Canada's Drug and Health Technology Agency

Summary Report (DRAFT)

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

Streamlined Drug Class Review

Date: January 4, 2024
DRAFT

Note: this version of the report has not been copy-edited. The final report will be posted concurrently with the final CADTH Formulary Management Expert Committee recommendation.

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Canada's Drug and Health Technology Agency

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse events
AMSTAR2	A MeaSurement Tool to Assess systematic Reviews 2
CI	confidence interval
CUA	cost utility analysis
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
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SGLT2	sodium glucose cotransporter-2
SMD	standardized mean difference
SR	systematic review

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 mortality, cardiovascular outcomes, renal, and patient-important outcomes (e.g., safety) has emerged.
- According to Canadian Institutes for Health Information (CIHI), diabetes drugs contributed the most to growth in spending in 2021.
- According to the 2023 CADTH Health Technology Review Living with type 2 diabetes, people living with type 2 diabetes want treatment options that are less invasive, more affordable, and that 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 since CADTH last conducted a Reimbursement Review (emergence of new evidence on clinically important outcomes and the introduction of SGLT2 inhibitor generics) highlights the opportunity to review the place in therapy of SGLT2 inhibitors in 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 and network meta-analyses to address timely policy questions. A literature search of published systematic reviews with network meta-analysis 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 license for branded versions of the drugs included in the class.
- 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 mortality, cardiovascular mortality, and non-fatal myocardial infarctions. In addition, SGLT2 inhibitors reduce hospitalization for heart failure and end stage renal disease.
    - Other benefits of SGLT2 inhibitors include lower risk for severe hypoglycemia, weight loss 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 mortality, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal 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 mortality or cardiorenal outcomes.
    - Sulfonylureas may increase all-cause mortality, although evidence is of low certainty.
    - Sulfonylureas and basal insulins can increase the risk of severe hypoglycemia and weight gain.
- Compared to SGLT2 inhibitors, DPP-4 inhibitors and sulfonylureas demonstrate improvement on all-cause mortality, reduction in hospitalization for heart failure, and reduction in end stage kidney disease.
- 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.

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 mortality, cardiovascular outcomes, 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.

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 about 10% among Canadians. 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 years[4] and the 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 and 70% of all non-traumatic 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 as well as targeting prevalent risk factors to promote weight loss.[7]

Diabetes is diagnosed based on pre-established diagnostic criteria with venous samples and laboratory methods[8]:

- Fasting plasma glucose ≥ 7.0mmol/L or,
- Glycated hemoglobin (A1C) ≥ 6.5% or,
- 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥ 11.1mmol/L or,
- Random plasma glucose ≥ 11.1mmol/L

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, pre-diabetes, physical inactivity, unhealthy eating, high blood pressure or 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 remains to be metformin, or with insulin if metabolic decompensation is present.[8] New Clinical Practice Guidelines place emphasis on adding or substituting for an drug with demonstrated cardiorenal benefit and 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 A1C (glycated hemoglobin), cost, risk of hypoglycemia and impact on weight gain or weight loss[8]. In addition, recent evidence also indicates 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 (6.15%) largest contributors to growth in spending, whereas GLP-1 agonists were the largest (11.7%) contributor to growth in spending. Expenditures for these two 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 changing prescribing guidelines[13] to encourage earlier use of SGLT2 inhibitors and GLP-1 agonists.

According to the 2023 CADTH Health Technology Review 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 network meta-analyses[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 inform on clinically important outcomes such as all-cause mortality[1] and 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 value-add and cost-savings opportunities in formulary management in Canada. Table 2 lists status of data protection and patent expiry for SGLT2 inhibitors.[1].

The new therapeutic landscape of SGLT2 inhibitors in Canada since CADTH last conducted a Reimbursement Review (emergence of new evidence on clinically important outcomes and the introduction of SGLT2 inhibitor generics) highlights the opportunity to review the place in therapy of SGLT2 inhibitors in type 2 diabetes. As the public funding of SGLT2 inhibitors currently range 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 the first-line use 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
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 200units/mL (Lantus), Insulin glargine 300units/mL (Toujeo)	Subcutaneous Subcutaneous	Sanofi-Aventis Canada

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

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/no)	Patent end date (for longest filed)	Patent expired (yes/no)
dapagliflozin	Forxiga	December 12, 2022	N/A	Y	March 21, 2028	N
dapagliflozin plus metformin	Xigduo	December 12, 2022	N/A	Y	November 12, 2030	N
canagliflozin	Invokana	May 23, 2022	N/A	Y	May 11, 2031	N
canagliflozin plus metformin	Invokamet	May 23, 2022	N/A	Y	July 7, 2030	N
	Invokamet XR	May 23, 2022	N/A	Y	May 11, 2031	N
empagliflozin	Jardiance	July 23, 2023	N/A	Y	April 16, 2034	N
empagliflozin plus metformin	Synjardy	July 23, 2023	N/A	Y	April 3, 2034	N

N = no; N/A = not applicable; NOC = notice of compliance; Y = yes

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, healthcare practitioner, and manufacturer perspectives on the needs for therapies in type 2 diabetes mellitus and scope of the drug class review.
- Economic considerations which 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, please refer to the 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 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. Within the International Association for Public Participation Spectrum, our engagement activities can be described as "Involve" 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. Refer to the 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 was thanked by name in the acknowledgements section of the report.

Reflections

Use of the GRIPP2 Short Form19 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	Past patient and clinician input including the Health Technology Review on Living with Type 2 diabetes emphasised the need for medications to cause little 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. Stakeholders asked CADTH to: • Consider the appropriateness of Shi et al, for a Canadian context. • Consider the adverse events that may impact patients regarding SGLT2 or DPP-4 treatments. • Consider aligning this review with Diabetes Canada's Clinical Practice Guidelines.	Project Scope, Table II Summary Report

Topic	Item	Section(s)
	• Consider cardiovascular outcomes, renal outcomes, hospitalization for heart failure, in addition to glycemic parameters and adverse event outcomes. • Consider including Urinary Tract Infections as a safety outcome.	
Discussion and conclusions	Dialogue between CADTH and the associations helped build trust and greater understanding of each others' goals. The engagement method, reliant on technology, may exclude certain populations, potentially limiting diverse perspectives on the challenges faced by Canadians living with type 2 diabetes mellitus.	
Reflections and critical perspective	The Living with Type 2 diabetes 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 for those living with type 2 diabetes mellitus.	

All Stakeholders: CADTH provides 10 business days for stakeholders to provide feedback at the following stages: proposed project scope (September 2023); draft summary report (available October 19, 2023); and draft recommendations (available December 2023). Feedback opportunities are communicated through the CADTH Weekly Summary emails to subscribers. Any interested stakeholders are welcome to contact CADTH, to learn more about this review by contacting Requests@cadth.ca

Summary of Patient and Clinician Associations 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 on Living With type 2 diabetes (cadth.ca).[14] The report highlights important treatment considerations for individuals with T2DM, 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 inhibitor 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 Health Technology Review on Living with Type 2 Diabetes that outlined disparities in access to T2DM treatment as well as the need for increased access to and affordability of medications. The report outlines that disparities in accessing T2DM 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 T2DM 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 one additional outcome, HbA1c.

Summary of Industry Input

Industry stakeholders provided feedback on the Network Meta Analysis informing this Streamlined Drug Class Review and made suggestions of supplementary publications that CADTH may wish to consider.
Furthermore, industry stakeholders proposed alternative data sources such as IQVIA for cost analysis. Given 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 stakeholder urged 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 (CUAs).

Summary of Drug Programs Input

CADTH has received several inputs 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 current exist for drugs included in this review that may not be reflective of list prices.

Clinical Review

Network meta-analyses (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 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 one or more existing evidence synthesis (e.g., SRs with MAs 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 according to 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 rationale for a search since 2016 is that the earliest evidence for mortality or cardiovascular benefits of SGLT2 inhibitors appears to have emerged around 2015-2016. [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 (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See 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 systematic reviews for inclusion based on the selection criteria. Potentially relevant records were retrieved, and their abstract or full text was examined by one reviewer.

To avoid overlap of primary studies which could introduce bias if outcome data from the same studies are 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 the outcomes of interest outlined in the research protocol were not found in a single NMA, additional supplemental evidence from other NMAs were considered.

The quality of the included NMAs were assessed using the AMSTAR2 (a MeaSurement Tool to Assess systematic Reviews) tool[20] and the IPSOR check list.[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 (any dosage with route of administration as per Table 1):** **GLP-1 agonists** • 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 determir, insulin degludec, insulin glargine, NPH insulin, Isophane insulin
Outcomes	**Efficacy:** • All cause mortality • Cardiovascular death • Non-fatal myocardial infarction • Non-fatal stroke • Admission to hospital for heart failure • End stage kidney disease • Health related quality of life score • Bodyweight change • Change in HbA1c **Safety:** • Genital infection • Amputation, • Ketoacidosis, • Severe gastrointestinal events • Severe hypoglycemia
Study design	Published SRs of RCTs with meta-analysis and/or network meta-analysis
Report dates	2016 up to 2023

SGLT2 = sodium-glucose cotransporter-2; GLP-1 = glucagon like peptide; DPP-4 = dipeptidyl peptidase-4; RCT = randomized controlled trial; SR = Systematic Review

Summary of Evidence

Included Systematic Reviews

The literature search identified 1110 records. Of these, 993 records were excluded due to irrelevant populations, comparators, or study designs; 177 records of potentially relevant articles (e.g., network meta-analyses) 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 was retrieved if the information was not available from the title and abstract. Appendix 1 presents the flow chart of the study selection.

Two SRs with NMAs 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 vs 1-2 other drug classes), inappropriate or few outcomes (e.g., renal outcomes only).

- Shi Q. et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomized controlled trials. BMJ 2023[1]
- Palmer et al. Sodium-glucose cotransporter protein-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomized controlled trials. BMJ 2021[16]

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 (HbA1c), an outcome of interest to this review, another NMA (Palmer et al. 2021) was included to supplement the evidence.

Methods of the Included Network Meta Analyses

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 to 14 October 2022 and T 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 receptor agonists, DPP-4 inhibitors, thiazolidinediones, sulfonylureas, metformin, α-glucosidase inhibitors, meglitinides, insulins, dual GIP/GLP-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists. The following outcomes were included: all cause death, cardiovascular death, non-fatal stroke, end stage kidney disease, amputation, non-fatal 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.

Below are the definitions of outcomes:

- All-cause death was defined as the number of patients who died due to any reason within follow-ups.
- 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.
- Non-fatal myocardial infarction was defined as the number of patients who suffered an acute myocardial infarction but not died within follow-ups.
- Non-fatal stroke was defined as the number of patients who suffered a stroke but not died within follow-ups.
- 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.
- 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 m^2, a sustained percent decline in eGFR of at least 40% or a doubling of serum creatinine, or kidney-related death.
- 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.
- Severe hypoglycemia was defined as the number of patients who suffered at least one hypoglycemia event which led to a medical assistance. The study prioritizes the definition above but adopted any other study-reported definition if unavailable.
- Severe gastrointestinal events were defined as the number of patients who suffered at least one severe gastrointestinal event or gastrointestinal event leading to discontinuation. The study prioritizes the definition above but adopted any other study-reported definition if unavailable.
- Genital infection was defined as the number of patients who suffered at least one genital infection event.
- Amputation is defined was the number of patients who suffered at least one amputation event.
- Ketoacidosis due to diabetes was defined as the number of patients who suffered at least one ketoacidosis event due to diabetes.
- Hyperkalemia leading to hospitalization was defined as the number of patients who suffered at least one hyperkalemia leading to hospitalization.
- Body weight change was defined as the change of absolute body weight in kilogram from baseline to follow-up end.

Data Synthesis

The authors conducted random effect network meta-analysis 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 one exception; based on the evidence,[23] the impact of GLP-1 receptor agonists on body weight change was not similar across drug class. The authors used the continuity correction to account for zero event by adding 0.5 to all cells of groups for RCTs with at least one 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 which could reflect publication bias.

The intransitivity was evaluated based on distribution comparisons of potential effect modifiers (i.e., baseline age, sex, body mass index, HbA1c, the proportion of patients with cardiovascular disease and duration of diabetes) for each direct comparison and outcome. Meta-regressions were also done on these parameters with treatment effect for each drug outcome.

Sensitivity Analyses

Sensitivity analyses were performed with the following scenarios:

- a Bayesian network meta-analysis adjusted by trial duration,
- a Mantel Haenszel fixed effect network meta-analysis 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 transplantation and death from kidney failure
- a meta-analysis pooling study reported hazard ratios for the trials with ≥ 2 years' follow-up.

Meta-Regression

Four meta-regressions were performed for trial and aggregated patient characteristics with continuous variables:

- Proportion of patients with established cardiovascular diseases (hypothesizing a larger relative effect in reducing death and cardiovascular and kidney outcomes in trials with a higher proportion of patients with cardiovascular diseases).

- Mean patients' estimated glomerular filtration rate at baseline (hypothesizing a larger relative effect in reducing death and cardiovascular and kidney outcomes in patients with lower estimated glomerular filtration rate).
- Mean patient's 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 larger follow-up).

The authors employed the ICEMAN tool to rate the credibility of any apparent subgroup effect (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 GRADE (Grading of Recommendations Assessment, Development and Evaluation) 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 non-zero effect (using the null as the threshold). The certainty was rated down for imprecision by two levels when the 95% confidence interval (CI) crossed more than one threshold of importance.

The null effect was chosen as the decision threshold and standard treatments as the reference intervention when categorizing the relative impact of interventions. The authors initially categorized treatments as different or not different from standard treatments. However, this was subsequently revised as different or not different from at least one of those with an established difference from standard treatments. Five categories of interventions were established from this process, with the best to the worst. The authors then separated these drugs as high, moderate low or very low certainty of evidence according to the certainty of evidence relative to standard treatments.

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Search methods and Study Eligibility Criteria

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

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

Data Synthesis

A frequentist pairwise meta-analysis was conducted for each direct comparison of two 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, two reviewers assessed risk of bias, with adjudication by a third reviewer. The domains include random sequence generation, allocation concealment, blinding, missing outcome data and selective reporting of outcomes. The authors reported low levels of reported blinding for participants, investigators, and outcome assessors. 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. 60.5% reported blinding for participants and investigators, and 13.7% reported blinding for outcome assessment. 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 have identified the limitations being the heterogeneity in clinical settings of the included trials. However, the authors have also pointed out that the consistency of the results across studies have 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 at baseline was 29.5 kg/m^2 (95% CI, 29.3 to 29.8). The mean HbA1c at baseline was 8.1% (95% CI, 8.1 to 8.2). Across RCTs, a mean 58.6% (95% CI, 40.9 to 74.9) 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 one of the six domains, mostly due to 62% lack of blinding (62%), missing outcome data (26%), or inadequate allocation concealment (25%). Table 5 is a summary of overall risk of bias according to drug classes across all six domains. This provides an overview that highlights some drug classes such as basal insulins and sulfonylureas have high percentage (52.7% and 27.3% respectively) with high risk of bias.

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

Drug Class	Total No. of Arms with High Risk of Bias across six domains	Total Number of Arms	% of High Risk of Bias
Basal Insulins	29	55	52.7
DPP-4 inhibitors	50	324	15.4
GLP-1 receptor agonists	41	239	14.2
SGLT2 Inhibitors	39	252	15.5
Standard treatments	55	522	10.5
Sulfonylureas	41	150	27.3

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Description of Findings

The following sections provide a summary of results from the network meta-analysis comparing SGLT2-inhibitors with other drug treatments in type 2 diabetes. The comparisons of each drug treatment are also presented with comparison to standard treatments as this is often important considerations in clinical practice. Standard treatment was defined as the treatment regimens that patient received prior to 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 drug of interest in the randomized trial.

I. Efficacy

Table 6: Efficacy Outcomes and HRQoL of drug treatments for type 2 diabetes compared to Standard Treatments

Interventions	All cause death (OR, 95% CI)	Cardiovascular death (OR, 95% CI)	Non-fatal myocardial infarction (OR, 95% CI)	Non-fatal stroke (OR, 95% CI)	Admission to hospital for heart failure (OR, 95% CI)	End stage kidney disease (OR, 95% CI)	Health related quality of life 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 receptor 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)

Interventions	All cause death (OR, 95% CI)	Cardiovascular death (OR, 95% CI)	Non-fatal myocardial infarction (OR, 95% CI)	Non-fatal stroke (OR, 95% CI)	Admission to hospital for heart failure (OR, 95% CI)	End stage kidney disease (OR, 95% CI)	Health related quality of life score (OR, 95% CI)
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 insulin	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

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Note that the authors have outcome data presented by risk strata, this information is provided in the following link: DiabetesNMA (shinyapps.io) which is also available from the original publication. Full text available here: https://www.bmj.com/content/381/bmj-2022-074068

For the outcome of non-fatal stroke by risk strata, the estimated absolute effects are reported in Appendix 7, Table S10.

All cause death

In the analysis of all cause death, there were 257 contributing RCTs with 342 237participants and 15371 events.

Compared to standard treatments, both SGLT2-inhibitors (OR 0.88, 95% CI 0.83 to 0.94; high certainty) and GLP-1 receptor agonists (OR 0.88, 95% CI 0.82 to 0.93; high certainty) reduce all cause mortality. Metformin may reduce all cause mortality (OR 0.84, 0.67 to 1.04; low certainty). Sulfonylureas may possibly increase all cause mortality (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 impact on the all cause mortality.

In comparison to SGLT2-inhibitors for the outcome of all cause death, the odds ratio (OR) for following interventions are as follow: GLP-1 agonist (OR 1.01, 95% CI 0.88 to 1.16; very low certainty), DPP-4 inhibitors (OR 0.87, 95% CI 0.79 to 0.96; moderate certainty), sulfonylureas (OR 0.80, 95% CI 0.69 to 0.93; moderate certainty) and basal insulin (OR 0.81, 95% CI 0.59 to 1.10; very low certainty).

Cardiovascular death

For the analysis on cardiovascular death, there were 144 contributing RCTs, including, 275 679 patients and 9120 events.

Compared to standard treatments, SGLT2 inhibitors and GLP-1 receptor agonists reduce cardiovascular death with the following odd ratios respectively, OR 0.86, 95% 0.83 to 0.94; high certainty and OR 0.87, 95% CI 0.81 to 0.94; high certainty. For other interventions including metformin, sulfonylureas, DPP-4 inhibitors, and basal insulins, they have little, no or uncertain effect on the outcome of cardiovascular death.

In comparison to SGLT2-inhibitors for the outcome of cardiovascular death, the OR for following interventions are as follow: GLP-1 agonist (OR 0.99, 95% CI 0.88 to 1.11; low certainty), DPP-4 inhibitors (OR 0.86, 95% CI 0.77 to 0.97; moderate certainty), sulfonylureas (OR 0.86, 95% CI 0.69 to 1.06; low certainty) and basal insulin (OR 0.39, 95% CI 0.04 to 3.85; low certainty).

Non-fatal myocardial infarction

The analysis on non-fatal myocardial infarction included 209 RCTs with 293 042 patients and 8906 events.

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

In comparison to SGLT2-inhibitors for the outcome of non-fatal myocardial infarction, the OR for following interventions are as follow: GLP-1 agonist (OR 0.98, 95% CI 0.88 to 1.10; low certainty), DPP-4 inhibitors (OR 0.88, 95% CI 0.78 to 1.01; low certainty), sulfonylureas (OR 0.89, 95% CI 0.72 to 1.10; very low certainty) and basal insulin (OR 0.92, 95% CI 0.43 to 1.92; very low certainty).

Non-fatal stroke

For the analysis of non-fatal stroke, the analysis included 178 RCTs with 283 728 patients and 4878 events.

Compared to standard treatments, GLP-1 receptor agonists have demonstrated with high certainty the ability to reduce non-fatal stroke with OR 0.85, 95% CI 0.77 to 0.94; high certainty. Compared to standard treatments, SGLT2-inhibitors have an OR of 0.99, 95% CI 0.88 to 1.11; low certainty. Metformin, sulfonylureas, DDP-4 inhibitors and basal insulins have little, no or uncertain effects on non-fatal stroke with the following results respectively: OR 0.97 (95% CI 0.71 to 1.33; low certainty), OR 1.05 (95% CI 0.84 to 1.32; low certainty), OR 0.91 (95% CI 0.80 to 1.03; low certainty) and OR 0.76 (95% CI 0.33 to 1.77; low certainty)

In comparison to SGLT2-inhibitors for the outcome of non-fatal stroke, the OR for following interventions are as follow: GLP-1 agonists (OR 1.16, 95% CI 1.00 to 1.35; low certainty), DPP-4 inhibitors (OR 1.10, 95% CI 0.93 to 1.30; low certainty), sulfonylureas (OR 0.94, 95% CI 0.73 to 1.20; very low certainty) and basal insulin (OR 1.30, 95% CI 0.56 to 3.03; very low certainty).

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

- For adults with 3 or fewer cardiovascular risk factors, the baseline (5 years) risk for non-fatal stroke is 26 per 1000 persons. The anticipated absolute effect (5 years) is 4 more non-fatal stroke (0-9) per 1000 persons; moderate certainty.
- For adults with more than 3 cardiovascular risk factors, the baseline (5 years) risk for non-fatal stroke is 50 per 1000 persons. The anticipated absolute effect (5 years) is 8 more non-fatal stroke (0 to 16 more) per 1000 persons; low certainty.

- For adults with cardiovascular disease only (no chronic kidney disease), the baseline (5 years) risk for non-fatal stroke is 93 per 1000 persons. The anticipated absolute effect (5 years) is 14 more (0 to 29 more) per 1000 persons; moderate certainty.
- For adults with chronic kidney disease only (no cardiovascular disease), the baseline (5 years) risk for non-fatal stroke is 104 per 1000 persons. The anticipated absolute effect (5 years) is 15 more (0 to 32 more) per 1000 persons; moderate certainty.
- For adults with established cardiovascular disease and chronic kidney disease, the baseline (5 years) risk for non-fatal stroke is 166 per 1000 persons. The anticipated absolute (5 years) is 22 more (0 to 46 more) per 1000 persons; moderate certainty.

Note that for the outcome of non-fatal stroke, the estimated absolute effects are reported in Appendix 7, Table S10.

Admission to hospital for heart failure

The analysis for this outcome included 142 RCTs with 252 055 participants and 6681 events.

Compared to standard treatments, SGLT2-inhibitors reduce admission to hospital for heart failure with OR of 0.66 (95% CI 0.60 to 0.73; high certainty). With moderate certainty, GLP-1-receptor agonists may reduce admission to hospital for heart failure with 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) have little, no or uncertain effects on this outcome.

In comparison to SGLT2-inhibitors for the outcome of admission to hospital for heart failure, the OR for following interventions are as follow: GLP-1 agonist (OR 0.73, 95% CI 0.64 to 0.83; moderate certainty), DPP-4 inhibitors (OR 0.63, 95% CI 0.55 to 0.72; moderate certainty), sulfonylureas (OR 0.67, 95% CI 0.53 to 0.85; moderate certainty) and basal insulin (OR 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 6972 events.

Compared to standard treatments, the authors have concluded that SGLT2 inhibitors (OR 0.61, 95% CI 0.55 to 0.67; high certainty) and GLP-1 receptor 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 reporting the kidney outcomes among the trials. The authors started that SGLT2 inhibitors are possibly superior to GLP-1 receptor 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 the end stage kidney disease, the OR for following interventions are as follow: GLP-1 agonist (OR 0.73, 95% CI 0.63 to 0.84; low certainty), DPP-4 inhibitors (OR 0.58, 95% CI 0.50 to 0.68; low certainty), sulfonylureas (OR 0.89, 95% CI 0.48 to 1.64; very low certainty) and basal insulin (OR 0.51, 95% CI 0.26 to 0.98; low certainty).

Body weight change

The mean difference 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 have varying effects on the body weight change, with semaglutide (subcutaneous) demonstrated the greatest body weight change, followed by semaglutide (oral), liraglutide, dulaglutide and lixisenatide.

As a drug class effect, SGLT2 inhibitors have the mean body weight change of -1.98kg (95% CI -2.18 to -1.78; moderate certainty). The mean body weight change of metformin is -0.83 with 95% CI -1.40 to -0.26kg, moderate certainty. Basal insulins have the following effect size in increasing body weight (Mean change of 2.15, 95% CI 1.74 to 2.56; high certainty). Sulfonylureas also result in mean body weight change of 1.78 (95% CI 1.50 to 2.06) with moderate certainty.

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

Table 7: Body weight impact of drug treatment for type 2 diabetes

Interventions	Body weight change, (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

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Glycated Hemoglobin A1C

This outcome has not been included for analysis by Shi et al[1]. Hence, another NMA[16] was consulted and used as a supplement to provide results for this outcome. A HbA1c drop by 0.5% is considered clinically meaningful. In this SR, the authors have 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 result in a mean difference of -0.60%, 95% CI -0.67 to -

0.54; low certainty). Compared to placebo, GLP-1 receptor agonists result in mean difference in HbA1C of -0.89% (95% CI -0.95 to -0.82; low certainty). The authors have also highlighted that GLP-1 receptor agonists reduced glycated haemoglobin A1c levels to a greater extend 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 are as follow; for GLP-1 receptor agonists, the result is 0.28 (95% CI 0.19 to 0.37); for sulfonylurea, the result is 0.05 (95% CI -0.05 to 0.15); for DPP-4 inhibitors, the result is -0.01 (95% CI -0.09 to 0.07); for basal insulin, the result is -0.14 (95% CI 0.01 to 0.26).

Table 8: Glycated hemolgobin A1C of drug treatments for type 2 diabetes

Interventions	Comparator	Mean Difference, (%, MD, 95% CI)
SGLT2 inhibitor	Placebo	-0.60 (-0.67 to -0.54)
GLP-1 receptor agonist	Placebo	-0.89 (-0.95 to -0.82)
SGLT2 inhibitor	GLP-1 receptor 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 -.63)

Source: Palmer SC, et al., Copyright 2021. This work is licensed under the Attribution-NonCommercial 4.0 International License. Full text available here: https://www.bmj.com/content/372/bmj.m4573

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 receptor agonists probably improve health related quality of life with standardized mean difference of 0.30, 95% CI 0.10 to 0.49; high certainty and 0.17, 95% 0.07 to 0.27; high certainty respectively. Other drugs including metformin, sulfonylureas, DPP-4 inhibitors (SMD and basal insulins (SMD -0.11, 95% CI -0.28 to 0.07; low certainty).

I. Safety

Severe hypoglycemia

Among the interventions of interest, sulfonylureas and basal insulins probably increase the risk of severe hypoglycemic events with OR of 5.22, 95% CI 3.88 to 7.01; high certainty and OR of 2.38, 95% CI 1.82 to 3.12; high certainty. 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 receptor agonists, the OR was 0.98 (95% CI 0.90 to 1.06; moderate certainty).

Table 9: Severe Hypoglycemia of drug treatments for type 2 diabetes

Interventions	Severe hypoglycemia (OR, 95% CI)

SGLT2 inhibitors	0.90 (0.79 to 1.02)
GLP-1 receptor 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 insulin	2.38 (1.82 to 3.12)
Standard treatments	Reference

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Genital Infection, Amputation & 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-inhibitor for amputation is 1.27 (95% CI 1.01 to 1.61; high certainty). When compared to standard treatments, the OR of SGLT2-inhibitor 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 receptor agonist 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-analysis. Clinical heterogeneity was also assessed by clinical experts.

To assess the intransitivity between direct comparisons, the authors compared their distribution of patients' characteristics. The authors chose the potential effect modifiers from the prognostic variables that have been 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, HbA1C, proportion of male 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 well in binary outcome settings than Egger's method. his 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 L-type estimator and R-type estimator to assess the robustness.

The authors also assessed the certainty of the evidence following the GRADE guidance. They concluded that evidence did not suggest global publication bias and 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 A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) tool, an instrument used to assess the methodological quality of systematic reivews.[20] The NMA scored 'high' using the AMSTAR 2 checklist (Appendix 4). A high AMSTAR 2 score indicates zero or one non-critical 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 credibility[21] was completed for both Shi et al., [1] and Palmer et al., [16] NMAs and results are included in Appendix 4.

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 Territory, 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 by the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes **(Appendix 5).** 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 Table S7 in **Appendix 6.** Cumulatively, over the four-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 over 8-fold, from 24,720 claimants in 2019 to 204,268 in 2022.
- The SGLT2 class demonstrated an increase in claimants across all three 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%.

Expenditure Trends for Antihyperglycemic Agents

The highest cumulative market share of expenditures over the four-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 Table S8 **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.

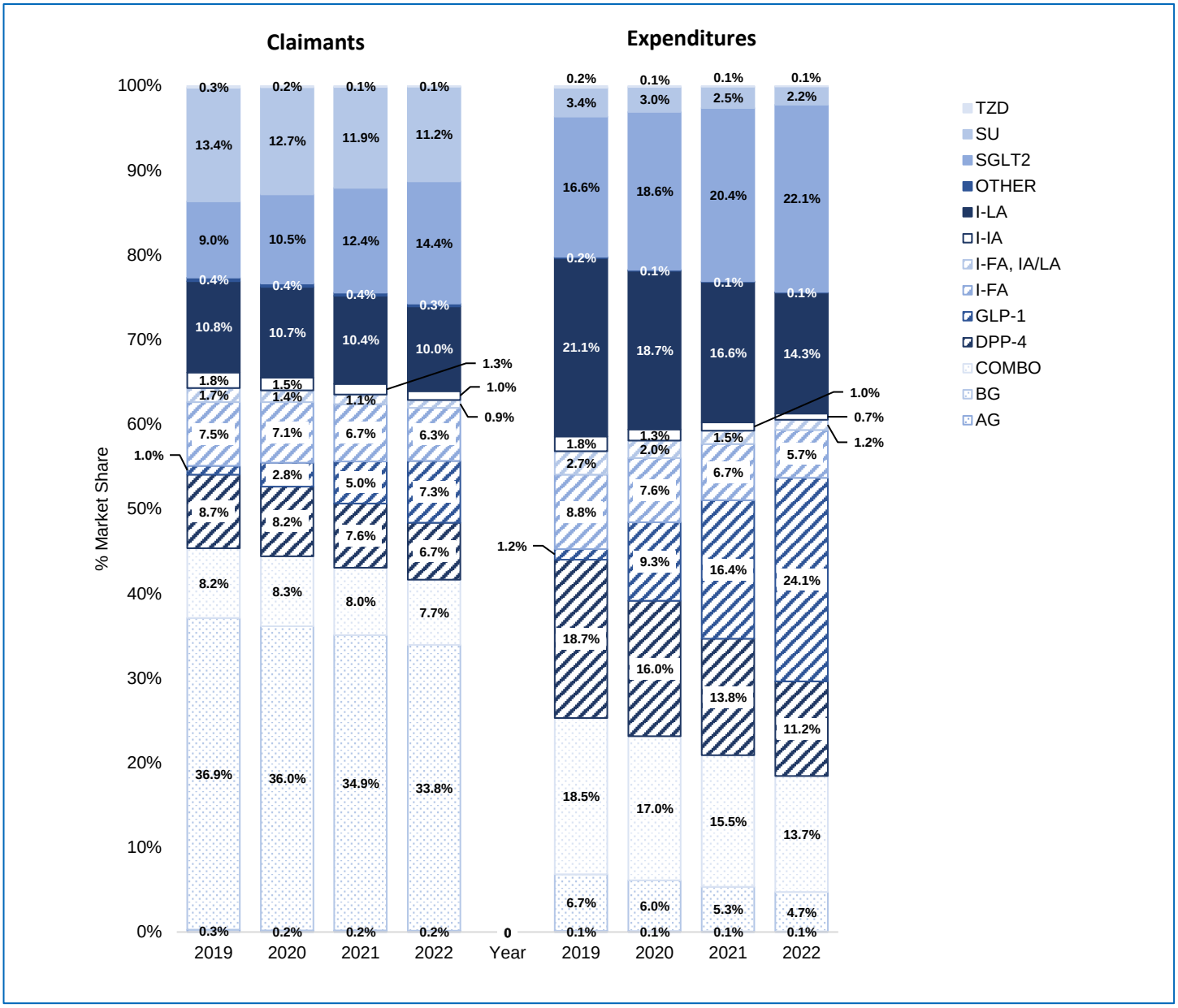
Table 11 provides a detailed breakdown of the expenditures for the antihyperglycemic agents by molecule:

- 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 2019 to $238.8 million in 2022, while the other insulin subclasses decreased in yearly expenditures.

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

Alt text: A bar graph presenting the market share of claimants and expenditures by antihyperglycemic drug class per year from 2019 to 2022. The x-axis represents each year and the y-axis represents the proportion of claimants or expenditures for each drug class in a given year. Market shares for both GLP-1 agonists and SGLT2 inhibitors increased year-over-year for both claimants and expenditures, while market shares for the other drug classes remained stable or declined during this period.



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, excl. insulins; SGLT2 = Sodium-glucose co-transporter 2 inhibitors; SU = Sulfonylureas; TZD = Thiazolidinediones

Table 10: Claimants for Antihyperglycemic Agents by Molecule (2019-2022)

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/DPP-4i	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/SGLT2i	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 & 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
SGLT2i	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

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

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/DPP-4i	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/SGLT2i	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
	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
GLP-1 Agonists	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

Class	Drug	2019 ($)	2020 ($)	2021 ($)	2022 ($)
	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 & 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
SGLT2i	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

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.

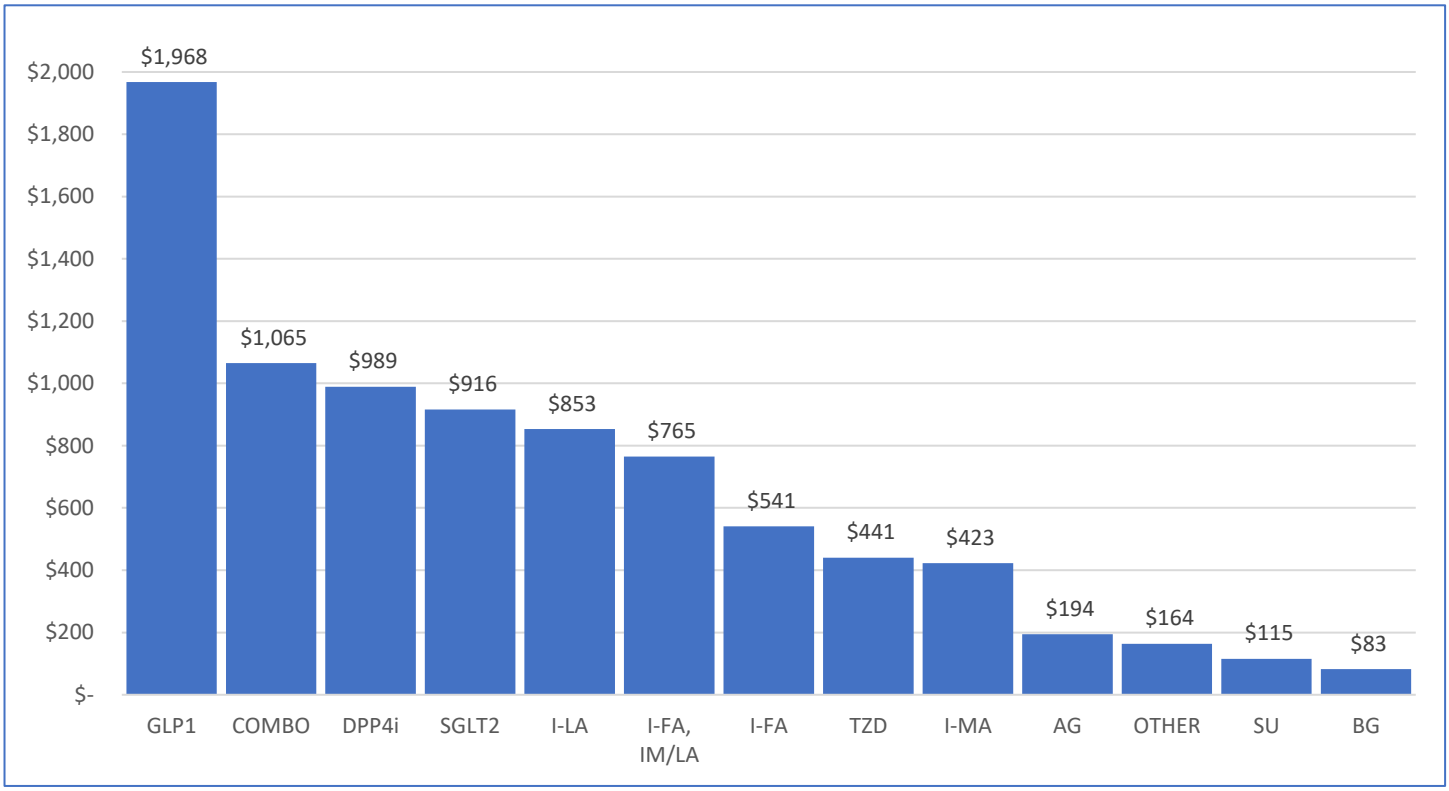
Table S9 in **Appendix 6** provides a detailed analysis for each drug within its respective class and demonstrates variations in average annual costs per beneficiary:

- Biguanides: Solely represented by metformin, remains the lowest at $83 per beneficiary.
- Oral combination therapies: Within the 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.
- DPP-4 inhibitors: Sitagliptin had the highest cost at $1,100 per beneficiary, while saxagliptin was the lowest at $629.
- GLP-1 Agonists: Semaglutide was the highest at $1,968 per beneficiary, whereas lixisenatide was substantially lower at $622.
- Insulin: Costs varied widely, from $92 for fast-acting insulin analogues to $1,348 for the insulin glargine and lixisenatide combination.
- SGLT2 inhibitors: Canagliflozin had the highest cost at $1,039 per beneficiary among SGLT2 inhibitors and dapagliflozin was the lowest at $830.
- Sulfonylureas: Glimepiride was markedly higher at $527 per beneficiary compared to gliclazide at $117 and glibenclamide at $94.

- Thiazolidinediones: Rosiglitazone was almost double the cost of pioglitazone per beneficiary at $804 and $412 respectively.

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

Alt text: A bar graph presenting the average annual cost of utilization per beneficiary by drug class in 2022. The x-axis represents each drug class and the y-axis represents the average annual cost of utilization per beneficiary in 2022. The average annual cost of utilization per beneficiary was highest for GLP-1 agonists, oral combination therapies, and DPP-4 inhibitors and lowest for biguanides and sulfonylureas.



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, excl. insulins; SGLT2 = Sodium-glucose co-transporter 2 inhibitors; SU = Sulfonylureas; TZD = Thiazolidinediones

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.

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/Technology reviews. As a result, the economic review consisted of only a cost comparison for various insulin and non-insulin anti-diabetic agents.

CADTH Analyses

The comparators presented in Table 12 have been deemed to be 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 price of comparators was based on public list prices from the Ontario Drug Benefit Formulary/Comparative Drug Index, accessed 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 Anti-Diabetic agents

Treatment	Strength/ Concentration	Form[a]	Price ($)[b]	Recommended dosage	Daily cost ($)	Annual cost ($)
Subtype 2 sodium-glucose transport protein (SGLT2) inhibitors						
Canagliflozin (Invokana) Canagliflozin (Invokana)	100 mg 300 mg	Tablet Tablet	2.8910	100 or 300 mg daily	2.89	1,056
Dapagliflozin (Forxiga, generics) Dapagliflozin (Forxiga, generics)	5 mg 10 mg	Tablet Tablet	0.6825	5 or 10 mg daily	0.68	249
Empagliflozin (Jardiance) 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 /metformin (Invokamet) Canagliflozin /metformin (Invokamet) Canagliflozin /metformin (Invokamet) Canagliflozin /metformin (Invokamet) Canagliflozin /metformin (Invokamet) Canagliflozin /metformin (Invokamet)	500/50 mg 850/50 mg 1000/50 mg 500/150 mg 850/150 mg 1000/150 mg	Tablet Tablet Tablet Tablet Tablet Tablet	1.6580[c]	Two tablets daily	3.32	1,211
Dapagliflozin /metformin (generics) Dapagliflozin /metformin (generics)	5 mg/850 mg 5 mg/1000 mg	Tablet Tablet	0.9647	Two tablets daily	1.93	705
Empagliflozin /metformin (Synjardy) Empagliflozin /metformin (Synjardy) Empagliflozin /metformin (Synjardy) Empagliflozin /metformin (Synjardy)	5 mg/500 mg 5 mg/850 mg 5 mg/1000 mg 12.5 mg/500 mg	Tablet Tablet Tablet Tablet	1.3932	Two tablets daily	2.79	1,018

Treatment	Strength/ Concentration	Form[a]	Price ($)[b]	Recommended dosage	Daily cost ($)	Annual cost ($)
	12.5 mg/850 mg 12.5 mg/1000 mg	Tablet Tablet				
Glucagon-like peptide-1 (GLP-1) receptor analogue						
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	Single use pre-filled pen 4 x 0.5 mL	216.3700[c]	0.75 mg to 1.5 mg once weekly	7.73	2,822
Exenatide (Byetta)	250 mcg/mL	Pre-filled 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	Pre-filled pen 3 mL (14 doses)	56.9800	Starting dose of 10 mcg once daily for 14 days, after which the dose should be increased to 20 mcg once daily	4.07	1,486
Liraglutide (Victoza)	6mg/mL	Pre-filled pen (10 to 30 doses) 2 x 3 mL 3 x 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)	1.34mg/mL	Pre-filled 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)	3mg 7mg 14mg	Tablet	7.2030 7.2030 7.2030	Loading dose of 3 mg daily for 30 days. Maintenance dose of 7mg or 14mg per day depending on glycemic control needs.	7.20	2,631
Glucagon-like peptide-1 (GLP-1) receptor analogue combinations						
Insulin degludec/ liraglutide (Xultophy, iDegLira)	100 U/mL / 3.6 mg/mL	Pre-filled pen 5 x 3 mL	308.8605[c]	16 to 50 U insulin degludec and 0.58 to 1.8 mg liraglutide once a day. Max daily dose: 50 U	3.29 (16 U) - 10.30 (50 U)	1,203 (16 U) - 3,760 (50 U)
Insulin glargine/ lixisenatide (Soliqua)	100 U/mL / 33 mcg/mL	Injectable Pen 5 x 3mL	198.3700	15 to 60 U insulin glargine and 5 to 20 mcg lixisenatide once a day. Starting dose not greater than 10 mcg lixisenatide. Max daily dose: 60 U	1.98 (15 U) to 7.93 (60 U)	725 (15 U) to 2,898 (60 U)
Dipeptidyl peptidase-4 (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/ Concentration	Form[a]	Price ($)[b]	Recommended dosage	Daily cost ($)	Annual cost ($)
Dipeptidyl peptidase-4 (DPP-4) inhibitors plus metformin fixed dose combinations						
Alogliptin/ metformin (Kazano)	12.5/500 mg 12.5/850 mg 12.5/1000 mg	Tablet Tablet Tablet	1.1950[c]	Two tablets daily	2.39	873
Linagliptin/ metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1000 mg	Tablet Tablet Tablet	1.4132	Two tablets daily	2.83	1,032
Saxagliptin/ metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1000 mg	Tablet Tablet Tablet	1.3482	Two tablets daily	2.70	985
Sitagliptin/ metformin (generics)	50 mg/500 mg 50 mg/850 mg 50 mg/1000 mg	Tablet Tablet Tablet	0.8893	Two tablets daily	1.78	650
Other first-line treatments for diabetes						
Biguanides						
Metformin (generics)	500 mg	Tablet	0.0247	500 mg three to four times daily	0.07 to 0.10	27 to 36
Sulfonylureas						
Gliclazide (generics)	80 mg	Tablet	0.0931	80 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

ER = extended release; MR = modified release; 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]
[a] If 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.
[b] The 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 x 3 mL) then price is per pack.
[c] Prices obtained from DeltaPA IQVIA database (accessed October 2023).
[d] If 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 Agents

Treatment	Strength/ Concentration	Form	Price ($)[a]	Cost per mL ($)
Long-acting insulin analogues				
Insulin glargine U-100 (Basaglar)	100 U/mL	Cartridge (5 x 3 mL) Disposable pens (5 x 3 mL)	76.1100 76.1100	5.07
Insulin glargine U-100 (Lantus)	100 U/mL	Cartridge (5 x 3 mL) Disposable pens (5 x 3 mL) 10 mL vial	92.8500 92.8500 61.6900	6.19 6.19 6.17
Insulin detemir U-100 (Levemir)	100 U/mL	Cartridge (5 x 3 mL) Disposable pens (5 x 3 mL)	110.4100 111.5000	7.36 7.43

Insulin glargine U-300 (Toujeo)	300 U/mL	Disposable pen (1 x 1.5 mL) Disposable pen (1 x 3 mL)	26.4333 52.8666	17.62
Insulin degludec U-100 (Tresiba)	100 U/mL	Disposable pens (5 x 3 mL)	111.5000	7.43
Insulin degludec U-200 (Tresiba)	200 U/mL	Disposable pens (3 x 3 mL)	133.8000	14.87
Rapid-acting insulin analogues				
Insulin aspart (NovoRapid)	100 U/mL	Cartridge (5 x 3 mL) Disposable pens (5 x 3 mL) 10 mL vial	61.2300 63.7500 30.1900	4.08 4.25 3.02
Insulin glulisine (Apidra)	100 U/mL	Cartridge (5 x 3 mL) Disposable pens (5 x 3 mL) 10 mL vial	52.6500 53.1500 26.5800	3.51 3.54 2.66
Insulin lispro (Humalog)	100 U/mL	Cartridge (5 x 3 mL) Disposable pens (5 x 3 mL) 10 mL vial	65.6400 69.3900 33.0400	4.38 4.63 3.30
Insulin lispro (Humalog)	200 U/mL	Disposable pens (5 x 3 mL)	121.3200	8.09
Insulin lispro (Admelog)	100 U/mL	Disposable pens (5 x 3 mL) 10 mL vial	45.0000 22.7000	3.00 2.27
Insulin NPH (Neutral Protamine Hagedorn)				
Humulin N	100 U/mL	Cartridge (5 x 3 mL)	53.3500	3.56
Novolin ge NPH	100 U/mL	Cartridge (5 x 3 mL) 10 mL vial	48.8200 24.8300	3.25 2.48

Note: All prices are from the Ontario Drug Benefit formulary (accessed October 2023) unless otherwise indicated and do not include dispensing fees.
[a] The 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 mortality (OR 0.88, 95% CI 0.83 to 0.94; high certainty), cardiovascular mortality (OR 0.86, 95% CI 0.80 to 0.94; high certainty), and non-fatal myocardial infarctions (OR 0.90, 95% CI 0.82 to 0.98; high certainty). There is also evidence in 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.
- GLP-1 agonists also, compared to standard treatments, offer additional clinical benefits including improvement in all-cause mortality (OR 0.88, 95% CI 0.82 to 0.93; high certainty), cardiovascular mortality (OR 0.87, 95% CI 0.81 to 0.94; high certainty), non-fatal myocardial infarction (OR 0.91, 95% CI 0.85 to 0.98; high certainty) and non-fatal stroke (OR 0.85, 95% CI 0.77 to 0.94; high certainty). There is also evidence in 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 outcome is also noted for GLP-1 agonists. Main safety concerns include severe gastrointestinal events.
- Other antihyperglycemics including DPP-4 inhibitors, sulfonylureas and basal insulins do not improve all-cause mortality. They also do not impact on cardiorenal outcomes. However, sulfonylureas may increase all-cause mortality (OR 1.10, 95% CI 0.97 to 1.26; low certainty), although 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 DPP-4 inhibitors and sulfonylureas, they have also demonstrated improvement on all-cause mortality (DPP-4 inhibitor, OR 0.87, 95% CI 0.79 to 0.96; moderate certainty, sulfonylureas, OR 0.80, 95% CI 0.69 to 0.93; moderate certainty), reduction in hospitalization for heart failure (GLP-1 agonist, OR 0.73, 95% CI 0.64 to 0.83; moderate certainty, DPP-4 inhibitor, OR 0.63, 95% CI 0.55 to 0.72; moderate certainty, sulfonylureas, OR 0.67, 95% CI 0.53 to 0.85; moderate certainty) and reduction in end stage kidney disease (GLP-1 agonist, OR 0.73, 95% CI 0.63 to 0.84; low certainty, DPP-4 inhibitors, 95% CI 0.50 to 0.68; low certainty).

Discussion

Summary of the Input from Project Scope and Draft Report & 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 mortality, cardiovascular mortality, renal outcomes and patient-important outcomes such as weight loss and low risk for hypoglycemia. Based on the evidence highlighted in the systematic reviews with NMA, SGLT2 inhibitors and GLP-1 agonists offer many clinical benefits as compared to standard treatments as well as 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., 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-inhibitor 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 NMA, SGLT2 inhibitors demonstrated reduction in all-cause mortality, cardiovascular mortality, non-fatal 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 mortality, cardiovascular mortality, and non-fatal 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 the amputation is 1.27 when comparing SGLT2 inhibitors to standard treatments, only one 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 who clarified that the definition of genital infections included both mycotic or bacterial causes. It did not include urinary tract infections 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 the network meta-analysis is largely driven by the available evidence. The search is also 1 year old; as such the SR will not include any new evidence published in the past year. It is possible that the results and their certainty may 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 score for older drugs including sulfonylurea, DPP-4 inhibitors and basal insulins, there was a 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, and 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 intra-class differences, and Shi et al. rated down the potential for intra-class differences (outside of weight loss benefits between GLP-1 agonists), a potential for intra-class 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 opinion differs from this view.

In response to stakeholder feedback on the project scope and draft report, the intra-class differences of GLP-1 agonists were further explored. The authors (Shi et al.) were contacted and asked to re-run 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 re-analysis are described in Appendix 8.

The results of the analysis (scenario 1) including semaglutide and dulaglutide are included in Appendix 9. This re-analysis compared the SGLT2 inhibitors to semaglutide and dulaglutide for the following outcomes: all-cause death (Figure S5), cardiovascular death (Figure S6), end-stage kidney disease (Figure S8), hospitalization for heart failure (Figure S10), non-fatal myocardial infarction (Figure S9), non-fatal stroke (Figure S7), as well as health-related quality of life (Figure S11). When SGLT2 inhibitors were compared to semaglutide and dulaglutide, results were as follows: all-cause death (OR 1.01, 95% CI 0.88 to 1.15), cardiovascular death (OR 1.03, 95% CI 0.84 to 1.24), end-stage kidney disease (OR 1.19, 95% CI 0.82 to 1.73), hospitalization for heart failure (OR 1.45, 95% CI 1.20 to 1.75), non-fatal myocardial infarction (OR 1.04, 95% CI 0.86 to 1.25), non-fatal stroke (OR 0.75, 95% CI 0.60 to 0.94) and the standardized mean difference for health-related quality of life (OR 0.06, 95% CI -0.21 to 0.33).

The results of the analysis (scenario 2) to include semaglutide are included in Appendix 10. This re-analysis compared the SGT2 inhibitors to semaglutide for the following outcomes: all-cause death (Figure S12), cardiovascular death (Figure S13), non-fatal stroke (Figure S14) and end-stage kidney disease (Figure S15). When SGLT2 inhibitors were compared to semaglutide only, results were as follows: all cause death (OR 0.96, 95% CI 0.71 to 1.28), cardiovascular death (OR 0.91, 95% CI 0.62 to 1.34), non-fatal stroke (OR 0.66, 95% CI 0.45 to 0.97) and end-stage kidney disease (OR 1.43, 95% CI 0.69 to 2.94). Both re-analyses 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, 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 the overall survival and other important patient-related outcomes, there is a need to update the current reimbursement landscape of drugs in 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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