.

Table 7: Body Weight Impact of Drug Treatments for Type 2 Diabetes

Intervention	Body weight change in kg, MD (95% CI)
Semaglutide (subcutaneous)	-4.62 (-5.22 to -4.03)
Semaglutide (oral)	-2.98 (-3.66 to -2.29)
Liraglutide	-2.21 (-2.58 to -1.85)
SGLT2 inhibitor	-1.98 (-2.18 to -1.78)
Lixisenatide	-0.83 (-1.40 to -0.26)
Dulaglutide	-1.40 (-1.93 to -0.88)
Metformin	-0.83 (-1.16 to -0.51)
DPP-4 inhibitors	0.28 (0.11 to 0.46)
Sulfonylureas	1.78 (1.50 to 2.06)
Basal insulins	2.15 (1.74 to 2.56)
Standard treatments	Reference

CI = confidence interval ;DPP-4 = dipeptidyl peptidase-4; MD = mean difference; SGLT2 = sodium-glucose cotransporter-2.

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Glycated Hemoglobin A1C

This outcome was not included for analysis by Shi et al.¹ Hence, another NMA¹⁶ was consulted and used as a supplement to provide results for this outcome. A hemoglobin A1C drop of 0.5% is considered clinically meaningful. In this SR, the authors included 606 RCTs with 242,745 patients in the analysis for glycated hemoglobin A1C, for a median follow-up of 6 months. Compared to placebo, SGLT2 inhibitors resulted in

a mean difference in hemoglobin A1C of -0.60% (95% CI, -0.67% to -0.54% ; low certainty). Compared to placebo, GLP-1 agonists resulted in a mean difference in hemoglobin A1C of -0.89% (95% CI, -0.95% to -0.82% ; low certainty). The authors also highlighted that GLP-1 agonists reduced glycated hemoglobin A1C levels to a greater extent than SGLT2 inhibitors (mean difference -0.28% ; 95% CI -0.37% to -0.19% ; high certainty). Other mean differences in glycated hemoglobin A1C as compared to placebo are listed in [Table 8](#).

When SGLT2 inhibitors are compared to other interventions, the percentage mean differences were as follows: for GLP-1 agonists, the mean difference was 0.28% (95% CI, 0.19% to 0.37%); for sulfonylurea, the mean difference was 0.05% (95% CI, -0.05% to 0.15%); for DPP-4 inhibitors, the mean difference was -0.01% (95% CI, -0.09% to 0.07%); for basal insulins, the mean difference was -0.14% (95% CI, 0.01% to 0.26%).

Table 8: Glycated Hemoglobin A1C With Drug Treatments for Type 2 Diabetes

Intervention	Comparator	Hemoglobin A1C %, MD (95% CI)
SGLT2 inhibitor	Placebo	-0.60 (-0.67 to -0.54)
GLP-1 agonist	Placebo	-0.89 (-0.95 to -0.82)
SGLT2 inhibitor	GLP-1 agonist	0.28 (0.19 to 0.37)
Metformin	Placebo	-0.80 (-0.89 to -0.71)
DPP-4 inhibitor	Placebo	-0.60 (-0.65 to -0.54)
Sulfonylureas	Placebo	-0.65 (-0.74 to -0.57)
Basal insulin	Placebo	-0.74 (-0.86 to -0.63)

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

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Health-Related Quality of Life

For the analysis of this outcome, there were 33 trials with 18,588 patients, using 13 types of questionnaires. SGLT2 inhibitors and GLP-1 agonists probably improve health-related quality of life, with a standardized mean difference (SMD) of 0.30 (95% CI, 0.10 to 0.49 ; high certainty) and 0.17 (95% CI, 0.07 to 0.27 ; high certainty), respectively. For other drugs including metformin (SMD = 0.04 ; 95% CI, -0.25 to 0.33), sulfonylureas (SMD = 0.23 ; 95% CI, -0.19 to 0.64), DPP-4 inhibitors (SMD = 0.03 ; 95% CI, -0.12 to 0.17), and basal insulins (SMD = -0.11 ; 95% CI, -0.28 to 0.07 ; low certainty), the results are less inconclusive.

Safety

Severe Hypoglycemia

Among the interventions of interest, sulfonylureas and basal insulins probably increase the risk of severe hypoglycemic events, with ORs of 5.22 (95% CI, 3.88 to 7.01 ; high certainty) and 2.38 (95% CI, 1.82 to 3.12 ; high certainty), respectively. For SGLT2 inhibitors, when compared to standard treatments, the OR for severe hypoglycemia was 0.90 (95% CI, 0.79 to 1.02 ; moderate certainty). For GLP-1 agonists, the OR was 0.98 (95% CI, 0.90 to 1.06 ; moderate certainty).

Table 9: Severe Hypoglycemia With Drug Treatments for Type 2 Diabetes

Intervention	Severe hypoglycemia, OR (95% CI)
SGLT2 inhibitors	0.90 (0.79 to 1.02)
GLP-1 agonists	0.98 (0.90 to 1.06)
Metformin	1.73 (0.89 to 3.37)
DPP-4 inhibitors	1.11 (1.00 to 1.23)
Sulfonylureas	5.22 (3.88 to 7.01)
Basal insulins	2.38 (1.82 to 3.12)
Standard treatments	Reference

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MD = mean difference; OR = odds ratio; SGLT2 = sodium-glucose cotransporter-2.

Source: Shi Q, et al., Copyright 2023. This work is licensed under the Attribution 4.0 International Licence. Full text available here: <https://www.bmj.com/content/381/bmj-2022-074068>

Genital Infection, Amputation, and Ketoacidosis due to Diabetes

These safety outcomes are only specific to SGLT2 inhibitors. When compared to standard treatments, the OR of SGLT2 inhibitors for genital infection is 3.30 (95% CI, 2.88 to 3.78; high certainty). When compared to standard treatments, the OR of SGLT2 inhibitors for amputation is 1.27 (95% CI, 1.01 to 1.61; high certainty). When compared to standard treatments, the OR of SGLT2 inhibitors for ketoacidosis due to diabetes is 2.07 (95% CI, 1.44 to 2.98; high certainty).

Severe Gastrointestinal Events

When compared to standard treatments, the OR for GLP-1 agonists for severe gastrointestinal events is 1.97 (95% CI, 1.39 to 2.80; high certainty). When compared to standard treatments, the OR for metformin for severe gastrointestinal events is 2.22 (95% CI, 0.64 to 7.71; low certainty). Other drugs have little or no effect compared with standard treatments.

Critical Appraisal of the Evidence

The authors of the NMAs included in this review used validated methods to assess risk of bias in individual studies which was assessed by pairs of reviewers independently, using the modified Cochrane risk-of-bias tool. Detailed assessments of risk of bias corresponding to each trial were outlined in the supplemental material of the publication.

The authors assessed the between-study heterogeneity for all comparisons in each outcome by several pairwise random-effect meta-analyses. Clinical heterogeneity was also assessed by clinical experts.

To assess the intransitivity between direct comparisons, the authors compared their distributions of patients' characteristics. The authors chose the potential effect modifiers from the prognostic variables that were identified by the prognostic research and the systematic review of risk prediction models. These include age, body mass index, proportion with cardiovascular disease, duration of baseline diabetes, hemoglobin A1C, sex, and cardiovascular death. They also assessed the incoherence (local inconsistency for each treatment

loop) by the ratio of OR (binary outcomes) or difference in mean difference (continuous outcomes) between direct estimates and indirect estimates, and the corresponding statistical tests for the ratio or difference.

To assess publication bias, the authors evaluated the small-study effect (a source of publication bias) using Harbord's score regression method in the pairwise meta-analyses for binary outcomes (Egger's method for continuous outcomes). The results demonstrated that Harbord's method performs better in binary outcome settings than Egger's method. This test was performed for the meta-analyses with at least 5 trials. The authors also performed the trim and fill analysis for the meta-analyses with at least 10 trials, using both the L-type estimator and R-type estimator to assess robustness.

The authors also assessed the certainty of the evidence following GRADE guidance. They concluded that the evidence did not suggest global publication bias or intransitivity for any outcome. The results also did not suggest relevant global inconsistency or incoherence in outcomes, except for health-related quality of life, body weight change, and amputation.

The NMA by Shi et al. (2023)¹ was critically appraised by CADTH using AMSTAR 2, an instrument used to assess the methodological quality of systematic reviews.²⁰ The NMA scored "high" using the AMSTAR 2 checklist (Appendix 4 in the [Supplemental Materials](#)). A high AMSTAR 2 score indicates no or 1 noncritical weakness; that is, the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question.

In addition, the ISPOR questionnaire to assess relevance and credibility²¹ was completed for both the Shi et al.¹ and Palmer et al.¹⁶ NMAs, and results are included in Appendix 4 in the [Supplemental Materials](#).

Utilization Analysis

Methods

Public drug claims data were sourced from the National Prescription Drug Utilization Information System (NPDUIS), including public drug plans from Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan, and Yukon, between January 1, 2019, and December 31, 2022. The drugs used in diabetes were identified by the drug identification numbers (DINs) assigned by Health Canada and the WHO Anatomic Therapeutic Chemical (ATC) codes (Appendix 5 in the [Supplemental Materials](#)). Only accepted drug claims, in which at least part of the claim was accepted by the public plan either toward a deductible (if applicable) or for payment, were included.

Trends in utilization and expenditures were compared between drug classes and between molecules within each drug class. Utilization was defined as the number of individuals who were dispensed a prescription for a publicly funded antihyperglycemic therapy per year from 2019 to 2022. Expenditures were based on the total prescription cost accepted by the drug plan. This is the total dollar amount of a prescription accepted by the drug plan as eligible toward a deductible or for reimbursement, as it relates to the quantity

accepted, which includes the drug cost as well as the associated professional fees and markup, if applicable. Total expenditures were calculated for each drug by year from 2019 to 2022, within each jurisdiction and aggregated for presentation at the national level. The average cost of utilization (total prescription cost accepted) per beneficiary nationally in 2022 was calculated for each drug class and each molecule.

Claims for drugs administered outside of public drug plans (e.g., through hospital-based programs or cancer agencies) and covered by jurisdictions are not submitted to NPDUIS. Costs do not reflect product listing agreements between drug plans and manufacturers. In accordance with the CIHI privacy policy, in cases in which the number of active beneficiaries were less than 5 (but greater than zero), this number and other associated values were suppressed to ensure confidentiality.

Results

Utilization Trends for Antihyperglycemic Agents

From 2019 to 2022, the number of claimants for antihyperglycemic agents across public drug plans rose from 2,361,734 to 2,794,525. The market shares (% of claimants) for the antihyperglycemic therapy classes for each year are detailed in [Figure 1](#). For additional insights, refer to the [Supplemental Materials](#) (Table 7 in Appendix 6). Cumulatively, over the 4-year period, biguanides maintained the highest market share of claimants (35.3%), followed by sulfonylureas (12.2%) and SGLT2 inhibitors (11.7%). Among the classes, only the market shares for GLP-1 agonists (from 1.0% in 2019 to 7.3% in 2022) and SGLT2 inhibitors (from 9.0% in 2019 to 14.4% in 2022) exhibited a year-over-year growth, whereas the market shares for other classes either remained stable or declined over the period.

[Table 10](#) provides a detailed breakdown of the claimants for the antihyperglycemic agents by molecule:

- The biguanides class, represented solely by metformin, maintained the highest number of claimants, with a peak of 943,245 claimants in 2022, representing an increase of 8.4% from 870,625 claimants in 2019.
- A notable year-over-year growth in claimants was observed for GLP-1 agonists, particularly for semaglutide, which increased more than 8-fold, from 24,720 claimants in 2019 to 204,268 in 2022.
- The SGLT2 class demonstrated an increase in claimants across all 3 drugs in the class, with total claimants rising from 216,716 in 2019 to 407,385 in 2022, an increase of 88.1%.
- The DPP-4 inhibitor plus biguanide combination class exhibited a decline in claimants from 2019 to 2022, mainly driven by a reduction in claimants for the metformin-sitagliptin combination.
- Insulin as a class showed a relatively stable trend in claimants from 2019 to 2022. Specifically, within the insulin subclasses, long-acting insulins saw an increase in claimants from 254,216 in 2019 to 280,054 in 2022, representing a growth of 10.2%.

Table 10: Number of Claimants for Antihyperglycemic Agents by Molecule (2019 to 2022)

Class	Drug	2019	2020	2021	2022
Alpha-glucosidase inhibitors	Acarbose	6,246	4,520	4,648	4,700
Biguanides	Metformin	870,625	876,295	913,753	943,245
Combination: biguanides and DPP-4 inhibitors	Metformin and linagliptin	18,089	16,802	14,683	13,396
	Metformin and saxagliptin	7,597	6,754	6,086	5,332
	Metformin and sitagliptin	154,976	153,954	151,852	147,379
Combination: biguanides and SGLT2 inhibitors	Metformin and dapagliflozin	7,185	9,683	12,925	15,843
	Metformin and empagliflozin	10,195	17,996	26,937	37,673
DPP-4 inhibitors	Linagliptin	77,003	79,061	81,298	77,599
	Saxagliptin	16,284	13,905	12,244	10,470
	Sitagliptin	115,510	110,682	107,616	102,473
GLP-1 agonists	Lixisenatide	—	7	29	69
	Semaglutide	24,720	68,802	130,666	204,199
Insulin	Insulin (human)	73,783	62,487	55,441	48,466
	Insulin (pork)	33	30	27	22
	Insulin aspart	85,799	81,878	83,751	82,459
	Insulin degludec	51,950	70,749	85,264	97,190
	Insulin detemir	24,892	18,696	16,069	14,166
	Insulin glargine	199,869	183,591	179,245	176,298
	Insulin glargine and lixisenatide	60	1,207	1,830	1,970
	Insulin glulisine	15,835	15,926	16,223	16,687
	Insulin lispro	88,655	86,302	85,066	85,264
	Insulin fast-acting	1,502	2,030	2,372	2,502
Meglitinides	Repaglinide	10,143	9,373	9,553	9,026
Sulfonylureas	Glibenclamide	43,787	39,046	37,875	35,811
	Gliclazide	275,851	270,839	275,821	278,222
	Glimepiride	342	306	287	236
SGLT2 inhibitors	Canagliflozin	48,370	53,428	59,501	62,451
	Dapagliflozin	32,666	39,625	55,436	81,008
	Empagliflozin	135,680	166,938	212,466	263,926
Thiazolidinediones	Pioglitazone	5,448	4,176	3,285	3,096
	Rosiglitazone	485	373	302	243

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

Expenditure Trends for Antihyperglycemic Agents

The highest cumulative market share of expenditures over the 4-year period was observed for the SGLT2 inhibitors (19.7%), followed by long-acting insulins (17.3%) and the oral combination class (15.9%) (Figure 1). For additional insights, refer to the [Supplemental Materials](#) (Table 8 in Appendix 6). Among the classes, only the market shares for GLP-1 agonists (from 1.2% in 2019 to 24.1% in 2022) and SGLT2 inhibitors (from 16.6% in 2019 to 22.1% in 2022) exhibited a year-over-year growth, whereas the market share for other classes either remained stable or declined over the period.

[Table 11](#) provides a detailed breakdown of the expenditures for the antihyperglycemic agents by molecule:

- GLP-1 agonists experienced a substantial rise in expenditures from \$13.5 million in 2019 to \$401.9 million in 2022, predominantly due to semaglutide, which increased from \$13.5 million to \$401.8 million during this period.
- Expenditures for the SGLT2 plus biguanide combination class increased from 2019 to 2022, particularly for the metformin plus empagliflozin combination, which saw an increase from \$5.3 million to \$31.6 million.
- The SGLT2 inhibitor class saw a consistent increase in expenditures from \$178.7 million in 2019 to \$369.5 million in 2022, with empagliflozin increasing from \$107.2 million to \$237.4 million during this period.
- The biguanides class, solely represented by metformin, maintained a relatively steady expenditure trend, with a slight increase to \$77.9 million in 2022 from \$72.4 million in 2019.

Insulins as a class made up 27% of the total expenditures from 2019 to 2022. While the total expenditures for insulins increased year over year during this period, their market share in expenditures decreased. Within the insulin subclasses, expenditures for long-acting insulins increased from \$227.5 million in 2019 to \$238.8 million in 2022, while the other insulin subclasses decreased in yearly expenditures.

Table 11: Expenditures for Antihyperglycemic Agents by Molecule (2019 to 2022)

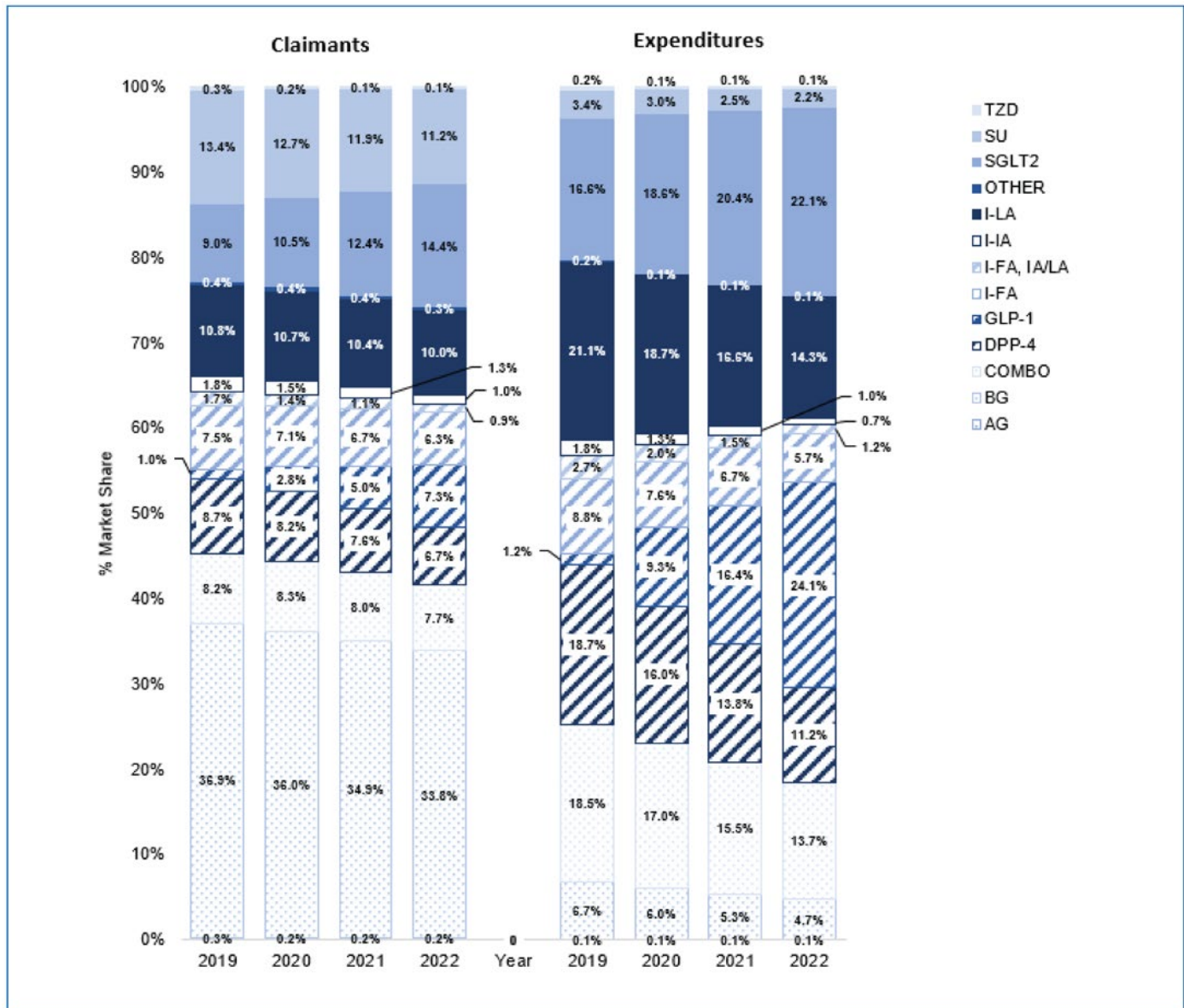
Class	Drug	2019 (\$)	2020 (\$)	2021 (\$)	2022 (\$)
Alpha-glucosidase inhibitors	Acarbose	1,438,182	1,184,141	906,446	911,667
Biguanides	Metformin	72,369,064	75,529,821	75,883,494	77,949,737
Combination: Biguanides and DPP-4 inhibitors	Metformin and linagliptin	15,760,778	14,945,240	12,672,474	12,131,595
	Metformin and saxagliptin	6,501,557	5,883,244	5,316,987	4,730,749
	Metformin and sitagliptin	166,948,958	172,033,852	174,257,969	168,894,680
Combination: Biguanides and SGLT2 inhibitors	Metformin and dapagliflozin	4,688,636	6,980,462	9,445,032	11,913,001
	Metformin and empagliflozin	5,343,470	14,174,493	21,881,609	31,638,304
DPP-4 inhibitors	Linagliptin	65,983,877	67,257,804	68,864,167	67,099,572



Class	Drug	2019 (\$)	2020 (\$)	2021 (\$)	2022 (\$)
GLP-1 agonists	Saxagliptin	16,796,622	14,735,574	10,307,715	6,587,652
	Sitagliptin	119,012,569	119,299,007	118,700,710	112,728,386
	Lixisenatide		5,690	21,214	42,921
	Semaglutide	13,480,989	116,725,191	235,447,243	401,790,045
Insulin	Insulin (human)	35,806,707	31,062,822	26,751,532	23,004,045
	Insulin (pork)	41,743	39,925	24,911	21,088
	Insulin aspart	50,307,159	49,317,062	49,519,105	47,553,734
	Insulin degludec	46,929,545	75,016,089	90,007,215	99,298,095
	Insulin detemir	26,549,133	20,701,532	17,470,033	14,798,301
	Insulin glargine	153,953,538	138,628,353	128,759,477	122,080,826
	Insulin glargine and lixisenatide	16,872	1,253,963	2,237,646	2,655,865
	Insulin glulisine	7,277,689	7,660,866	7,852,749	7,784,429
	Insulin lispro	50,241,267	49,408,937	47,766,914	48,089,221
	Insulin fast-acting	135,906	187,938	229,234	229,387
Meglitinides	Repaglinide	1,665,424	1,631,267	1,564,956	1,478,648
Sulfonylureas	Glibenclamide	4,209,496	3,931,993	3,655,521	3,360,427
	Gliclazide	32,614,573	33,173,589	32,576,555	32,532,322
	Glimepiride	80,240	80,953	123,338	124,475
SGLT2 inhibitors	Canagliflozin	43,937,481	52,936,214	60,114,733	64,881,565
	Dapagliflozin	27,560,645	33,932,158	46,569,864	67,233,278
	Empagliflozin	107,186,469	147,570,805	187,359,859	237,376,514
Thiazolidinediones	Pioglitazone	2,032,286	1,474,713	1,325,213	1,274,370
	Rosiglitazone	402,362	311,244	249,666	195,287

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

Figure 1: Market Share of Claimants and Expenditures for Antihyperglycemic Agents by Class (2019 to 2022)



AG = alpha-glucosidase inhibitors; BG = biguanides; COMBO = combinations of oral blood glucose-lowering drugs; I-FA = insulins and analogues for injection, fast-acting; I-FA, IA/LA = insulins and analogues for injection, intermediate- or long-acting combined with fast-acting; I-IA = insulins and analogues for injection, intermediate-acting; I-LA = insulins and analogues for injection, long-acting; OTHER = Other blood glucose-lowering drugs, excluding insulins; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

Average Annual Cost of Utilization per Beneficiary for Antihyperglycemic Agents

[Figure 2](#) provides the average annual cost of utilization (total prescription cost accepted) per beneficiary nationally in 2022 for each drug class. GLP-1 agonists had the highest average cost per beneficiary at \$1,968. This was followed by the oral combination class and DPP-4 inhibitors with average costs per beneficiary of \$1,065 and \$989, respectively. Biguanides represented the lowest average cost per beneficiary at \$83, followed by sulfonylureas at \$115. Insulin classes were relatively moderate in terms of cost, with long-acting insulins having an average cost per beneficiary of \$853, while combined intermediate, long-acting, and fast-acting insulins and fast-acting insulins had average costs of \$765 and \$541, respectively.

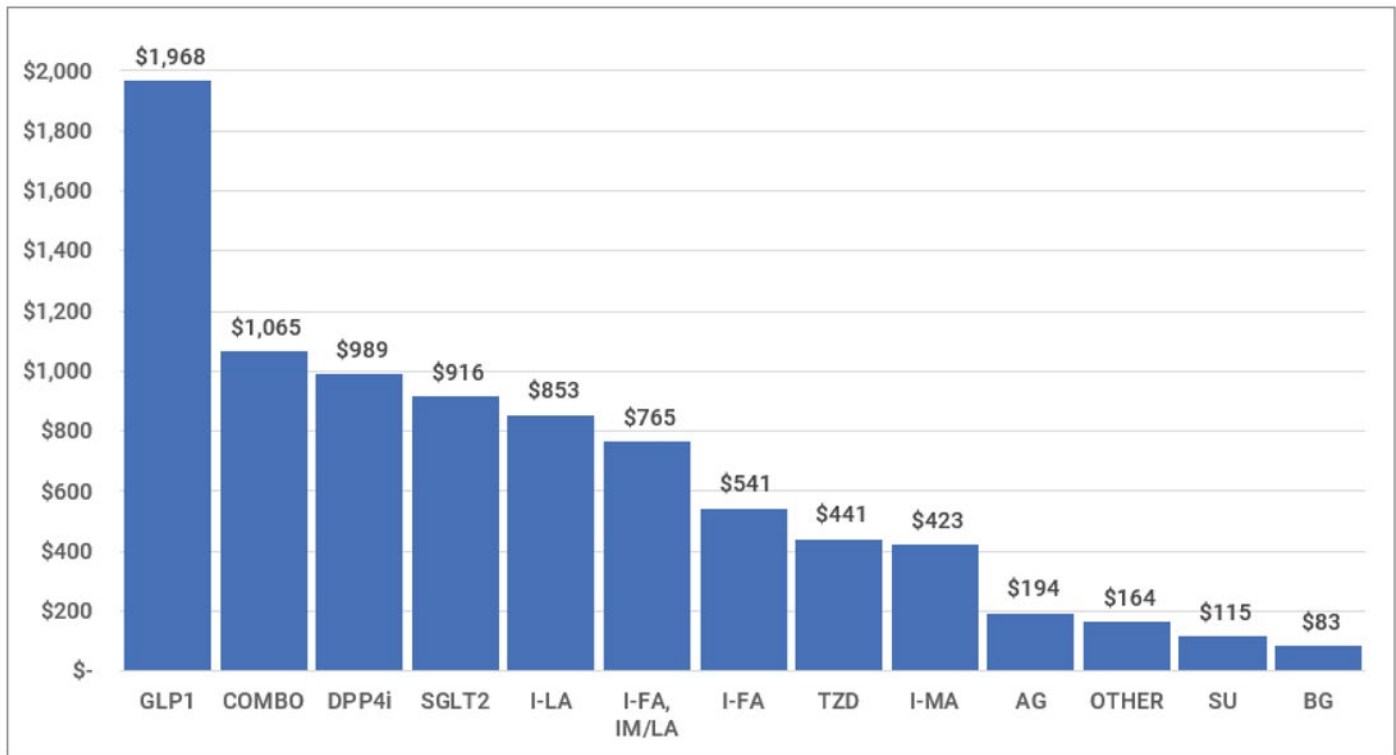
Table 9 in Appendix 6 in the [Supplemental Materials](#) provides a detailed analysis for each drug within its respective class and demonstrates variations in average annual costs per beneficiary:

- The cost for biguanides, solely represented by metformin, remains the lowest at \$83 per beneficiary.
- For oral combination therapies, the cost per beneficiary ranged from \$752 for the metformin plus dapagliflozin combination to \$1,146 for the metformin plus sitagliptin combination.
- For DPP-4 inhibitors, sitagliptin had the highest cost at \$1,100 per beneficiary, while saxagliptin had the lowest at \$629.
- For GLP-1 agonists, semaglutide had the highest cost at \$1,968 per beneficiary, whereas the cost for lixisenatide was substantially lower at \$622.
- For insulin, costs varied widely, from \$92 for fast-acting insulin analogues to \$1,348 for the insulin glargine and lixisenatide combination.
- For SGLT2 inhibitors, canagliflozin had the highest cost at \$1,039 per beneficiary and dapagliflozin had the lowest cost at \$830.
- For sulfonylureas, the cost of glimepiride was markedly higher at \$527 per beneficiary, compared to gliclazide at \$117 and glibenclamide at \$94.
- For thiazolidinediones, rosiglitazone had almost double the cost of pioglitazone per beneficiary, at \$804 and \$412, respectively.

Summary

From 2019 to 2022, there was notable growth in the utilization and expenditures of specific blood glucose-lowering therapies. GLP-1 agonists, particularly semaglutide, and SGLT2 inhibitors, especially empagliflozin, showed notable growth in both claimants and expenditures; GLP-1 agonists also exhibited the highest average annual cost of utilization per beneficiary. Biguanides (i.e., metformin) maintained consistent expenditures over the years. Insulins retained a steady utilization in the market, with long-acting formulations indicating an upward trend in utilization.

Figure 2: Average Annual Cost of Utilization per Beneficiary for Antihyperglycemic Agents by Class (2022)



AG = alpha-glucosidase inhibitors; BG = biguanides; COMBO = combinations of oral blood glucose-lowering drugs, I-FA =insulins and analogues for injection, fast-acting; I-FA, IA/LA = insulins and analogues for injection, intermediate- or long-acting combined with fast-acting; I-IA = insulins and analogues for injection, intermediate-acting; I-LA = insulins and analogues for injection, long-acting; OTHER = other blood glucose-lowering drugs, excluding insulins; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

Economic Analysis

This review is part of the CADTH Streamlined Drug Class Review program, in which an application filed by a sponsor is absent. CADTH does not have access to an economic model for SGLT2 inhibitors for adults with type 2 diabetes from previous CADTH Therapeutic Reviews or Technology Reviews. As a result, the economic review consisted only of a cost comparison for various insulin and non-insulin antidiabetic agents.

CADTH Analyses

The comparators presented in [Table 12](#) have been deemed appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product’s respective product monographs. Existing product listing agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans for all comparators. The prices of comparators were based on public list prices from the Ontario Drug Benefit Formulary/Comparative Drug Index, accessed in October 2023.

The annual maintenance costs for publicly reimbursed SGLT2 inhibitors ranged from \$249 to \$1,056. The annual maintenance costs for all other publicly reimbursed non-insulin comparators ranged from \$12 to \$3,760, based on the recommended dosages.

Table 12: CADTH Cost Comparison Table for Non-Insulin Antidiabetic Drugs

Treatment	Strength or concentration	Form ^a	Price (\$) ^b	Recommended dosage	Daily cost (\$)	Annual cost (\$)
SGLT2 inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	Tablet Tablet	2.8910	100 or 300 mg daily	2.89	1,056
Dapagliflozin (Forxiga, generics)	5 mg 10 mg	Tablet Tablet	0.6825	5 or 10 mg daily	0.68	249
Empagliflozin (Jardiance)	10 mg 25 mg	Tablet Tablet	2.7671	10 or 25 mg daily	2.77	1,011
SGLT2 inhibitors plus metformin fixed-dose combinations						
Canagliflozin and metformin (Invokamet)	500 mg/50 mg 850 mg/50 mg 1,000 mg/50 mg 500 mg/150 mg 850 mg/150 mg 1,000 mg/150 mg	Tablet Tablet Tablet Tablet Tablet Tablet	1.6580 ^c	2 tablets daily	3.32	1,211
Dapagliflozin and metformin (generics)	5 mg/850 mg 5 mg/1,000 mg	Tablet Tablet	0.9647	2 tablets daily	1.93	705
Empagliflozin and metformin (Synjardy)	5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	Tablet Tablet Tablet Tablet Tablet Tablet	1.3932	2 tablets daily	2.79	1,018
GLP-1 receptor analogues						
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	Single-use prefilled pen 4 × 0.5 mL	216.3700 ^c	0.75 mg to 1.5 mg once weekly	7.73	2,822
Exenatide (Byetta)	250 mcg/mL	Prefilled pen 1.2 mL (60 doses) 2.4 mL (60 doses)	143.6700 ^c 143.6700 ^c	5 mcg to 10 mcg twice daily	4.79	1,749
Lixisenatide (Adlyxine)	0.05 mg/mL 1 mg/mL	Prefilled pen 3 mL (14 doses)	56.9800	Starting dose of 10 mcg once daily for 14 days, after which the dose should be	4.07	1,486

Treatment	Strength or concentration	Form ^a	Price (\$) ^b	Recommended dosage	Daily cost (\$)	Annual cost (\$)
				increased to 20 mcg once daily		
Liraglutide (Victoza)	6 mg/mL	Prefilled pen (10 to 30 doses) 2 × 3 mL 3 × 3 mL	136.9800 ^c 205.4700 ^c	1.2 mg to 1.8 mg daily	4.57 to 6.85	1,668 to 2,502
Semaglutide (Ozempic)	1.34 mg/mL	Prefilled pen 1.5 mL (4 doses) 3 mL (4 doses)	210.8700 210.8700	0.5 to 1.0 mg once weekly	7.53	2,751
Semaglutide (Rybelsus)	3 mg 7 mg 14 mg	Tablet	7.2030 7.2030 7.2030	Loading dose: 3 mg daily for 30 days Maintenance dose: 7 mg or 14 mg per day depending on glycemic control needs	7.20	2,631
GLP-1 receptor analogue combinations						
Insulin degludec and liraglutide (Xultophy, iDegLira)	100 units/mL, 3.6 mg/mL	Prefilled pen 5 × 3 mL	308.8605 ^c	16 to 50 units of insulin degludec and 0.58 to 1.8 mg liraglutide once a day; maximum daily dose 50 units	3.29 (16 units) to 10.30 (50 units)	1,203 (16 units) to 3,760 (50 units)
Insulin glargine and lixisenatide (Soliqua)	100 units/mL, 33 mcg/mL	Injectable pen 5 × 3 mL	198.3700	15 to 60 units of insulin glargine and 5 to 20 mcg of lixisenatide once a day; starting dose not greater than 10 mcg lixisenatide; maximum daily dose: 60 units	1.98 (15 units) to 7.93 (60 units)	725 (15 units) to 2,898 (60 units)
DPP-4 inhibitors						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tablet Tablet Tablet	2.2000 ^c	25 mg daily ^d	2.20	804
Linagliptin (Trajenta)	5 mg	Tablet	2.6954	5 mg daily ^d	2.67	984
Saxagliptin (generics)	2.5 mg 5.0 mg	Tablet Tablet	1.2650 1.5195	5 mg daily ^d	1.52	555
Sitagliptin (generics)	25 mg 50 mg 100 mg	Tablet Tablet Tablet	0.8197	100 mg daily ^d	0.82	299

Treatment	Strength or concentration	Form ^a	Price (\$) ^b	Recommended dosage	Daily cost (\$)	Annual cost (\$)
DPP-4 inhibitors plus metformin fixed-dose combinations						
Alogliptin and metformin (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	Tablet Tablet Tablet	1.1950 ^c	2 tablets daily	2.39	873
Linagliptin and metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet Tablet Tablet	1.4132	2 tablets daily	2.83	1,032
Saxagliptin and metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet Tablet Tablet	1.3482	2 tablets daily	2.70	985
Sitagliptin and metformin (generics)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tablet Tablet Tablet	0.8893	2 tablets daily	1.78	650
Other first-line treatments for diabetes						
Biguanides						
Metformin (generics)	500 mg	Tablet	0.0247	500 mg, 3 to 4 times daily	0.07 to 0.10	27 to 36
Sulfonylureas						
Gliclazide (generics)	80 mg	Tablet	0.0931	80 mg to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37	34 to 136
Gliclazide long-acting (generics)	30 mg 60 mg	SR Tablet ER Tablet	0.0931 0.0632	30 mg to 120 mg daily	0.06 to 0.19	22 to 68
Glimepiride (generics)	1 mg 2 mg 4 mg	Tablet Tablet Tablet	0.4900	1 mg to 4 mg daily	0.49	179
Glyburide (generics)	2.5 mg 5.0 mg	Tablet Tablet	0.0321 0.0573	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23	12 to 84

DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; MR = modified-release; SGLT2 = sodium-glucose cotransporter-2; SR = sustained release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed October 2023) unless otherwise indicated and do not include dispensing fees. Recommended dosages are from each product's respective monograph.³²⁻⁵⁸

^aIf supplied in a form other than a tablet, the size of the product is noted. If the pen is part of a pack, the quantity in the pack has been noted. If the pen has a set number of doses, these have been stated.

^bThe price listed is the price per tablet, pen, or pack. If the "form" column states the size only (e.g., 3 mL) then the price is per form (e.g., tablet or pen). If the "form" column states size and a quantity (e.g., 2 × 3 mL) then the price is per pack.

^cPrices obtained from DeltaPA IQVIA database (accessed October 2023).

^dIf patients have moderate or severe renal impairment or end-stage renal disease requiring dialysis, a lower dose should be used.

Table 13: CADTH Cost Comparison of Basal Insulin Drugs

Treatment	Strength or concentration	Form	Price (\$)ª	Cost per mL (\$)
Long-acting insulin analogues				
Insulin glargine U-100 (Basaglar)	100 units/mL	Cartridge (5 × 3 mL)	76.1100	5.07
		Disposable pens (5 × 3 mL)	76.1100	
Insulin glargine U-100 (Lantus)	100 units/mL	Cartridge (5 × 3 mL)	92.8500	6.19
		Disposable pens (5 × 3 mL)	92.8500	6.19
		10 mL vial	61.6900	6.17
Insulin detemir U-100 (Levemir)	100 units/mL	Cartridge (5 × 3 mL)	110.4100	7.36
		Disposable pens (5 × 3 mL)	111.5000	7.43
Insulin glargine U-300 (Toujeo)	300 units/mL	Disposable pen (1 × 1.5 mL)	26.4333	17.62
		Disposable pen (1 × 3 mL)	52.8666	
Insulin degludec U-100 (Tresiba)	100 units/mL	Disposable pens (5 × 3 mL)	111.5000	7.43
Insulin degludec U-200 (Tresiba)	200 units/mL	Disposable pens (3 × 3 mL)	133.8000	14.87
Rapid-acting insulin analogues				
Insulin aspart (NovoRapid)	100 units/mL	Cartridge (5 × 3 mL)	61.2300	4.08
		Disposable pens (5 × 3 mL)	63.7500	4.25
		10 mL vial	30.1900	3.02
Insulin glulisine (Apidra)	100 units/mL	Cartridge (5 × 3 mL)	52.6500	3.51
		Disposable pens (5 × 3 mL)	53.1500	3.54
		10 mL vial	26.5800	2.66
Insulin lispro (Humalog)	100 units/mL	Cartridge (5 × 3 mL)	65.6400	4.38
		Disposable pens (5 × 3 mL)	69.3900	4.63
		10 mL vial	33.0400	3.30
Insulin lispro (Humalog)	200 units/mL	Disposable pens (5 × 3 mL)	121.3200	8.09
Insulin lispro (Admelog)	100 units/mL	Disposable pens (5 × 3 mL)	45.0000	3.00
		10 mL vial	22.7000	2.27
Insulin NPH				
Humulin N	100 units/mL	Cartridge (5 × 3 mL)	53.3500	3.56
Novolin GE NPH	100 units/mL	Cartridge (5 × 3 mL)	48.8200	3.25
		10 mL vial	24.8300	2.48

NPH = neutral protamine hagedorn.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed October 2023) unless otherwise indicated and do not include dispensing fees.

ªThe price listed is the price per pack or vial.

Issues for Consideration

- SGLT2 inhibitors offer additional clinical benefits compared to standard treatments, including improvement in all-cause death (OR = 0.88; 95% CI, 0.83 to 0.94; high certainty), cardiovascular death (OR = 0.86; 95% CI, 0.80 to 0.94; high certainty), and nonfatal myocardial infarctions (OR = 0.90; 95% CI, 0.82 to 0.98; high certainty). There is also evidence for reducing hospitalization for heart failure (OR = 0.66; 95% CI, 0.60 to 0.73; high certainty) and end-stage renal disease (OR = 0.61; 95% CI, 0.55 to 0.67; high certainty). Other benefits include less risk for severe hypoglycemia, weight loss benefits, and improvement in health-related quality of life. However, there are also safety concerns, including ketoacidosis, amputation, and genital infections.
- Compared to standard treatments, GLP-1 agonists also offer additional clinical benefits, including improvement in all-cause death (OR = 0.88; 95% CI, 0.82 to 0.93; high certainty), cardiovascular death (OR = 0.87; 95% CI, 0.81 to 0.94; high certainty), nonfatal myocardial infarction (OR = 0.91; 95% CI, 0.85 to 0.98; high certainty) and nonfatal stroke (OR = 0.85; 95% CI, 0.77 to 0.94; high certainty). There is also evidence for reducing end-stage renal disease. GLP-1 agonists are associated with less risk for severe hypoglycemia. GLP-1 agonists offer greater weight loss as compared to other therapeutics. Improvement in health-related quality of life outcomes is also noted for GLP-1 agonists. The main safety concerns include severe gastrointestinal events.
- Other antihyperglycemics, including DPP-4 inhibitors, sulfonylureas, and basal insulins, do not improve all-cause death. They also do not have an impact on cardiorenal outcomes. However, sulfonylureas may increase all-cause death (OR = 1.10; 95% CI, 0.97 to 1.26; low certainty), although the evidence is of low certainty. Sulfonylureas and basal insulins can increase the risk of severe hypoglycemia and result in weight gain.
- When SGLT2 inhibitors are compared to other drug classes such as GLP-1 agonists, DPP-4 inhibitors, and sulfonylureas, they also demonstrate improvement in the following outcomes:
 - all-cause death (for DPP-4 inhibitors, OR = 0.87 [95% CI, 0.79 to 0.96; moderate certainty]; for sulfonylureas, OR = 0.80 [95% CI, 0.69 to 0.93; moderate certainty])
 - reduction in hospitalization for heart failure (for GLP-1 agonists, OR = 0.73 [95% CI, 0.64 to 0.83; moderate certainty]; for DPP-4 inhibitors, OR = 0.63 [95% CI, 0.55 to 0.72; moderate certainty]; for sulfonylureas, OR = 0.67 [95% CI, 0.53 to 0.85; moderate certainty])
 - reduction in end-stage kidney disease (for GLP-1 agonists, OR = 0.73 [95% CI, 0.63 to 0.84; low certainty]; for DPP-4 inhibitors, OR = 0.58 [95% CI, 0.50 to 0.68; low certainty]).

Discussion

Summary of the Input From Project Scope, Draft Report, and Evidence

Input from patient organizations and clinician groups highlighted a need for treatments in type 2 diabetes mellitus that are easy to administer, affordable, and provide improvement in meaningful outcomes such as

improvement in all-cause death, cardiovascular death, renal outcomes, and patient-important outcomes such as weight loss and low risk for hypoglycemia. Based on the evidence highlighted in the SRs with NMAs, SGLT2 inhibitors and GLP-1 agonists offer many clinical benefits compared to standard treatments and other antihyperglycemic agents, including sulfonylureas, DPP-4 inhibitors, and basal insulins. Feedback from industry was generally supportive of the scope of this project. However, some highlighted that there may be intra-drug class differences (e.g., among GLP-1 agonists) that may require further consideration, which may not be feasible within a Streamlined Drug Class Review.

The NMAs by Shi et al.¹ and Palmer et al.¹⁶ form the evidence base for this Streamlined Drug Class Review of SGLT2 inhibitors for type 2 diabetes mellitus, providing the most up-to-date and comprehensive evidence regarding the clinical efficacy and harms of SGLT2 inhibitors and other antihyperglycemic agents for type 2 diabetes mellitus. In the NMAs, SGLT2 inhibitors demonstrated reduction in all-cause death, cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, and end-stage kidney disease when compared to standard treatments. GLP-1 agonists also demonstrated reductions in all-cause death, cardiovascular death, and nonfatal stroke. Both SGLT2 inhibitors and GLP-1 agonists have different safety profiles; SGLT2 inhibitors may increase the risk of ketoacidosis, amputation, and genital infection, whereas GLP-1 agonists may increase the risk of gastrointestinal events.

Furthermore, the clinical experts consulted for this review noted that while the OR for amputation is 1.27, when comparing SGLT2 inhibitors to standard treatments, only 1 trial demonstrated an association with amputations, and subsequent trials with the same medication in a higher risk population did not show an increase in this adverse event. The FDA has removed the black box warning, and numerous studies have not identified amputation as a recurrent or consistent adverse event. It is unlikely that SGLT2 inhibitors result in an increase in amputation rates.⁵⁹

Additional clarification was sought with the original authors regarding genital infections; they clarified that the definition of genital infections included both mycotic and bacterial causes. It did not include urinary tract infection, which is noted to be very different from genital infection, with evidence indicating it is not related to SGLT2 inhibitors.⁶⁰

Both SGLT2 inhibitors and GLP-1 agonists were associated with weight reduction, although the effect size was higher in general for most GLP-1 agonists. Both SGLT2 inhibitors and GLP-1 agonists were associated with less risk for severe hypoglycemia.

Limitations of the Evidence

The main limitation of this review is that NMAs are largely driven by the available evidence. Also, the search occurred 1 year ago; as such, the SR will not include any new evidence published in the past year. It is possible that the results and their certainty would be different if the SR were to be updated. In addition, the risk of bias assessment was not conducted at the level of the reported effect. Since the risk of bias can differ by reported effect, this would be another notable limitation of the NMAs.

For outcomes that are important to patients (such as all-cause death and health-related quality of life), for older drugs including sulfonylurea, DPP-4 inhibitors, and basal insulins, there was low to very low certainty in

the evidence. The authors also acknowledge the composite outcome definition for end-stage kidney disease is challenging to interpret; thus, the certainty of evidence was graded down to moderate for the effects of all drugs on end-stage kidney disease.

The review included many drugs that are not available in Canada. Therefore, the results may not be fully generalizable to the Canadian context. The issue of intra-drug class difference was also raised as a potential limitation for a Streamlined Drug Class Review by stakeholders. By evaluating antihyperglycemic drugs by class, this Streamlined Drug Class Review assumes no intra-drug class differences. Although no evidence was identified to establish intraclass differences, and Shi et al. rated down the potential for intraclass differences (outside of weight loss benefits between GLP-1 agonists), a potential for intraclass differences cannot be entirely ruled out. The clinical experts consulted by FMEC indicated that SGLT2 inhibitors are generally viewed as having a class effect, although they also noted that some opinions differ from this view.

In response to stakeholder feedback on the project scope and draft report, the intraclass differences of GLP-1 agonists were further explored. The authors (Shi et al.) were contacted and asked to rerun the analyses to include GLP-1 agonists available in Canada. Two analyses were conducted; the first scenario included semaglutide and dulaglutide, and the second scenario included only semaglutide. Lixisenatide was excluded on the basis that it has not demonstrated any mortality or cardiovascular benefits in RCTs. Based on consultation with clinical experts, liraglutide was excluded, as it requires daily injection and has very low uptake in clinical practice. The methods of this reanalysis are described in Appendix 8 in the [Supplemental Materials](#).

The results of the analysis (scenario 1) including semaglutide and dulaglutide are presented in the [Supplemental Materials](#) (in Appendix 9). This reanalysis compared SGLT2 inhibitors to semaglutide and dulaglutide for the following outcomes: all-cause death (Figure 5 in the [Supplemental Materials](#)), cardiovascular death (Figure 6 in the [Supplemental Materials](#)), end-stage kidney disease (Figure 8 in the [Supplemental Materials](#)), hospitalization for heart failure (Figure 10 in the [Supplemental Materials](#)), nonfatal myocardial infarction (Figure 9 in the [Supplemental Materials](#)), nonfatal stroke (Figure 7 in the [Supplemental Materials](#)), and health-related quality of life (Figure 11 in the [Supplemental Materials](#)). When SGLT2 inhibitors were compared to semaglutide and dulaglutide, results were as follows: for all-cause death, the OR was 1.01 (95% CI, 0.88 to 1.15); for cardiovascular death, the OR was 1.03 (95% CI, 0.84 to 1.24); for end-stage kidney disease, the OR was 1.19 (95% CI, 0.82 to 1.73); for hospitalization for heart failure, the OR was 1.45 (95% CI, 1.20 to 1.75); for nonfatal myocardial infarction, the OR was 1.04 (95% CI, 0.86 to 1.25); for nonfatal stroke, the OR was 0.75 (95% CI, 0.60 to 0.94); and the SMD for health-related quality of life had an OR of 0.06 (95% CI, -0.21 to 0.33).

The results of the analysis (scenario 2) including semaglutide are presented in the [Supplemental Materials](#) (in Appendix 10). This reanalysis compared SGLT2 inhibitors to semaglutide for the following outcomes: all-cause death (Figure 12 in the [Supplemental Materials](#)), cardiovascular death (Figure 13 in the [Supplemental Materials](#)), nonfatal stroke (Figure 14 in the [Supplemental Materials](#)) and end-stage kidney disease (Figure 15 in the [Supplemental Materials](#)). When SGLT2 inhibitors were compared to semaglutide

only, results were as follows: for all-cause death, the OR was 0.96 (95% CI, 0.71 to 1.28); for cardiovascular death, the OR was 0.91 (95% CI, 0.62 to 1.34); for nonfatal stroke, the OR was 0.66 (95% CI, 0.45 to 0.97); and for end-stage kidney disease, the OR was 1.43 (95% CI, 0.69 to 2.94). Both reanalyses revealed consistent findings compared to the original NMA results. These findings suggest there is a lack of intraclass variability.

Conclusions and Implications for Decision-Making

This Streamlined Drug Class Review summarized recent evidence supporting the use of SGLT2 inhibitors and GLP-1 agonists for their outcome benefits in patients with type 2 diabetes. Compared to other antihyperglycemic drugs, SGLT2 inhibitors and GLP-1 agonists show benefits for clinically important outcomes beyond glycemic control, including all-cause mortality, cardiovascular outcomes, renal outcomes, and patient-important outcomes (such as safety).

Given the evolved therapeutic landscape for SGLT2 inhibitors in type 2 diabetes mellitus, coupled with new evidence for SGLT2 inhibitors and the desire from stakeholders to improve overall survival and other important patient-related outcomes, there is a need to update the current reimbursement landscape of drugs for type 2 diabetes based on new evidence. The place in therapy of SGLT2 inhibitors in type 2 diabetes from a reimbursement perspective should be revisited to ensure the policy reflects the current evidence, while also allowing clinicians to individualize therapies based on patients' preferences and individual risk factors.

This Streamlined Drug Class Review Summary Report was used to inform the CADTH FMEC deliberation and subsequent reimbursement recommendations.

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