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CADTH THERAPEUTIC REVIEW

New Drugs for Type 2 Diabetes: Second-Line Therapy – Science Report

Product Line:	Therapeutic Review
Volume:	Volume 4
Issue:	No. 1b
Publication Date:	September 2017
Report Length:	401 pages

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Cite As: New drugs for type 2 diabetes: second-line therapy – science report. Ottawa: CADTH; 2017 Sep. (CADTH therapeutic review; vol.4, no.1b).

ISSN: 1929-7440

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.

Funding: For this project, CADTH worked in partnership with the Methods and Applications Group for indirect Comparisons (MAGIC), funded by the Canadian Institutes of Health Research (CIHR) through the Drug Safety and Effectiveness Network (DSEN) initiative.

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Abbreviations

A1C	glycated hemoglobin
BMI	body mass index
DC	Diabetes Canada
CERC	Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DDD	defined daily dose
DPP-4	dipeptidyl peptidase-4
EQ-5D	EuroQol 5-Dimensions questionnaire
GLP-1	glucagon-like peptide-1
HDL	high-density lipoprotein
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
IHD	ischemic heart disease
LDL	low-density lipoprotein
MACE	major adverse cardiovascular events
MI	myocardial infarction
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
OR	odds ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
ROB	risk of bias
SGLT-2	sodium-glucose cotransporter-2
SD	standard deviation
TIA	transient ischemic attack
TZD	thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study

Executive Summary

Context and Policy Issues

Pharmacologic treatment of type 2 diabetes following the failure of conventional diet and exercise interventions begins with metformin (except where contraindicated). Inadequate glycemic control with metformin is common. Treatment algorithms recommend the addition of oral or injectable antidiabetic drugs or insulin to metformin as a next step (second-line therapy). Previous CADTH reports (2013) on second-line therapy provided comparative efficacy and cost-effectiveness recommendations. Since then, a new drug class has entered the Canadian market for the treatment of patients with type 2 diabetes — sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In addition, a fourth dipeptidyl peptidase-4 (DPP-4) inhibitor (alogliptin) as well as a third glucagon-like peptide-1 (GLP-1) analogue (dulaglutide) have appeared on the Canadian market, and new data on the impact on cardiovascular outcomes of some of the new drugs (e.g., GLP-1 agonists, DDP-4 inhibitors, and SGLT-2 inhibitors) have been published recently. As a result, there is a need to reassess the comparative efficacy, safety, and cost-effectiveness of the available drug classes for the treatment of patients with type 2 diabetes.

Objectives and Research Questions

Clinical Review

The objective of this project is to update a previous CADTH systematic review, network meta-analyses, and cost-effectiveness analysis of second-line therapies for type 2 diabetes. In addition, we aim to review pharmacologic treatments for patients with type 2 diabetes who are at high risk for cardiovascular events.

The research questions for the review are the following:

1. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative efficacy and safety of using a drug from one of the following classes as a second-line drug?
    a. Sulfonylurea
    b. Insulin
    c. DPP-4 inhibitor
    d. GLP-1 analogue
    e. SGLT-2 inhibitor.
2. For adults with type 2 diabetes, what are the comparative cardiovascular effects of drugs belonging to one of the following classes?
    a. Insulin
    b. DPP-4 inhibitor
    c. GLP-1 analogue
    d. SGLT-2 inhibitor.
3. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative cost-effectiveness of the following drug classes as second-line therapy?

a. Sulfonylurea
b. Insulin
c. DPP-4 inhibitor
d. GLP-1 analogue
e. SGLT-2 inhibitor.

Methods

Clinical Review

Clinical evidence was selected systematically according to a predefined protocol. Randomized controlled trials (RCTs) were selected for inclusion in the systematic review and subsequent analyses if they were carried out in patients with type 2 diabetes (either with inadequate control on metformin monotherapy or at high risk for cardiovascular events), included treatment with an oral or injectable antidiabetic drug or insulin, and reported outcomes of interest. Trials not reporting outcomes of interest were not excluded from the systematic review but were not summarized.

A total of 37 outcomes were extracted, including glycated hemoglobin (A1C), weight and body mass index, blood pressure, cholesterol, overall or severe hypoglycemia, and important long-term cardiovascular outcomes (major adverse cardiovascular events, cardiovascular mortality, hospitalization for heart failure, and all-cause mortality).

Next, RCTs for the drugs identified in the systematic review were used for a mixed treatment comparison (MTC) that consisted of a network meta-analysis (NMA) for each of the aforementioned outcomes for which data were available and analysis was appropriate. Finally, the results of the MTC were used to inform a separate cost-effectiveness analysis of the drug classes. Results of the associated economic evaluation for this project will be presented in a separate report.

Pharmacoeconomic Review

The updated pharmacoeconomic study utilized methodology similar to that in the original analysis, except that GLP-1 analogues and SGLT-2 inhibitors were included as treatment options. Other key revisions to the previous methods were as follows:

- The latest United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (version 2.0, May 2015) was used to forecast diabetes-related complications, costs, and consequences, and to estimate incremental cost-utility ratios (ICURs) for each drug class added to metformin.[1]
- Treatment effect estimates were obtained from CADTH's updated systematic review and network meta-analysis.
- Costs for drugs were updated to 2016; costs for disease management and long-term diabetes complications were adjusted for inflation.

Key Clinical Findings

Research Question 1

For research question 1, the systematic review identified 175 unique RCTs that each evaluated the efficacy and/or safety of the antidiabetic drugs in participants who had inadequate control on metformin monotherapy. Of these, 166 reported outcomes of interest. Evidence was available for the following eight drug classes: sulfonylureas, SGLT-2

inhibitors, DPP-4 inhibitors, thiazolidinediones (TZDs), GLP-1 analogues, basal insulin, alpha-glucosidase inhibitors, meglitinides, and biphasic insulin. No studies of bolus insulin reported outcomes of interest.

NMAs were conducted for 18 outcomes for the reference case of drug class comparisons. Selected NMA results found the following:

- **A1C:** Relative to metformin monotherapy, all of the selected classes significantly reduced mean difference in the change from baseline for A1C. When the classes were compared with each other, DPP-4 inhibitors did not decrease A1C as much as sulfonylureas or GLP-1 agonists (84 RCTs).
- **Nonsevere hypoglycemia:** Compared with metformin monotherapy, the odds of nonsevere hypoglycemia were higher with sulfonylurea and basal and biphasic insulin. When the classes were compared, all classes except biphasic insulin significantly reduced odds of nonsevere hypoglycemia relative to sulfonylurea (67 RCTs).
- **Body weight:** Relative to metformin monotherapy, sulfonylurea and basal insulin increased mean body weight (range 2.1 kg to 2.8 kg) with no significant differences between these classes. SGLT-2 inhibitors and GLP-1 agonists were associated with significant reductions in mean body weight relative to metformin monotherapy (range –1.4 kg to –2.2 kg). All noninsulin treatments added to metformin resulted in significant reductions in mean body weight relative to sulfonylurea (range –1.9 kg to –4.3 kg). SGLT-2 inhibitors and GLP-1 agonists also resulted in significant reductions in mean body weight relative to DPP-4 inhibitors (70 RCTs).
- **Systolic blood pressure:** SGLT-2 inhibitors and GLP-1 agonists added to metformin resulted in a significantly lower mean difference in the change from baseline for systolic blood pressure relative to metformin monotherapy, sulfonylureas, and DPP-4 inhibitors. Basal insulin added to metformin resulted in a significantly higher mean difference in the change from baseline for systolic blood pressure relative to SGLT-2 inhibitors (29 RCTs).
- **Total adverse events:** Compared with metformin monotherapy, GLP-1 agonists and basal or biphasic insulin significantly increased the total number of adverse events. When the classes were compared, basal and biphasic insulin significantly increased total adverse events when compared with all other classes. GLP-1 agonists significantly increased total adverse events when compared with DPP-4 and SGLT-2 inhibitors (57 RCTs).
- **Low-density lipoprotein (LDL) cholesterol:** SGLT-2 inhibitors added to metformin resulted in significant increases in the mean difference of the change from baseline for LDL cholesterol relative to metformin alone and significant increases relative to DPP-4 inhibitors (31 RCTs).

There were limited data for mortality and clinically important long-term complications of diabetes.

Research Question 2

For research question 2, the systematic review identified 17 unique RCTs that each evaluated the efficacy and/or safety of the antidiabetic drugs in participants on any background therapy who were at high risk for cardiovascular events. Of these, 11 reported outcomes of interest. Evidence was predominantly available for SGLT-2 inhibitors, DPP-4 inhibitors, TZDs, and GLP-1 analogues.

NMAs were conducted for 12 outcomes for the reference case of drug class comparisons. Select NMA results found the following:

- **Major adverse cardiovascular events** (6 RCTs), **cardiovascular mortality** (5 RCTs), **hospitalizations for heart failure** (5 RCTs), **total adverse events** (3 RCTs): When compared with placebo, SGLT-2, DPP-4 inhibitors, and GLP-agonists did not significantly increase or decrease the relative risk of events.
- **Severe hypoglycemia:** There was a significantly lower risk of severe hypoglycemia with GLP-1 agonists relative to DPP-4 inhibitors and placebo (8 RCTs).
- **All-cause mortality:** Compared with placebo and DPP-4 inhibitors, SGLT-2 inhibitors reduced the risk of all-cause mortality. None of the other treatments reduced the risk of all-cause mortality (8 RCTs).

Key Economic Findings

The results of the updated economic evaluation were similar to those of the previous analysis. Sulfonylureas remained the most cost-effective second-line therapy in patients inadequately controlled on metformin, with an ICUR of $38,653 per quality-adjusted life-year (QALY) gained. This was due primarily to the lower cost of drugs in this drug class compared with insulin and newer classes. The ICUR of SGLT-2 inhibitors was approximately $135,000 per QALY versus sulfonylureas, and the ICUR of GLP-1 analogues was approximately $182,000 per QALY versus SGLT-2 inhibitors. DPP-4 inhibitors were extendedly dominated (i.e., they were less effective and more costly than combinations of other treatment strategies). Both insulin strategies were also dominated: associated with more costs and fewer benefits than the previous most-effective strategy.

Cost-effectiveness results were robust to most variations in model inputs and assumptions, with the exception of disutility associated with weight gain, and the cost and utilization of self-monitoring of blood glucose. Threshold analyses indicated that the costs of DPP-4 inhibitors, GLP-1 analogues, and SGLT-2 inhibitors would have to be reduced by 60% to 70% in order to surpass sulfonylureas as the most cost-effective second-line treatment option.

Strengths and Limitations

Clinical Review

Strengths and limitations in this review were similar to those reported in previous CADTH reviews.

Strengths

- The updated systematic review was conducted according to a protocol specified in advance, using standard approaches for identification of evidence, data extraction, quality assessment, and analysis.
- By conducting an NMA, both direct and indirect estimates of effect were captured, and results are reported in a manner that is practical for health care professionals and decision-makers.
- Results from the NMA were generally consistent with those from direct pairwise comparisons across all outcomes, a finding that adds validity to the analysis.

Limitations

- For populations inadequately controlled with first-line metformin monotherapy who required a second-line drug, most identified trials included patients using varied and unspecified antidiabetes drugs at baseline which limited their inclusion in this review.

  - This specifically impacted the inclusion of results from emerging trials reporting clinically important outcomes (e.g., EMPA-REG OUTCOME and LEADER) in the analyses for research question 1. Outcomes from these studies could not be considered in the economic evaluation, as only NMA results from research question 1 informed the analyses.
- For populations inadequately controlled on metformin, there was little evidence for the effect of second-line drugs on long-term diabetes-related complications.
- Low events rates limited the ability to perform NMA for many outcomes. When feasible and appropriate, the best possible alternative synthesis approach was used (meta-analysis, narrative).
- Statistical approaches to Bayesian NMA rely on a number of key assumptions, including transitivity, consistency, and homogeneity. The NMA analyses presented in this report for research questions 1 and 2 were generally assessed to be valid; however, we were unable to statistically assess the consistency assumption for some outcomes reported due to the limited number of studies informing the evidence network.
- The varied baseline characteristics of the participants included in research question 2 may also have produced some heterogeneity, which was difficult to investigate comprehensively due to the limited number of studies reporting outcomes of interest.

Pharmacoeconomic Review

With respect to limitations of the pharmacoeconomic analysis, it should be noted that the UKPDS model does not explicitly incorporate a number of diabetes-related morbidities (e.g., peripheral neuropathy and ulceration) or intermediate states (e.g., retinopathy and nephropathy) that may themselves be associated with reduced quality of life. Hence, the UKPDS model may result in an overestimation of incremental cost-effectiveness ratios. However, the impact of this factor on cost-effectiveness estimates is likely small, given the minimal differences in glycemic control across drug classes.

There was considerable uncertainty regarding the disutility associated with weight gain and hypoglycemia (mild, moderate, and severe). These are important potential drivers of the cost-effectiveness of second-line options, particularly for newer classes, such as the SGLT-2 inhibitors and DPP-4 inhibitors, which are associated with low risks of hypoglycemia and are weight-neutral or cause modest weight loss. In the absence of sound data for these inputs, conservative estimates were used for the reference case analysis, but these were tested in sensitivity analyses.

In the reference case analysis, it was assumed that metformin plus the second-line treatment were continued at constant doses for the lifetime of the patient. Although this assumption allows for attribution of costs and consequences to the treatments in question, it does not represent the progressive nature of type 2 diabetes and the inevitable need for intensification of therapy over time. This limitation was addressed through a sensitivity analysis in the 2013 review in which neutral protamine Hagedorn (NPH) insulin was added to all noninsulin second-line treatments once A1C reached 9%. Sulfonylureas remained the most cost-effective option in that analysis. Although this sensitivity analysis was not performed as part of the current analysis, it is expected that it would not change the conclusion that sulfonylureas are the most cost-effective second-line option.

Conclusions

Clinical Review

Results from the systematic review align with other class-level systematic reviews and meta-analyses that have assessed the comparative efficacy of antidiabetes drugs in patients with inadequate glycemic control on metformin monotherapy, although this review includes significantly more RCTs and examines many more clinical outcomes and adverse events. Results also support current clinical practice guidelines for this patient population by Diabetes Canada. Similar to the previous CADTH review and other systematic reviews on oral antidiabetes drugs, there remained a lack of conclusive evidence regarding the effects of various therapies on the long-term complications of diabetes.

There are clear correlations between type 2 diabetes and the long-term health impacts related to heart disease, premature death, and cardiovascular complications. Many of the large cardiovascular outcome RCTs were powered for cardiovascular safety outcomes yet limited in the reporting of many other efficacy outcomes. As a result, it is difficult to place the noted cardiovascular benefits in context with other outcomes related to glycemic control. Although it was not possible to consider the data from the recent large clinical trials (e.g., EMPA-REG OUTCOME and LEADER) in the NMA for research question 1, results show benefit in the high-risk populations studied. Treatment options for patients at high risk for cardiovascular disease should consider these study results in context with the results from the NMA.

Pharmacoeconomic Review

Treatment strategies for patients with type 2 diabetes must consider more than glycemic control and take individual requirements for treatment into consideration. This review has identified some risks that may partially offset benefits for some treatments and effect estimates varied across both treatment classes and outcomes. Choice of treatment must be considered in context, with recommendations and guidelines in mind.

The results of the updated cost-effectiveness analysis comparing second-line treatments for type 2 diabetes after inadequate control with metformin monotherapy were congruent with the results of the previous analysis. Sulfonylureas added to metformin represented the most cost-effective second-line therapy, a finding that was robust in numerous sensitivity analyses. SGLT-2 inhibitors and GLP-1 analogues were found to be associated with high ICURs and were unlikely to be cost-effective, according to generally accepted thresholds. In order to surpass sulfonylureas as the most cost-effective second-line therapy, reductions in cost of 60% or more would be required for the SGLT-2 inhibitors and 70% or more for the DPP-4 inhibitors and GLP-1 analogues. Key areas of uncertainty in the analysis were the effective prices of antihyperglycemic drugs, hypoglycemia incidence, and the impact of hypoglycemia and weight change on quality of life.

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Table of Contents

Rationale

In August 2010, CADTH published an Optimal Therapy Report that assessed the clinical and cost-effectiveness of second-line therapies for patients with type 2 diabetes inadequately controlled on metformin.[2] The results from the CADTH review indicated that there were no apparent differences in efficacy across drug classes and that sulfonylureas were the most cost-effective treatment option. Based on these analyses, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC) recommended that most patients requiring a second treatment after metformin should be prescribed a sulfonylurea.

The original clinical review was updated in July 2013 to include new drugs approved for use in Canada and to expand the recommendations based on these updates and those from an updated economic evaluation.[3]

Since then, a new drug class has entered the Canadian market for the treatment of patients with type 2 diabetes — sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In addition, a fourth dipeptidyl peptidase-4 (DPP-4) inhibitor (alogliptin) as well as a third glucagon-like peptide-1 (GLP-1) analogue (dulaglutide) have appeared on the Canadian market. As well, new data on the impact on cardiovascular outcomes of some of the new drugs (e.g., GLP-1 agonists, DDP-4 inhibitors, and SGLT-2 inhibitors) have been published. The Diabetes Canada (DC) also recently released an interim focused update of its clinical practice guidelines for the pharmacologic management of type 2 diabetes.[4] There is therefore a need to determine the comparative clinical and cost-effectiveness of new drugs for the treatment of patients with type 2 diabetes.

Of note, this evaluation is conducted within the policy context currently prevailing in Canadian publicly funded drug programs for the reimbursement of drugs for type 2 diabetes. This review will include assessment of second-line therapies (Table 1, Table 2). Third-line therapies will be assessed in a separate report. Cost-effectiveness will also be assessed in a separate report.

Issue

Patients diagnosed with type 2 diabetes are prescribed lifestyle-changing regimens or educational interventions that aim to improve diet and physical activity levels and reduce body weight when appropriate. Current guidelines from Diabetes Canada (DC) recommend initiation of pharmacologic treatment with metformin monotherapy if a target glycated hemoglobin (A1C) level is not reached within two or three months (or insulin if metformin is not indicated). Most people with type 2 diabetes will require continuous pharmacologic treatment in order to maintain normal or near-normal glycemic targets, and blood glucose levels may continue to rise gradually over an individual's life-course.[5]

When initial therapy with lifestyle interventions and metformin monotherapy are unsuccessful, a second oral or injectable drug is recommended. This is referred to as "second-line therapy." There are a number of available drugs that can be used in combination with metformin: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), DPP-4 inhibitors, SGLT-2 inhibitors (Table 1), GLP-1 agonists, basal insulins, bolus insulins, and biphasic insulins (Table 2). Historically, insulin or sulfonylureas have been the preferred second-line drugs because of efficacy, side-effect

profiles, long-term safety, and relative cost. Given the newer drugs recently approved in Canada and additional randomized controlled trial (RCT) results published since 2013 for the existing drugs, there is a need to revisit comparative efficacy, safety, and cost.

Table 1: Oral Drugs Currently Available in Canada Included in the Clinical Review

Drug Class	Drug	Trade Name	DDD
Single Drug Products			
DPP-4 inhibitors	Alogliptin	Nesina	25 mg
	Linagliptin	Trajenta	5 mg
	Saxagliptin	Onglyza	5 mg
	Sitagliptin	Januvia	100 mg
SGLT-2 inhibitors	Canagliflozin	Invokana	200 mg
	Dapagliflozin	Forxiga	10 mg
	Empagliflozin[a]	Jardiance	17.5 mg
Sulfonylureas	Chlorpropamide	Generic	375 mg
	Gliclazide[b]	Diamicron	160 mg
		Diamicron MR	60 mg
	Glimepiride[b]	Amaryl	2 mg
	Glyburide[b]	Diabeta	10 mg
	Tolbutamide	Generic	1,500 mg
TZDs	Pioglitazone	Actos	30 mg
	Rosiglitazone	Avandia	6 mg
Meglitinides	Nateglinide	Starlix	360 mg
	Repaglinide	Gluconorm	4 mg
AGIs	Acarbose	Glucobay	300 mg
Fixed-Dose Combination Drug Products			
DPP-4 inhibitors/biguanides	Alogliptin/metformin	Kazano	25 mg
	Linagliptin/metformin	Jentadueto	5 mg
	Saxagliptin/metformin	Komboglyze	5 mg
	Sitagliptin/metformin	Janumet	100 mg
		Janumet XR	not available
SGLT-2 inhibitors/biguanides	Dapagliflozin/metformin	Xigduo	10 mg
	Empagliflozin/metformin	Synjardy	17.5 mg
	Canagliflozin/metformin[c]	Invokamet	200 mg

AGI = alpha-glucosidase inhibitor; DDD = World Health Organization Defined Daily Dose; DPP-4 = dipeptidyl peptidase-4 inhibitor; SGLT-2 = sodium-glucose cotransporter-2, TZD = thiazolidinedione.

[a] Not included in *Therapeutic Choices*.
[b] Generic products also available.
[c] Pre-Notice of Compliance CADTH Common Drug Review submission received on February 3, 2016 (https://www.cadth.ca/canagliflozin-and-metformin-hydrochloride).
Notes: Table adapted from Table 8 in Endocrine and Metabolic Disorders: Diabetes Mellitus Chapter of *Therapeutic Choices*. Canadian Pharmacists Association, 2015. All rights reserved. Source: https://www.e-therapeutics.ca/tc.showChapter.action?documentId = c0079#tablc0079n00043. Accessed: July 29, 2015.Other information sources include Product Monograph available from the Health Canada Drug Product Database (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) as well as CADTH 2013 (Updated) Optimal Use Reports on the optimal use of second- and third-line therapies for type 2 diabetes mellitus (https://www.cadth.ca/second-third-line-therapies-type-2-diabetes).

Table 2: GLP-1 Analogues, Insulin, and Insulin Analogues Available in Canada

GLP-1 Analogue Products		Trade Name	DDD
Dulaglutide		Trulicity	0.16 mg
Exenatide		Byetta	15 mcg
Exenatide extended-release		Bydureon	286 mcg
Liraglutide		Victoza	1.2 mg
Albiglutide		Eperzan	5.7 mg
Insulin and Insulin Analogue Products[a]	**Insulin and Insulin Analogue Types**	**Trade Name**	**DDD**
Insulin aspart	Very rapid-acting insulin analogue	NovoRapid	40 U
Insulin glulisine	Very rapid-acting insulin analogue	Apidra	
Insulin lispro	Very rapid-acting insulin analogue	Humalog	
Insulin, regular	Rapid-acting insulin	Humulin R, Novolin ge Toronto	
Insulin, pork	Rapid-acting insulin	Hypurin Regular	
Insulin, NPH	Intermediate-acting insulin	Humulin N, Novolin ge NPH	
Insulin, pork	Intermediate-acting insulin	NPH/Hypurin NPH	
Insulin detemir	Long-acting insulin analogue	Levemir	
Insulin glargine	Long-acting insulin analogue	Lantus, Toujeo, Basaglar	
Insulin regular/insulin, NPH	Mixed (regular/NPH) human insulin	Humulin 30/70, Novolin ge 30/70, 40/60, 50/50	
Insulin lispro/lispro protamine	Mixed insulin analogue	Humalog Mix25, Humalog Mix50	
Insulin aspart/aspart protamine	Mixed insulin analogue	NovoMix 30	

DDD = World Health Organization Defined Daily Dose; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn.
[a] All concentrations of insulin and insulin analogue products will be considered, if appropriate (e.g., insulin glargine 100 units/mL and 300 units/mL; insulin lispro 100 units/mL and 200 units/mL). Insulin and insulin analogue products include subsequent entry biologics.
Source of information: *Therapeutic Choices*. Canadian Pharmacists Association, 2015. [Source: https://www.e-therapeutics.ca/tc.showChapter.action?documentId = c0079#tablc0079n00043; Accessed; July 29 2015 (proprietary)]

Objective

The objective of this review is to update the previous CADTH systematic review and network meta-analyses (NMAs) of second-line therapies for type 2 diabetes. In addition, we aim to review pharmacologic treatments for patients with type 2 diabetes who are at high risk for cardiovascular events.

Research Questions

The research questions for this project are presented in this section. These reflect the information needs of CADTH jurisdictional clients with regard to comparative efficacy, safety, and cost-effectiveness.

1. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative efficacy and safety of using a drug from one of the following classes as a second-line drug?
    a. Sulfonylurea
    b. Insulin
    c. DPP-4 inhibitor
    d. GLP-1 analogue
    e. SGLT-2 inhibitor.
2. For adults with type 2 diabetes, what are the comparative cardiovascular effects of drugs belonging to one of the following classes?
    a. Insulin
    b. DPP-4 inhibitor
    c. GLP-1 analogue
    d. SGLT-2 inhibitor.
3. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative cost-effectiveness of the following drug classes as second-line therapy?
    a. Sulfonylurea
    b. Insulin
    c. DPP-4 inhibitor
    d. GLP-1 analogue
    e. SGLT-2 inhibitor.

Clinical Review

Methods

Scope and Protocol

To inform the final scope of the therapeutic review and protocol development, a proposed scope was posted to the CADTH website (www.cadth.ca) for stakeholder feedback following review with CADTH jurisdictional clients. Patient-group input was also solicited.

The protocol was registered with the International prospective register of systematic reviews (PROSPERO) before screening and study selection (registry number CRD42016038144). Portions of the protocol related to the assessment of third-line treatments will be detailed in a separate report.

Literature Search Strategy

The search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searches were executed on March 5, 2016. Using the Ovid platform, we searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase

Classic + Embase. We also searched Cochrane CENTRAL on Wiley. PubMed was searched for the most recent and unindexed citations only.

Strategies utilized a combination of controlled vocabulary (e.g., "Diabetes Mellitus, Type 2," "Hypoglycemic Agents," "Dipeptidyl-Peptidase IV Inhibitors") and keywords (e.g., "T2DM," "anti-diabetic," "DPP 4 inhibitors," "SGLT 2 inhibitors"). Vocabulary and syntax were adjusted across databases. The 2008 sensitivity- and precision-maximizing version of the Cochrane highly sensitive search strategy was used to identify RCTs. When possible, animal-only studies and opinion pieces were removed from the results. Retrieval was not limited by publication year or language. A second search for a small number of newly identified drugs was performed in the same databases on April 7, 2016. Database searches were updated in PubMed until July 3, 2016. Specific details regarding the strategies appear in Appendix 1.

We performed a grey literature search of clinical trial registries and other relevant trial sources on March 17 and 18, 2016. The trial registry search was limited to completed trials with results.

Selection Criteria

RCTs were eligible for inclusion if they met the study design, population, intervention, comparator criteria, and had outcomes of interest outlined in Table 3. Interventions of interest, including fixed-dose combinations and mixed insulin products, are further detailed in Tables 1 and 2. Weight-loss drugs (e.g., orlistat, sibutramine) included in previous CADTH reviews were not included in this update, as the primary role of such drugs is to lower body weight rather than to treat hyperglycemia. Other drugs not included in Table 3 (e.g., meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, insulin degludec) were included as comparators as long as they meet the eligibility requirements.

Table 3: Population, Intervention, Comparator, Outcome, and Study Designs of Interest

Population	For research question 1: Adults with type 2 diabetes on pharmacotherapy with inadequate glycemic control[a] For research question 2: Adults with type 2 diabetes	
Interventions[b]	**SGLT-2 inhibitors**	canagliflozin, dapagliflozin, empagliflozin
	GLP-1 analogues	dulaglutide, exenatide, liraglutide, albiglutide
	DPP-4 inhibitors	alogliptin, linagliptin, saxagliptin, sitagliptin
Comparators[b]	**SGLT-2 inhibitors**	canagliflozin, dapagliflozin, empagliflozin
	GLP-1 analogues	dulaglutide, exenatide, liraglutide
	DPP-4 inhibitors	alogliptin, linagliptin, saxagliptin, sitagliptin
	Sulfonylureas	chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide
	Insulin, insulin analogues, and insulin analogue biosimilars	Regular insulin, pork insulin, insulin aspart, insulin lispro, insulin glulisine, insulin NPH, insulin detemir, insulin glargine, mixed regular insulin/insulin NPH, mixed insulin lispro/lispro protamine and mixed insulin aspart/aspart protamine (see Table 2)
	Metformin	
	Placebo	

Outcomes	**Clinical benefits**[c]	Reduction in: • composite of death from cardiovascular causes/nonfatal myocardial infarction/nonfatal stroke • death from cardiovascular causes • all-cause mortality • fatal and nonfatal myocardial infarction • fatal and nonfatal stroke • unstable angina • hospitalization for unstable angina • heart failure • hospitalization for heart failure • transient ischemic attack • coronary revascularization procedure • blood pressure • body weight • body mass index • hemoglobin A1C Discontinuation of: • blood pressure medication
	Clinical harms	• total adverse events • serious adverse events • withdrawals due to adverse events
	Other notable harms	• hypoglycemia • urogenital adverse events • renal adverse events • lipids • ketoacidosis • bone fractures • bladder cancer • pancreatitis • pancreatic cancer

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; SGLT-2 = sodium-glucose cotransporter-2.
[a] In the previous CADTH reviews, inadequate control was defined as hemoglobin A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.
[b] Interventions may include regimens combining the above drugs with metformin, a sulfonylurea, insulin product and/or other drug (e.g., pioglitazone) as indicated in the Health Canada product monographs. Other drugs (including meglitinides, alpha-glucosidase inhibitors, thiazolidinediones or insulin degludec) may also be included as comparators in the network meta-analysis.
[c] Based on a reduction in events, or a change in clinical measurement signifying improvement or clinical benefit.
[d] A decrease in weight will be considered a clinical benefit, while an increase in weight will be considered a harm.

Two reviewers independently reviewed the titles and abstracts of studies identified by the search strategy in a standardized method using electronic tools customized to the project in DistillerSR, an online systematic review software tool (https://distillercer.com/products/distillersr-systematic-review-software/). Use of the online tool by the review team maximized efficiency in the review process and facilitated consistency across reviewers for literature screening, selection (and data extraction).

Table 4: Detailed Selection Criteria for Randomized Controlled Trials

Inclusion criteria	Studies were included if:
For all research questions	They report an active and/or placebo-controlled randomized controlled trial.
	They are published in English.
For research question 1	Study participants must have inadequately controlled type 2 diabetes and receive a second-line drug as an add-on to, or switch from, metformin monotherapy or a combination of metformin and another intervention. This includes studies that employ a metformin monotherapy run-in period before the addition of study interventions. Studies in which adults with type 2 diabetes require alternative hypoglycemic therapy due to intolerance of current therapy were also included. Studies were included regardless of metformin dosage at baseline or treatment history before receiving metformin.
For research question 2	Eligible study participants must have type 2 diabetes and be receiving one of the eligible interventions of interest, and the studies must report cardiovascular end points as a primary outcome.
Exclusion criteria	**Studies were excluded if:**
For all research questions	Treatment duration is less than 4 weeks.
	Language of full-text publication is not English.
	They are reported only in abstract format.
	More than 15% of patients in the total study population did not have type 2 diabetes.
For research question 1	Second-line antidiabetes drugs added to metformin monotherapy were compared with switching to second-line therapy (i.e., discontinuation of metformin monotherapy).
	Switch from metformin to another antidiabetes drug(s) was compared with switch to placebo or no therapy (i.e., no active comparator).
	More than 15% of the patients used a drug other than metformin monotherapy at baseline and no results were reported for the subgroup of metformin users.

Data Extraction

Data extraction was performed using data extraction forms designed a priori. Data extraction was performed by one reviewer and verified by a second reviewer. Any disagreements were resolved by consensus when possible; otherwise, the judgment of a third reviewer was considered final.

All information was extracted using a standardized form in an online systematic review management software to maximize efficiency and consistency across reviewers (DistillerSR). Data extraction included: 1) characteristics of trial participants, including inclusion and exclusion criteria, outcome definitions for hypoglycemia, and key baseline characteristics; 2) interventions studied, including dosing, titration, and background therapy; and 3) results of the clinical safety and efficacy outcomes of the intervention.

The original, primary publication for each unique study included was used for data extraction, except when multiple publications for a single RCT were found. Multiple publications for a unique RCT (e.g., supplemental online appendices, companion publications reporting additional outcomes or populations from the original study) were handled by extracting the most recently adjudicated data for each outcome specified in the

protocol. Data extracted from clinical trial registry records reporting study results (e.g., clinicaltrials.gov) were used when published articles did not report an outcome of interest.

Studies included from the previous therapeutic reviews went through *de novo* data extraction process for outcomes and baseline characteristics not previously evaluated (e.g., body mass index [BMI], blood pressure outcomes etc.) following identical methods and procedures as articles identified in the literature search.

If included evidence reported multiple time points for outcome assessment, we extracted the longest period reported for which the original randomization schedule/allocation was preserved. Data were extracted from graphs and/or figures when not reported in the publication text using WebPlotDigitizer (www.arohatgi.info/WebPlotDigitizer) in order to maximize accuracy and to improve consistency across multiple reviewers.

For urogenital adverse events, renal adverse events, and bone fractures, we extracted the total number of events at any time during the treatment period and/or the total number of participants who experienced at least one event during that same time period. Often, different types of study-reported outcomes needed to be summed to determine a total number of events in each of our outcomes of interest. For example, for our outcome "urogenital adverse events," urinary tract infections and genital mycotic infections were of interest. Across studies, however, these outcomes were often reported separately and, thus, needed to be summed to create a total count of urogenital adverse events. When outcomes were reported as the number of participants who experienced a particular outcome, and those outcomes needed to be summed together for our purposes, the number of patients experiencing each type of event was summed, but the data were then extracted as the total number of *events*. We used this approach in most cases because, based on the way outcomes were reported, it was largely unclear whether the same participants experienced more than one type of event.

For events that may occur more than once in a single study participant (counts of events), person-time rate data were prioritized. If RCTs reported a count of total number of events, we also extracted person-time-at-risk so that rates could be calculated. Few studies reported rate data or person-time-at-risk, and event counts were synthesized separately from people who experienced at least one event for each outcome of interest if necessary.

All-cause mortality, cardiovascular mortality and fatal myocardial infarction (MI) or stroke were inferred to be zero if the RCT explicitly stated that no deaths occurred.

Risk of Bias Assessment

The Cochrane Collaboration's Risk of Bias (ROB) tool was applied to each of the included RCTs in this review, including the RCTs included in previous CADTH therapeutic reviews. The ROB tool is a two-part instrument addressing six specific domains; namely, sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and "other issues" (excluded for this assessment). Each domain includes one or more specific entries in an ROB table, and a form was created in line with the Cochrane Collaboration's ROB template. The first part of the form involves describing what was reported to have happened in the study; and the second part involves assigning a judgment relating to the ROB for that entry by answering a pre-specified question about the adequacy of the study in relation to the entry, including a judgment of "LOW", "HIGH," or "UNCLEAR" or unknown ROB. Only one entry was considered for the domain "blinding" for assessments of outcomes that were objective.

For each unique RCT, we assessed the original primary publication, but additional relevant study literature was also used to conduct the ROB assessment, including, when available, design and rationale documents, companion study publications, protocols, and clinical trial registry records.

Assessments were performed by one reviewer, and verified by a second reviewer. Disagreements were resolved through consensus, or by a third reviewer if consensus could not be reached.

Data Conversion and Imputation

If studies reported outcomes using different units (for example, A1C in % or mmol/mol), we converted outcomes to a common unit before synthesis.

For continuous outcomes, mean difference from baseline to end of follow-up was the desired measure. When an RCT did not provide a mean difference, we extracted all other available data.

Data Analysis

The study and patient characteristics for the included studies were presented narratively and summarized to accompany synthesized data.

When data were available, were sufficiently similar, and were of sufficient quality, NMAs methods were used to synthesize the evidence. The NMAs from the 2013 CADTH second-line type 2 diabetes review were updated with data from the newly identified trials and for interventions of interest added in this review. To compare with the previous results, the same analysis approach was used so that any differences in the findings would attributed to the addition of new drugs and data from newly identified trials.

WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) was used to conduct the Bayesian NMAs. A binomial likelihood model with logit link was used for dichotomous outcomes and a normal likelihood model with identity link was used for continuous outcomes developed at the Universities of Bristol and Leicester.[6] Vague priors, $N(0, 100^2)$, were assigned for basic parameters of the treatment effects in the model. Metformin monotherapy or the addition of placebo to metformin was used as the default reference group for the NMAs.

Point estimates and 95% credible intervals (odds ratio for dichotomous outcomes, mean difference for continuous outcomes) were estimated using Markov chain Monte Carlo methods. Both fixed- and random-effects NMAs were conducted. For the random-effects binomial likelihood model, informative priors proposed by Turner et al. 2012 were applied for the between-study variance parameter to improve precision and reduce the heterogeneity between studies.[7] For safety outcomes, continuity correction was also applied before NMA to adjust for studies reporting zero events by adding a fraction of the reciprocal of the size of the opposite treatment arm to the event. Continuity corrections impact model convergence for outcomes with zero events and affect the efficiency of parameter estimates. Assessment of model fit and choice of model was based on the assessment of the deviance information criterion and comparison of residual deviance to number of unconstrained data points. Model diagnostics, including trace plots and the Brooks–Gelman–Rubin statistic, were considered to assess model convergence. Three chains were fit into WinBUGS for each analysis, each employing ≥ 10,000 iterations, with a burn-in of ≥ 10,000 iterations.[8-11]

Inconsistency between direct evidence and indirect evidence was formally assessed by comparing the deviance and deviance information criterion statistics of the consistency and inconsistency models. To help identify the loops in which inconsistency is present, the posterior mean deviance of the individual data points in the inconsistency model was plotted against their posterior mean deviance in the consistency model.

Frequentist pairwise meta-analysis was performed using RevMan when the data were insufficient to derive a robust NMA model. A random-effects model was used for the reference case in all pairwise meta-analyses using an inverse variance approach. As in the previous CADTH second-line type 2 diabetes reviews, three different evidence networks were completed:

1. drug-class level network (reference case)
2. dose-stratified network
3. individual-drug network.

The reference-case analysis is based on a drug-class level network in which moderate to high fixed-dose and titrated-dose studies were pooled into a single node, and low fixed-dose studies were excluded. Low doses were defined as below the World Health Organization Defined Daily Dose (DDD) (www.whocc.no/atc_ddd_index/). For background therapy with metformin, low dose was defined as below 1,500 mg per day based on advice from projects' clinical experts in diabetology. A sensitivity analysis was carried out using the DDD for metformin (2,000 mg per day). Other drugs (e.g., meglitinides, alpha-glucosidase inhibitors, TZDs, insulin degludec) were included as comparators in the NMA; however, results for the additional comparisons are presented in the appendices only.

To account for differences in dosage across studies and to avoid excluding the low-dose data, a dose-stratified model was conducted which each class of add-on drug was stratified into three separate nodes representing distinct dosage strategies in the evidence network:

- individually titrated dosage
- moderate to high fixed doses (i.e., ≥ DDD)
- low fixed doses (i.e., < DDD).

A third network model of individual drugs was also conducted. Each class was separated into their respective individual drugs. For research question 2, only trials aiming to evaluate cardiovascular end points as primary outcomes were included in related analyses (index node = placebo).

Results for Research Question 1

Selection of Primary Studies

After removal of duplicates, a total of 22,238 citations were identified in the literature search. Of these, 18,294 citations were excluded, based on titles and/or abstracts. Full-text articles of the remaining 3,944 citations were assessed. For research question 1, 175 unique RCTs and 78 companion publications[12-255] were included in the systematic review. A total of 166 RCTs[14-16,19,21-26,28-38,40,42-46,48-52,54,55,57-59,61,62,67,69-74,78,79,81,82,84,88,92,93,95-99,101,102,105-107,109,110,112-118,121,122,124,125,127,130,131,134-138,140-143,145,146,148-150,152-154,156,157,159,160,162-168,170-176,180-192,196-202,204-212,214-216,220-227,232,236,238,239,241,243,245,247,249,253,255] reported study outcomes of interest. A complete list of included studies is available in Appendix 2.

Study Characteristics

In total (original review plus the update), for research question 1, data were available for all of the drug classes of interest added to metformin with the exception of bolus insulins. Detailed trial characteristics of the included studies reporting outcomes of interest are provided in Table 5. All RCTs were parallel with the exception of two crossover studies. Forty-eight RCTs included a group receiving metformin plus placebo. Sample sizes ranged from 21 to 2,789. The threshold baseline A1C for inclusion in trials was typically in the range of 7.0% to 10%; however, a small number of studies employed a threshold as low as 6.5% or as high as 12.0%. The mean baseline A1C of trial subjects was 8.0%. The baseline duration of diabetes ranged from 3.7 to 12.3 years. The majority of studies were sponsored by the pharmaceutical industry. Approximately half were multinational studies. Similar to previous therapeutic reviews, there were some differences in the duration and dosage of metformin monotherapy before the addition of second-line drugs.

Treatment history before randomization was poorly reported and often unspecified. Patients using a variety of oral antidiabetes drugs often underwent a run-in period with metformin monotherapy upon trial entry and were randomized to add-on therapy if glycemic control was inadequate at the end of the run-in period. No studies assessed the effects of switching from metformin to another antidiabetes drug due to intolerable adverse effects, development of contraindications, or inadequate glycemic control.

RCTs generally reported populations of inadequately controlled patients with type 2 diabetes with a variety of co-morbid conditions. There were some RCTs of patients with type 2 diabetes and specific conditions (e.g., microalbuminuria [n = 5,671], metabolic disorder [n = 1,892, 5,504], dyslipidemia [n = 3,290]) or patient characteristics (e.g., restricted to women, Caucasians, or patients in a specific country).

Table 5: Summary of Trial Characteristics

Trial Characteristics	Categories	Number of Included Studies
Publication status	Unique RCTs	175
	Unique RCTs reporting outcomes of interest	166
Country	Multinational	83
	Single country	73
	Not reported	10
Study design	Parallel RCTs	164
	Crossover RCTs	2
Sponsors	Industry	119
	Public funding	9
	Not reported	36
Intervention comparison	Placebo control	48
	Active control	87
	Both	31
Duration of stable background therapy		Range: ≥ 4 weeks to ≥ 12 weeks
Publication year		Range: 1997 to 2016
Randomized sample size		Range: 21 to 2,789
Duration of study treatment		Range: 4 to 156 weeks

RCT = randomized controlled trial.

Table 6: Summary of Baseline Characteristics

Baseline Characteristics	Pooled Baseline Estimates (Range)
Mean age (years)	56.4 (43.4 to 72.6)
Gender (% male)	52.8 (17.5 to 76.7)
Mean duration of diabetes (yrs)	6.4 (3.7 to 12.3)
Current smoker (%)	25 (0 to 55.0)
BMI (mean, kg/m^2)	30.4 (24.5 to 36.8)
A1C (%)	8.01 (6.4 to 9.9)
Systolic blood pressure (mm Hg)	131.73 (123.7 to 152.7)
HDL cholesterol (mg/dL)	45.97 (34.4 to 179.2)
LDL cholesterol (mg/dL)	112.18 (61.9 to 159.2)

A1C = glycated hemoglobin; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Note: Table includes RCTs reporting outcomes of interest.

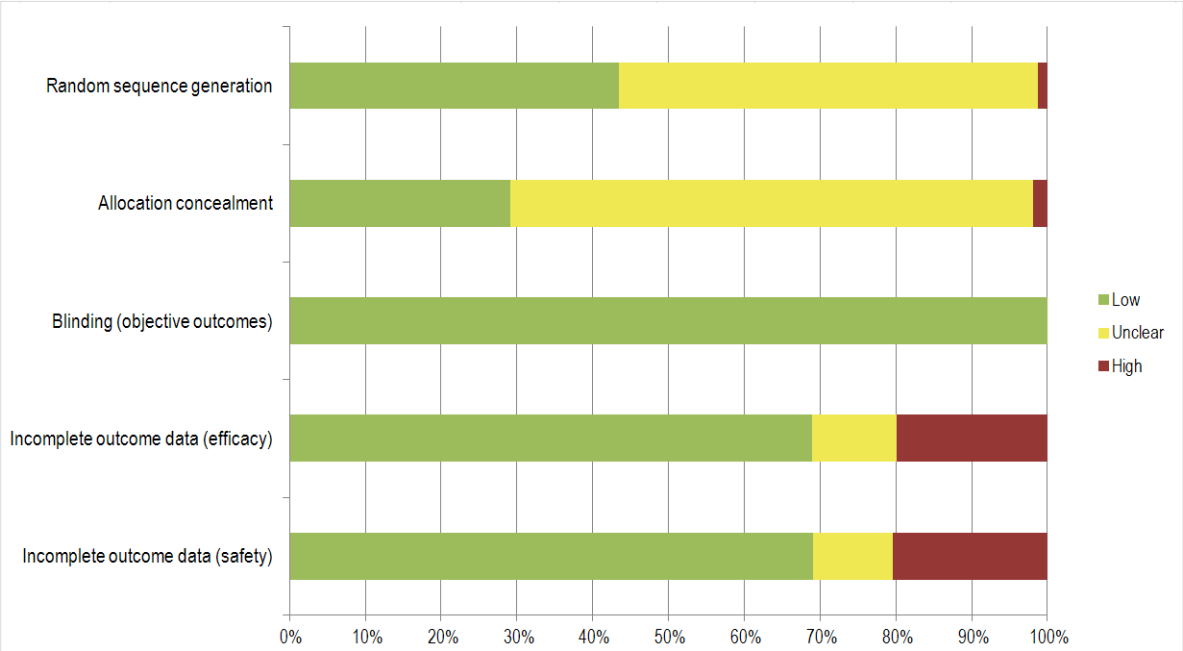
Risk of Bias

ROB was assessed for all studies *de novo* using the Cochrane Collaboration's ROB tool.[256] Figure 1 provides a summary of the results for all included RCTs, and Appendix 8 reports study-level results. Following ROB assessment, all included studies reporting outcomes were included in the analyses. Included RCTs generally had a moderate ROB. RCTs commonly failed to adequately report their methods for random sequence generation and allocation concealment. At least 20% of the studies were assessed to be at high ROB related to incomplete reporting of efficacy or safety outcomes.

Overall assessment of the internal and external validity of the included RCTs noted limitations in several areas that have been highlighted in previous CADTH therapeutic reviews. This included the use of surrogate end points (e.g., A1C) versus more clinically meaningful end points, limited sample sizes, and duration of follow-up. Many RCTs failed to register in a trial registry (e.g., clinicaltrials.gov) or to publish a study protocol.

Poor reporting was a common issue across trials. Failure to report protocol definitions for study outcomes (e.g., hypoglycemia), true intention-to-treat analyses (i.e., an analysis including all randomized patients), and dose and/or duration of stable metformin therapy before randomization. Many studies failed to adequately report details about the dosage of metformin background therapy while on treatment, which resulted in their exclusion from reference-case analyses (DDD could not be adjudicated). In addition, several RCTs used an A1C threshold of 6.5% to define adequate control; this threshold differs from the threshold commonly used in Canadian practice (7.0%).

Figure 1: Summary of Risk of Bias Assessment



Data Synthesis

NMAs were conducted for 18 outcomes for the reference case of class comparisons. The choice of outcomes for NMA was based on clinical relevance and the sufficiency of the data available to derive robust and consistent network models. Selected class comparisons of interest are presented. The full results for all class comparisons, as well as model diagnostics for the fixed- and random-effects models are presented in Appendix 9. Results from the dose-stratified and individual-drug (intra-class) NMAs are summarized in Appendix 10 and Appendix 11 respectively. Any additional sensitivity analyses are also discussed in context with outcomes in section 6.3.2. Full NMA results for all sensitivity analyses are available in Appendix 12.

For each outcome, the mean differences or odds ratios from the NMA of the reference case are provided, comparing each drug class added on to metformin background therapy with metformin monotherapy. Results for select head-to-head comparisons of interest (sulfonylurea, SGLT-2 and DPP-4 inhibitors, GLP-1 agonists, and insulins) are presented for each outcome for which data were available. The full results for all class comparisons random-effects model results, as well as model diagnostics for the fixed- and random-effects models, are presented in Appendix 9. Results from the dose-stratified and individual-drug NMAs are summarized in Appendix 10 and Appendix 11 respectively. Any additional sensitivity analyses are also discussed in context with outcomes in section 6.3.2. Full NMA results for all sensitivity analyses are available in Appendix 12.

Table 7: Overview of Evidence and Analyses Performed

Outcome	Network Meta-Analysis	Network Meta-Analysis Model	Meta-Analysis Only	Descriptive Analysis Only
A1C	Y	Normal likelihood, identity link	–	–
Nonsevere hypoglycemia	Y	Binomial likelihood, Logit link	–	–
Severe hypoglycemia	Y	Binomial likelihood, Logit link	–	–
Nocturnal hypoglycemia	Y	Binomial likelihood, Logit link	–	–
Body mass index	Y	Normal likelihood, identity link	–	–
Weight	Y	Normal likelihood, identity link	–	–
Systolic blood pressure	Y	Normal likelihood, identity link	–	–
Diastolic blood pressure	Y	Normal likelihood, identity link	–	–
LDL cholesterol	Y	Normal likelihood, identity link	–	–
HDL cholesterol	Y	Normal likelihood, identity link	–	–
Total adverse events	Y	Normal likelihood, identity link	–	–
Serious adverse events	Y	Binomial likelihood, Logit link	–	–
Withdrawals due to adverse events	Y	Binomial likelihood, Logit link	–	–
Urogenital adverse events	Y	Binomial likelihood, Logit link	–	–
Renal adverse events	Y	Binomial likelihood, Logit link	–	–
Unstable angina	Y	Binomial likelihood, Logit link	–	–
Hospitalization for unstable angina	–	Binomial likelihood, Logit link	–	Y
Heart failure	–	–	Y	Y
Transient ischemic attack	Y	–	–	–
Hospitalization for heart failure	–	Binomial likelihood, Logit link	–	–
Fractures	Y	–	–	–
Major adverse cardiovascular events	–	Binomial likelihood, Logit link	–	Y
All-cause mortality	–	–	Y	Y
Cardiovascular mortality	–	–	Y	Y
Nonfatal stroke	–	–	Y	Y
Fatal stroke	–	–	–	Y
Nonfatal myocardial infarction	–	–	Y	Y
Fatal myocardial infarction	–	–	–	–
Ketoacidosis	–	–	–	Y
Pancreatitis	–	–	–	Y
Bladder cancer	–	–	–	Y
Pancreatic cancer	–	–	–	Y
Coronary revascularization procedures	–	–	–	Y

A1C = glycated hemoglobin, Y = yes.

None of the included RCTs reported use of bolus insulin. NMA could not be conducted for a number of outcomes due to low event rates observed in many studies. Data from several RCTs could not be included in any of the network or pairwise meta-analyses because there

was variation in the methods of reporting for key outcomes, there were zero events in one or both study arms (not robust with continuity corrections), or the study compared two treatments within the same drug class.

Table 8 provides the reference rates for the index node (metformin monotherapy) and the sample size for each NMA conducted. For binary outcomes, the reference rate presents the probability of events in the reference group (metformin monotherapy) estimated from the NMA model. For continuous outcomes, the reference rate represents the mean and standard deviation (SD) in the reference group (metformin monotherapy) estimated from the NMA model.

Table 8: Reference Rates for the Index Node and Sample Sizes for Analysis Populations — Reference Case NMA

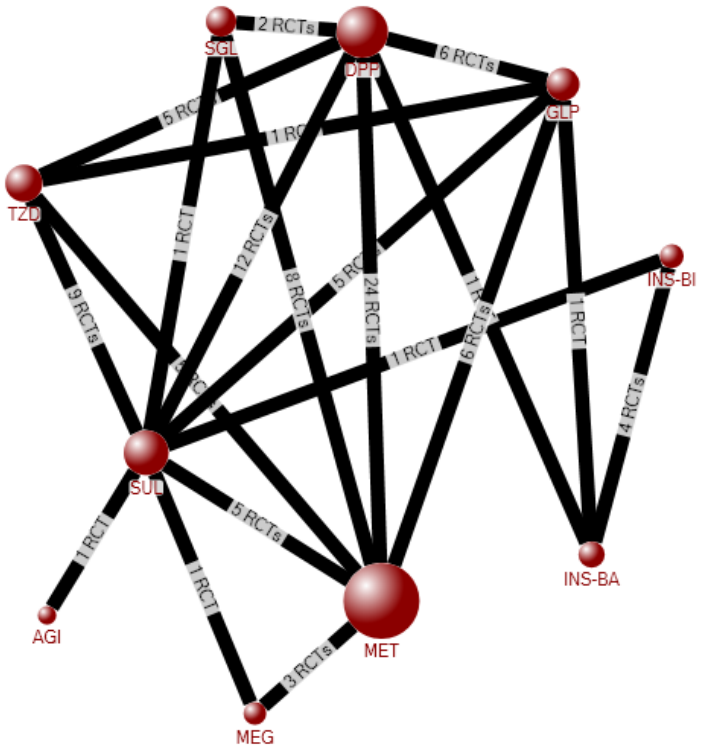
Outcome	Number of RCTs Included in Reference Case NMA	Reference Rate for Metformin Monotherapy (Index Node)	Sample Size (N)
Continuous Outcomes (MD ± SD)			
A1C	84	0.13 ± 0.02	34,895
Body mass index	14	–0.78 ± 0.11	2,252
Weight	70	–1.16 ± 0.12	32,000
Systolic blood pressure	29	–0.44 ± 0.30	12,911
Diastolic blood pressure	26	–0.29 ± 0.46	11,843
LDL cholesterol	31	0.019 ± 0.017	14,190
HDL cholesterol	36	0.060 ± 0.034	15,047
Dichotomous Outcomes (OR [95% CrI])			
Nonsevere hypoglycemia	67	0.015 (0.012 to 0.020)	27,413
Severe hypoglycemia	48	0.0028 (0.0013 to 0.0051)	23,287
Nocturnal hypoglycemia	7	0.030 (0.018 to 0.046)	1,595
Total adverse events	57	0.48 (0.46 to 0.51)	28,763
Serious adverse events	66	0.023 (0.018 to 0.029)	34,339
Withdrawals due to adverse events	78	0.029 (0.024 to 0.034)	35,933
Urogenital adverse events	21	0.027 (0.020 to 0.034)	12,490
Unstable Angina	17	0.0048 (0.0019 to 0.0102)	11,676
Transient Ischemic Attack	14	0.0067 (0.0017 to 0.0178)	10,389
Fractures	15	0.0031 (0.0012 to 0.0062)	6,767

A1C = glycated hemoglobin; CrI = credible interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MD = mean difference; NMA = network meta-analysis; OR = odds ratio; RCTs = randomized controlled trials; SD = standard deviation.

Glycated Hemoglobin

Eighty-four RCTs[14-16,22,25,28,30-33,44-46,48,52,55,59,61,67,72,74,79,81,88,92,93,95,99,105,107,109,110,112,113,115,117,122,125,127,130,134-138,143,145,146,149,154,157,159,162,163,165,166,168,170,174-176,181,182,185,186,188-190,192,199,206,207,209,212,214,220-222,224-226,232,241,253] that reported mean change from baseline in A1C were included in the reference-case NMA. Data were available for all drug classes. Figure 2 shows an example of the treatment network, with each treatment node representing a drug class or metformin monotherapy for this outcome.

Figure 2: Treatment Network for A1C



The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected treatment class comparisons are presented in Table 9. Relative to metformin monotherapy, all of the selected classes significantly reduced mean difference in the change from baseline for A1C. When the classes were compared with each other, DPP-4 inhibitors did not decrease A1C as much as sulfonylureas or GLP-1 agonists.

Table 9: Glycated Hemoglobin (%) — Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI) Reference Case	MD (95% CrI) Sensitivity
MET+SUL	MET	**–0.70 (–0.83 to –0.58)**	**–0.93 (–1.24 to –0.62)**
MET+DPP-4		**–0.58 (–0.68 to –0.48)**	**–0.92 (–1.23 to –0.62)**
MET+SGLT-2		**–0.67 (–0.84 to –0.49)**	–0.60 (–1.26 to 0.07)
MET+GLP-1		**–0.88 (–1.05 to –0.71)**	**–0.73 (–1.15 to –0.29)**
MET+INS-BA		**–0.85 (–1.16 to –0.53)**	**–0.93 (–1.76 to –0.09)**
MET+INS-BI		**–0.94 (–1.41 to –0.48)**	**–1.27 (–2.37 to –0.15)**
MET+DPP-4	MET+SUL	**0.12 (0.01 to 0.24)**	0.00 (–0.34 to 0.35)
MET+SGLT-2		0.04 (–0.16 to 0.24)	0.33 (–0.40 to 1.06)
MET+GLP-1		–0.18 (–0.35 to 0.00)	0.20 (–0.28 to 0.70)
MET+INS-BA		–0.15 (–0.45 to 0.17)	0.00 (–0.87 to 0.87)

Treatment	Reference	MD (95% CrI) Reference Case	MD (95% CrI) Sensitivity
MET+INS-BI		–0.24 (–0.69 to 0.21)	–0.35 (–1.47 to 0.81)
MET+SGLT-2	MET+DPP-4	–0.09 (–0.28 to 0.10)	0.33 (–0.40 to 1.05)
MET+GLP-1		**–0.30 (–0.46 to –0.13)**	0.20 (–0.31 to 0.72)
MET+INS-BA		–0.27 (–0.57 to 0.04)	0.00 (–0.89 to 0.87)
MET+INS-BI		–0.36 (–0.82 to 0.10)	–0.35 (–1.48 to 0.82)
MET+GLP-1	MET+SGLT-2	–0.21 (–0.45 to 0.03)	–0.13 (–0.91 to 0.66)
MET+INS-BA		–0.18 (–0.53 to 0.18)	–0.33 (–1.39 to 0.74)
MET+INS-BI		–0.27 (–0.76 to 0.22)	–0.68 (–1.95 to 0.62)
MET+INS-BA	MET+GLP-1	0.03 (–0.27 to 0.33)	–0.20 (–0.92 to 0.50)
MET+INS-BI		–0.06 (–0.53 to 0.41)	–0.55 (–1.57 to 0.49)
MET+INS-BI	MET+INS-BA	–0.09 (–0.56 to 0.37)	–0.35 (–1.07 to 0.40)
Random-effects model	Residual deviance	166 vs. 179 data points	48.77 vs. 55 data points
	Deviance information criteria	–170.795	–25.194

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; MD = mean difference; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea, vs. = versus.
Note: Bolded values indicate statistically significant results.

A sensitivity analysis was conducted to exclude treatment combinations with metformin background therapy doses below the DDD of 2,000 mg daily. There were 27 RCTs[46,61,67,72,74,81,88,93,95,127,135,138,157,159,174,175,181,186,206,207,209,212,220,221,224,226,241] that reported this dose of metformin (N = 9,011) (Table 9, full results available in Appendix 12. Results relative to metformin monotherapy were robust in the sensitivity analysis except for the SGLT-2 inhibitors which did not significantly reduce A1C relative to metformin. None of classes significantly lowered A1C when compared with each other in sensitivity analysis.

Hypoglycemia

Severe Hypoglycemia

Severe hypoglycemia was typically defined as an event requiring third-party assistance. There were 48 RCTs[14,15,19,28,45,48-50,55,58,61,74,99,105,107,109,112,130,131,134,135,138,143,145,148,149,154,162,163,165-167,176,181-183,190,192,205,206,209,220-222,224,226,232,253] that reported severe hypoglycemia and were included in the reference-case NMA.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected treatment classes are presented in Table 10. Only metformin plus a sulfonylurea significantly increased severe hypoglycemia when compared with metformin monotherapy. When compared with each other, the GLP-1 agonists and the SGLT-2 and DPP-4 inhibitors significantly reduced the risk of severe hypoglycemia relative to sulfonylureas.

Table 10: Severe Hypoglycemia — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	**6.40 (2.24,17.51)**
MET+DPP-4		0.91 (0.34,2.41)
MET+SGLT-2		0.61 (0.13,2.36)
MET+GLP-1		1.80 (0.63,5.96)
MET+INS-BA		3.08 (0.65,27.65)
MET+INS-BI		3.36 (0.33,91.77)
MET+DPP-4	MET+SUL	**0.14 (0.07,0.26)**
MET+SGLT-2		**0.09 (0.02,0.44)**
MET+GLP-1		**0.29 (0.09,0.89)**
MET+INS-BA		0.52 (0.10,2.83)
MET+INS-BI		0.55 (0.06,8.71)
MET+SGLT-2	MET+DPP-4	0.66 (0.15,2.98)
MET+GLP-1		2.02 (0.68,6.16)
MET+INS-BA		3.61 (0.74,20.31)
MET+INS-BI		3.92 (0.42,60.32)
MET+GLP-1	MET+SGLT-2	2.97 (0.61,17.70)
MET+INS-BA		5.25 (0.73,56.37)
MET+INS-BI		5.54 (0.44,139.60)
MET+INS-BA	MET+GLP-1	1.73 (0.36,12.74)
MET+INS-BI		1.91 (0.18,34.90)
MET+INS-BI	MET+INS-BA	1.04 (0.16,11.39)
Random-effects model	Residual deviance	57.31 vs. 100 data points
	Deviance information criteria	299.795

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.
Note: Bolded values indicate statistically significant results.

Non-Severe Hypoglycemia

There were 67 RCTs[14-16,19,28,30,33,37,44,45,48,52,55,58,59,61,72,74,79,88,92,93,99,105,107,109,112,113,115,130,135-138,141,143,145,154,157,162,163,170,174,176,181-183,185,186,188-190,192,206,207,209,212,214,220-222,224-226,232,241,253] that reported at least one episode of nonsevere hypoglycemia and were included in the reference-case NMA. There was variability in the clinical definitions of this outcome across the included RCTs. Similar to previous reviews, the most common differences were the specific blood glucose threshold for hypoglycemia and whether patients were required to validate symptoms of hypoglycemia with self-monitoring of blood glucose.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model for selected treatment class comparisons are presented in Table 11. Compared with metformin monotherapy, the odds of nonsevere hypoglycemia were higher with sulfonylurea and with basal and biphasic insulin. When the classes were compared, all classes except biphasic insulin significantly reduced odds of nonsevere hypoglycemia relative to sulfonylurea.

Relative to DPP-4 and SGLT-2 inhibitors and GLP-1 agonists, basal and biphasic insulin significantly increased odds of nonsevere hypoglycemia. Biphasic insulin significantly increased odds of nonsevere hypoglycemia relative to basal insulin.

Table 11: Non-Severe Hypoglycemia — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI) Reference Case	OR (95% CrI) Sensitivity
MET+SUL	MET	**7.59 (5.25 to 11.22)**	**13.49 (8.26 to 23.20)**
MET+DPP-4		0.77 (0.55 to 1.10)	0.97 (0.62 to 1.56)
MET+SGLT-2		1.00 (0.62 to 1.58)	1.22 (0.68 to 2.12)
MET+GLP-1		0.75 (0.46 to 1.25)	0.93 (0.57 to 1.56)
MET+INS-BA		**3.18 (1.73 to 5.80)**	**4.56 (2.57 to 8.25)**
MET+INS-BI		**6.92 (3.34 to 14.52)**	**10.81 (5.33 to 21.66)**
MET+DPP-4	MET+SUL	**0.10 (0.07 to 0.14)**	**0.07 (0.05 to 0.10)**
MET+SGLT-2		**0.13 (0.08 to 0.21)**	**0.09 (0.04 to 0.17)**
MET+GLP-1		**0.10 (0.06 to 0.16)**	**0.07 (0.04 to 0.11)**
MET+INS-BA		**0.42 (0.24 to 0.72)**	**0.34 (0.21 to 0.55)**
MET+INS-BI		0.91 (0.46 to 1.77)	0.80 (0.44 to 1.41)
MET+SGLT-2	MET+DPP-4	1.29 (0.79 to 2.07)	1.25 (0.67 to 2.20)
MET+GLP-1		0.97 (0.60 to 1.56)	0.95 (0.58 to 1.56)
MET+INS-BA		**4.13 (2.35 to 7.05)**	**4.68 (2.87 to 7.65)**
MET+INS-BI		**8.96 (4.47 to 17.61)**	**11.10 (5.94 to 19.93)**
MET+GLP-1	MET+SGLT-2	0.75 (0.41 to 1.41)	0.76 (0.38 to 1.59)
MET+INS-BA		**3.19 (1.63 to 6.38)**	**3.74 (1.85 to 8.06)**
MET+INS-BI		**6.96 (3.17 to 15.54)**	**8.88 (4.00 to 20.71)**
MET+INS-BA	MET+GLP-1	**4.25 (2.34 to 7.52)**	**4.92 (2.87 to 8.20)**
MET+INS-BI		**9.25 (4.40 to 19.24)**	**11.63 (5.92 to 22.49)**
MET+INS-BI	MET+INS-BA	**2.18 (1.24 to 3.85)**	**2.38 (1.43 to 3.80)**
Random-effects model	Residual deviance	128.8 vs. 140 data points	94.33 vs. 98 data points
	Deviance information criteria	678.986	463.356

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.
Note: Bolded values indicate statistically significant results.

A sensitivity analysis included only studies that reported sufficient information to allow the classification of nonsevere hypoglycemia based on the DC criteria for mild or moderate hypoglycemia. A total of 48 RCTs[14,15,19,28,30,33,37,44,45,48,58,59,61,72,74,88,92,105,107,112,113,115,130,135,136,138,143,162,163,176,181-183,186,189,192,206,207,212,214,220-222,224,226,232,241,253] reported this outcome (N = 17,827) (Table 11). The rate for the reference class was 0.012 (95% CrI, 0.007 to 0.015). Results for the selected class comparisons were robust to the sensitivity analysis; however, the magnitude of the effect estimates increased in all statistically significant comparisons.

Nocturnal Hypoglycemia

There were seven RCTs[14,107,130,206,214,224,226] that reported nocturnal hypoglycemia and were included in the reference-case NMA. Two RCTs[206,214] comparing metformin with

meglitinides could not be connected to the network and were excluded from the NMA. Data were available for DPP-4 inhibitors, GLP-1 agonists, and both basal and biphasic insulin.

Consistency could not be evaluated, as the evidence network included only two-arm studies. The results of the random-effects NMA model of selected class comparisons are presented in Table 12. Based on a limited number of studies reporting this outcome, basal and biphasic insulin both had significantly higher odds of nocturnal hypoglycemia relative to DPP-4 inhibitors. Odds of nocturnal hypoglycemia events were also significantly higher with biphasic insulin when compared with GLP-1 agonists. No studies of metformin monotherapy or SGLT-2 inhibitors in the evidence network reported nocturnal hypoglycemia as an outcome. Given the very low occurrence of nocturnal hypoglycemia across all trials, the power to detect any differences between drugs was extremely limited.

Table 12: Nocturnal Hypoglycemia — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+GLP-1	MET+DPP-4	1.45 (0.44,5.10)
MET+INS-BA		**5.92 (1.82,20.08)**
MET+INS-BI		**9.72 (2.37,41.27)**
MET+INS-BA	MET+GLP-1	4.09 (0.73,22.49)
MET+INS-BI		**6.74 (1.02,43.42)**
MET+INS-BI	MET+INS-BA	1.64 (0.77,3.65)
Random-effects model	Residual deviance	10.97 vs. 10 data points
	Deviance information criteria	61.45

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; OR = odds ratio; vs. = versus.
Note: Bolded values indicate statistically significant results.

Body Mass Index and Weight

Body Mass Index

There were 14 RCTs[25,46,67,72,88,93,95,115,117,122,190,209,212,220] that reported change from baseline in BMI and were included in the reference-case NMA. Data were available for all drug classes, with the exception of SGLT-2 inhibitors and biphasic insulin.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 13. Compared with metformin monotherapy, none of the classes significantly decreased mean difference in change of BMI from baseline.

When the treatment classes were compared, GLP-1 agonists significantly decreased mean changes from baseline BMI when compared with sulfonylureas (mean difference –1.91 (95% CrI, –3.39 to
–0.49). There was a significantly higher mean difference in change from baseline BMI in basal insulin relative to GLP-1 inhibitors.

Table 13: Body Mass Index — Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
MET+SUL	MET	0.80 (–0.36 to 2.08)
MET+DPP-4		–0.33 (–1.30 to 0.58)
MET+GLP-1		–1.11 (–2.54 to 0.38)
MET+INS-BA		2.57 (–1.04 to 6.20)
MET+DPP-4	MET+SUL	–1.13 (–2.78 to 0.32)
MET+GLP-1		**–1.91 (–3.39 to –0.49)**
MET+INS-BA		1.77 (–1.86 to 5.41)
MET+GLP-1	MET+DPP-4	–0.78 (–2.43 to 1.04)
MET+INS-BA		2.89 (–0.78 to 6.61)
MET+INS-BA	MET+GLP-1	**3.68 (0.36 to 7.01)**
Random-effects model	Residual deviance	28.3 vs. 28 data points
	Deviance information criteria	41.431

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; MD = mean difference; MET = metformin; SUL = sulfonylurea; vs. = versus.
Note: Bolded values indicate statistically significant results.

Body Weight

There were 70 RCTs[14-16,22,28,31-33,37,44,45,48,52,55,58,59,61,67,72,74,81,88,93,95,99,105,107,109,110,112,113,122,125,130,134,135,137,138,143,145,146,149,154,157,159,162,163,165,166,170,174-176,181,182,186,188,190,199,206,207,209,214,220-222,224,226,232,253] that reported changes from baseline in body weight (in kilograms) and were included in the reference-case NMA. Data were available for all drug classes.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected treatment class comparisons are presented in Table 14.

Relative to metformin monotherapy, sulfonylurea and basal insulin combinations with metformin significantly increased mean body weight (range 2.1 kg to 2.8 kg), with no significant differences between these classes. SGLT-2 inhibitors and GLP-1 agonists added on to metformin were associated with significant reductions in mean body weight relative to metformin monotherapy (range –1.4 kg to –2.2 kg).

When the treatment classes were compared, all noninsulin treatments added to metformin resulted in significant reductions in mean body weight relative to sulfonylurea (range –1.9 kg to –4.3 kg). SGLT-2 inhibitors and GLP-1 agonists also resulted in significant reductions in mean body weight relative to DPP-4 inhibitors, while basal insulin resulted in significant increases in mean body weight change from baseline. Basal and biphasic insulin added to metformin significantly increased mean body weight change from baseline relative to SGLT-2 inhibitors and GLP-1 agonists.

Table 14: Body Weight — Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
MET+SUL	MET	**2.11 (1.59 to 2.63)**
MET+DPP-4		0.18 (–0.22 to 0.58)
MET+SGLT-2		**–2.21 (–2.75 to –1.67)**
MET+GLP-1		**–1.44 (–2.07 to –0.81)**
MET+INS-BA		**2.76 (1.56 to 4.01)**
MET+INS-BI		2.91 (0.85 to 5.04)
MET+DPP-4	MET+SUL	**–1.93 (–2.37 to –1.49)**
MET+SGLT-2		**–4.32 (–5.00 to –3.66)**
MET+GLP-1		**–3.55 (–4.26 to –2.85)**
MET+INS-BA		0.65 (–0.57 to 1.95)
MET+INS-BI		0.80 (–1.26 to 2.96)
MET+SGLT-2	MET+DPP-4	**–2.39 (–2.98 to –1.80)**
MET+GLP-1		**–1.62 (–2.25 to –0.99)**
MET+INS-BA		**2.59 (1.41 to 3.82)**
MET+INS-BI		2.73 (0.70 to 4.84)
MET+GLP-1	MET+SGLT-2	0.78 (–0.02 to 1.57)
MET+INS-BA		**4.98 (3.68 to 6.31)**
MET+INS-BI		**5.13 (3.03 to 7.30)**
MET+INS-BA	MET+GLP-1	**4.20 (3.03 to 5.40)**
MET+INS-BI		**4.35 (2.33 to 6.46)**
MET+INS-BI	MET+INS-BA	0.15 (–1.54 to 1.82)
Random-effects model	Residual deviance	138.4 vs. 148 data points
	Deviance information criteria	307.531

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MD = mean difference; MET = metformin; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.
Note: Bolded values indicate statistically significant results.

Blood Pressure

Systolic Blood Pressure

There were 29 RCTs[14,15,32,37,44,45,52,55,59,67,72,107,109,112,117,125,143,145,149,153,157,159,188,209,220,221,224,232,253] that reported change from baseline in systolic blood pressure and were included in the reference-case NMA. Data were available for all drug classes.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected treatment class comparisons are presented in Table 15. SGLT-2 inhibitors and GLP-1 agonists added to metformin resulted in a significantly lower mean difference in the change from baseline for systolic blood pressure relative to metformin monotherapy, sulfonylureas, and DPP-4 inhibitors. Basal insulin added to metformin

resulted in a significantly higher mean difference in the change from baseline for systolic blood pressure relative to SGLT-2 inhibitors.

Table 15: Systolic Blood Pressure — Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
MET+SUL	MET	0.28 (–1.54 to 2.06)
MET+DPP-4		–1.04 (–2.34 to 0.22)
MET+SGLT-2		**–4.06 (–5.24 to –2.89)**
MET+GLP-1		**–2.79 (–4.57 to –1.07)**
MET+INS-BA		1.01 (–3.04 to 5.16)
MET+INS-BI		0.15 (–5.62 to 5.93)
MET+DPP-4	MET+SUL	–1.31 (–3.19 to 0.57)
MET+SGLT-2		**–4.33 (–6.17 to -2.47)**
MET+GLP-1		**–3.07 (–5.35 to –0.78)**
MET+INS-BA		0.73 (–3.61 to 5.10)
MET+INS-BI		–0.13 (–6.10 to 5.84)
MET+SGLT-2	MET+DPP-4	**–3.02 (–4.39 to –1.61)**
MET+GLP-1		**–1.75 (–3.46 to –0.02)**
MET+INS-BA		2.05 (–1.85 to 6.03)
MET+INS-BI		1.18 (–4.47 to 6.87)
MET+GLP-1	MET+SGLT-2	1.27 (–0.71 to 3.21)
MET+INS-BA		**5.07 (0.96 to 9.21)**
MET+INS-BI		4.20 (–1.61 to 10.06)
MET+INS-BA	MET+GLP-1	3.80 (–0.43 to 8.12)
MET+INS-BI		2.94 (–2.95 to 8.85)
MET+INS-BI	MET+INS-BA	–0.86(–4.96 to 3.22)
Random-effects model	Residual deviance	58.75 vs. 62 data points
	Deviance information criteria	208.403

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MD = mean difference; MET = metformin; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.
Note: Bolded values indicate statistically significant results.

Diastolic Blood Pressure

There were 26 RCTs[14,15,32,44,45,52,55,59,72,102,109,112,117,125,130,143,145,149,159,175,181,188,209,221,224,253] that reported change from baseline in diastolic blood pressure and were included in the reference-case NMA. Data were available for all drug classes. Two RCTs[130,224] comparing basal and biphasic insulins were disconnected from the evidence network and could not be included in the NMA.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 16. Relative to metformin monotherapy, all treatments added to metformin, except sulfonylurea, resulted in significantly lower mean differences in the change from baseline for diastolic blood pressure. When the classes were compared, SGLT-2 inhibitors added to metformin

significantly lowered the mean difference in the change from baseline for diastolic blood pressure relative to sulfonylurea and DPP-4 inhibitors.

Table 16: Diastolic Blood Pressure — Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
MET+SUL	MET	–0.30 (–1.43 to 0.80)
MET+DPP-4		**–1.07 (–1.87 to –0.21)**
MET+SGLT-2		**–2.22 (–2.99 to –1.41)**
MET+GLP-1		**–1.09 (–2.13 to –0.01)**
MET+DPP-4	MET+SUL	–0.77 (–1.89 to 0.42)
MET+SGLT-2		**–1.92 (–3.05 to –0.73)**
MET+GLP-1		–0.79 (–2.11 to 0.58)
MET+SGLT-2	MET+DPP-4	**–1.15 (–2.15 to –0.14)**
MET+GLP-1		–0.02 (–1.04 to 0.99)
MET+GLP-1	MET+SGLT-2	1.13 (–0.11 to 2.36)
Random-effects model	Residual deviance	49.78 vs. 53 data points
	Deviance information criteria	141.401

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; MD = mean difference; MET = metformin; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.
Note: Bolded values indicate statistically significant results.

No other blood pressure outcomes were reported.

Cholesterol

Low-Density Lipoprotein Cholesterol

There were 31 RCTs[14,15,37,45,55,59,67,72,99,107,109,110,125,143,145,149,159,163,170,175,176,185,190,199,206,207,212,214,220,221,253] that reported change from baseline in low-density lipoprotein (LDL) cholesterol and were included in the reference-case NMA. Data were available for all drug classes with the exception of biphasic insulin.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 17. Relative to metformin monotherapy, none of the classes added to metformin resulted in significantly lower mean differences in the change from baseline for LDL cholesterol. SGLT-2 inhibitors added to metformin resulted in significant increases in the mean difference in the change from baseline for LDL cholesterol relative to metformin alone and significant increases relative to DPP-4 inhibitors added to metformin. The mean difference in the change from baseline for LDL cholesterol with basal insulin was significantly lower with basal insulin when compared with SGLT-2 inhibitors.

Table 17: LDL Cholesterol — Mean Differences in the Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
MET+SUL	MET	0.06 (–0.09,0.20)
MET+DPP-4		–0.02 (–0.12,0.08)
MET+SGLT-2		**0.14 (0.02,0.27)**
MET+GLP-1		–0.02 (–0.17,0.13)
MET+INS-BA		–0.18 (–0.47,0.11)
MET+DPP-4	MET+SUL	–0.07 (–0.22,0.07)
MET+SGLT-2		0.08 (–0.10,0.27)
MET+GLP-1		–0.08 (–0.27,0.11)
MET+INS-BA		–0.24 (–0.55,0.07)
MET+SGLT-2	MET+DPP-4	**0.16 (0.02,0.30)**
MET+GLP-1		0.00 (–0.15,0.15)
MET+INS-BA		–0.16 (–0.43,0.11)
MET+GLP-1	MET+SGLT-2	–0.16 (–0.35,0.02)
MET+INS-BA		**–0.32 (–0.63,–0.02)**
MET+INS-BA	MET+GLP-1	–0.16(–0.45,0.13)
Random-effects model	Residual deviance	71.91 vs. 68 data points
	Deviance information criteria	–131.999

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; MD = mean difference; MET = metformin; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Note: Bolded values indicate statistically significant results.

High-Density Lipoprotein Cholesterol

There were 36 RCTs[14,15,22,32,37,45,46,55,59,67,72,99,107,109,110,125,143,145,149,159,163,170,175,176,185,190,192,199,206,207,209,212,214,220,221,253] that reported change from baseline in high-density lipoprotein (HDL) cholesterol and were included in the reference-case NMA. Data were available for all drug classes with the exception of biphasic insulin.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 18. SGLT-2 inhibitors added to metformin resulted in significant increases in the change in mean difference from baseline for HDL cholesterol relative to metformin alone, and to sulfonylureas, DPP-4 inhibitors, and GLP-1 agonists added to metformin.

Table 18: HDL Cholesterol — Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
MET+SUL	MET	–0.02 (–0.06 to 0.01)
MET+DPP-4		–0.01 (–0.03 to 0.02)
MET+SGLT-2		**0.06 (0.03 to 0.09)**
MET+GLP–1		–0.02 (–0.06 to 0.02)
MET+INS-BA		–0.02 (–0.09 to 0.06)

Treatment	Reference	MD (95% CrI)
MET+INS-BI		0.03 (–0.05 to 0.11)
MET+DPP-4	MET+SUL	0.02 (–0.01 to 0.05)
MET+SGLT-2		**0.09 (0.05 to 0.13)**
MET+GLP-1		0.01 (–0.04 to 0.05)
MET+INS-BA		0.01 (–0.07 to 0.08)
MET+INS-BI		0.05 (–0.02 to 0.12)
MET+SGLT-2	MET+DPP-4	**0.07 (0.04 to 0.10)**
MET+GLP-1		–0.01 (–0.04 to 0.03)
MET+INS-BA		–0.01 (–0.08 to 0.06)
MET+INS-BI		0.03 (–0.04 to 0.11)
MET+GLP-1	MET+SGLT-2	**–0.08 (–0.12 to –0.03)**
MET+INS-BA		–0.08 (–0.16 to 0.00)
MET+INS-BI		–0.04 (–0.12 to 0.05)
MET+INS-BA	MET+GLP-1	0.00 (–0.08 to 0.08)
MET+INS-BI		0.04 (–0.04 to 0.13)
MET+INS-BI	MET+INS-BA	0.04 (–0.06 to 0.15)
Random-effect model	Residual deviance	84.6 vs. 78 data points
	Deviance information criteria	–333.356

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MD = mean difference; MET = metformin; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Note: Bolded values indicate statistically significant results.

Adverse Events

Total Adverse Events

There were 57 RCTs[14-16,28,30,33,37,44,45,48,52,59,61,67,74,92,99,105,107,109,112,113,115,134,136,137,141,145,146,149,157,162,165,166,170,174-176,181,182,185,186,188,191,192,199,206,207,209,212,221,222,224-226,232,243] that reported number of total adverse events and were included in the reference-case NMA. Data were available for all drug classes.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 19. Compared with metformin monotherapy, GLP-1 agonists and basal or biphasic insulin significantly increased the total number of adverse events. When the classes were compared, basal and biphasic insulin significantly increased total adverse events when compared with all other classes. GLP-1 agonists significantly increased total adverse events when compared with DPP-4 and SGLT-2 inhibitors.

Table 19: Total Adverse Events — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	1.14 (0.99 to 1.32)
MET+DPP-4		0.97 (0.87 to 1.08)
MET+SGLT-2		1.03 (0.88 to 1.21)
MET+GLP-1		**1.38 (1.12 to 1.68)**
MET+INS-BA		**2.20 (1.47 to 3.33)**
MET+INS-BI		**2.32 (1.42 to 3.79)**
MET+DPP-4	MET+SUL	0.85 (0.76 to 0.95)
MET+SGLT-2		0.90 (0.75 to 1.10)
MET+GLP-1		1.20 (0.96 to 1.50)
MET+INS-BA		**1.93 (1.29 to 2.89)**
MET+INS-BI		**2.03 (1.26 to 3.27)**
MET+SGLT-2	MET+DPP-4	1.07 (0.90 to 1.27)
MET+GLP-1		**1.42 (1.16 to 1.73)**
MET+INS-BA		**2.28 (1.54 to 3.37)**
MET+INS-BI		**2.39 (1.48 to 3.87)**
MET+GLP-1	MET+SGLT-2	**1.33 (1.04 to 1.71)**
MET+INS-BA		**2.13 (1.39 to 3.30)**
MET+INS-BI		**2.25 (1.36 to 3.74)**
MET+INS-BA	MET+GLP-1	**1.60 (1.04 to 2.49)**
MET+INS-BI		**1.69 (1.01 to 2.85)**
MET+INS-BI	MET+INS-BA	1.06 (0.67 to 1.63)
Random-effects model	Residual deviance	118.5 vs. 120 data points
	Deviance information criteria	828.862

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Note: Bolded values indicate statistically significant results.

Serious Adverse Events

There were 66 RCTs [14-16,28,30,33,37,44,45,48,52,59,61,67,74,92,99,105,107,109,110,112,113,115,125,130,134,136-138,141,143,145,146,149,154,157,159,162,163,165,166,170,174-176,181-183,185,186,188-190,199,207,209,212,214,221,222,224,225,232,243,253] that reported serious adverse events and were included in the reference-case NMA. Data were available for all drug classes.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 20. Compared with metformin monotherapy and with each other, none of the classes significantly increased or decreased odds of serious adverse events.

Table 20: Serious Adverse Events — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	0.96 (0.76 to 1.21)
MET+DPP-4		0.91 (0.72 to 1.15)
MET+SGLT-2		1.11 (0.83 to 1.51)
MET+GLP-1		1.05 (0.71 to 1.51)
MET+INS-BA		1.48 (0.63 to 3.74)
MET+INS-BI		1.73 (0.42 to 8.43)
MET+DPP-4	MET+SUL	0.95 (0.82 to 1.10)
MET+SGLT-2		1.17 (0.87 to 1.55)
MET+GLP-1		1.10 (0.74 to 1.61)
MET+INS-BA		1.54 (0.67 to 3.83)
MET+INS-BI		1.83 (0.45 to 8.70)
MET+SGLT-2	MET+DPP-4	1.23 (0.91 to 1.66)
MET+GLP-1		1.16 (0.80 to 1.66)
MET+INS-BA		1.63 (0.72 to 4.02)
MET+INS-BI		1.93 (0.47 to 9.13)
MET+GLP-1	MET+SGLT-2	0.94 (0.60 to 1.49)
MET+INS-BA		1.33 (0.55 to 3.34)
MET+INS-BI		1.57 (0.38 to 7.77)
MET+INS-BA	MET+GLP-1	1.41 (0.61 to 3.46)
MET+INS-BI		1.68 (0.39 to 7.83)
MET+INS-BI	MET+INS-BA	1.18 (0.37 to 4.11)
Random-effects Model	Residual Deviance	129.3 vs. 140 data points
	Deviance Information Criteria	701.988

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Withdrawals Due to Adverse Events

There were 78 RCTs[14-16,25,28,30,31,33,37,44,45,48,52,55,59,61,67,72,74,88,92,93,99,105,107,109,110,112,113,115,117,122,125,130,134-138,141,143,145,146,149,157,159,162,163,165,166,170,174-176,181-183,185,186,188-190,192,199,206,207,209,212,220-222,224-226,232,241,243,253] that reported number of withdrawals due to adverse events. Of these, 70 were included in the reference-case NMA. Seven RCTs[28,31,37,183,220,226,243] were not included in the analysis because there were zero events in all study arms. A single RCT[25] had to be removed from the analysis, as it was the only study reporting alpha-glucosidase inhibitors (zero events for alpha-glucosidase inhibitors versus one event for sulfonylurea).

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 21. Relative to metformin monotherapy, sulfonylureas, DPP-4 inhibitors, and basal insulin, GLP-1 agonists were the only class added to metformin that significantly increased the odds of withdrawals due to

adverse events. Biphasic insulin significantly increased the odds of withdrawals due to adverse events relative to basal insulin.

Table 21: Withdrawals Due to Adverse Events — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	0.74 (0.51 to 1.11)
MET+DPP-4		0.78 (0.56 to 1.09)
MET+SGLT-2		1.00 (0.61 to 1.66)
MET+GLP-1		**1.81 (1.12 to 2.99)**
MET+INS-BA		0.33 (0.07 to 1.40)
MET+INS-BI		3.27 (0.41 to 54.86)
MET+DPP-4	MET+SUL	1.04 (0.76 to 1.45)
MET+SGLT-2		1.34 (0.76 to 2.39)
MET+GLP-1		**2.42 (1.46 to 4.10)**
MET+INS-BA		0.45 (0.09 to 1.90)
MET+INS-BI		4.38 (0.56 to 75.00)
MET+SGLT-2	MET+DPP-4	1.28 (0.74 to 2.22)
MET+GLP-1		**2.33 (1.44 to 3.79)**
MET+INS-BA		0.43 (0.09 to 1.78)
MET+INS-BI		4.21 (0.53 to 72.11)
MET+GLP-1	MET+SGLT-2	1.82 (0.93 to 3.56)
MET+INS-BA		0.33 (0.07 to 1.51)
MET+INS-BI		3.29 (0.38 to 57.58)
MET+INS-BA	MET+GLP-1	**0.19 (0.04 to 0.77)**
MET+INS-BI		1.80 (0.22 to 31.25)
MET+INS-BI	MET+INS-BA	**9.89 (1.32 to 161.30)**
Random-effects model	Residual deviance	146 vs. 149 data points
	Deviance information criteria	773.773

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; INS-BI = biphasic insulin; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Note: Bolded values indicate statistically significant results.

Urogenital Adverse Events

The total number of urogenital adverse events at any time during the study and the total number of participants who experienced at least one urogenital adverse event over that same time period were extracted. Counts of the urogenital adverse events could not be analyzed, as no information of person-time-at-risk was available; however, the number of participants who experienced at least one urogenital adverse event were analyzed. Two types of urogenital adverse events were included in this outcome: urinary tract infections and genital (mycotic) infections.

Percentage of Participants Who Experienced at Least One Urogenital Adverse Event

There were 21 RCTs[14-16,52,55,59,92,99,105,113,115,136,137,143,145,157,163,174,181,182,185] that reported participants who experienced at least one urogenital adverse events and were included in the reference-case NMA. Data were available for all drug classes except biphasic insulin.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 22. Compared with metformin monotherapy and with each other, none of the classes added to metformin significantly increased or decreased the risk of urogenital adverse events.

Table 22: Number of Participants Who Experienced at Least One Urogenital Adverse Event — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	1.02 (0.69 to 1.49)
MET+DPP-4		1.23 (0.90 to 1.72)
MET+SGLT-2		1.06 (0.70 to 1.58)
MET+GLP-1		1.17 (0.59 to 2.27)
MET+INS-BA		0.87 (0.07 to 6.51)
MET+DPP-4	MET+SUL	1.21 (0.91 to 1.66)
MET+SGLT-2		1.03 (0.71 to 1.55)
MET+GLP-1		1.13 (0.59 to 2.27)
MET+INS-BA		0.86 (0.07 to 6.43)
MET+SGLT-2	MET+DPP-4	0.85 (0.57 to 1.30)
MET+GLP-1		0.95 (0.50 to 1.79)
MET+INS-BA		0.71 (0.06 to 5.19)
MET+GLP-1	MET+SGLT-2	1.11 (0.52 to 2.30)
MET+INS-BA		0.83 (0.07 to 6.24)
MET+INS-BA	MET+GLP-1	0.75 (0.07 to 4.81)
Random-effects model	Residual deviance	41.08 vs. 46 data points
	Deviance information criteria	247.955

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS-BA = basal insulin; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Renal Adverse Events

Counts of renal adverse events at any time during the study and the total number of participants who experienced at least one renal adverse event over that same time period were extracted. Renal adverse events included in this outcome were as follows:

- cancer (carcinoma, stage I)
- noncancerous tumours (adenoma, oncocytoma)
- inflammation of renal tissue (pyelonephritis)
- nephrolithiasis (renal, urinary, and bladder calculi)

- renal dysfunction/worsening renal function (renal failure, impairment, colic, cysts, embolism, and neoplasm)
- urinary events related to renal dysfunction (hematuria, azotemia, ketonuria, proteinuria, urinary retention, and urinary tract obstruction)

Data for this outcome could not be analyzed. There were 18 RCTs[37,44,48,52,55,99,107,110,112,125,136-138,143,145,159,232,253] that reported number of renal adverse events but no data for person-time-at-risk for the event counts. The NMA for the participants who experienced at least one event was not robust due to a small number of RCTs reporting the outcome and a high proportion of zero events. There were seven RCTs[37,105,110,143,163,165,181] that reported number of participants who experienced at least one adverse event (N = 2,396).

Fractures

Number of Participants Who Experienced at Least One Fracture

There were 15 RCTs[16,28,44,52,67,105,110,112,115,145,154,174,232,241,253] that reported the number of participants with fracture events and were included in the reference-case NMA. Data were not available for GLP-1 agonists, basal or biphasic insulin classes.

The NMA based on this evidence network was consistent. The results of the random-effects NMA model of selected class comparisons are presented in Table 23. Compared with metformin monotherapy and each other, none of the classes added to metformin significantly increased or decreased the odds of fracture.

Table 23: Number of Participants Who Experienced at Least One Fracture — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	1.15 (0.35 to 3.89)
MET+DPP-4		2.02 (0.63 to 6.75)
MET+SGLT-2		1.35 (0.48 to 4.20)
MET+DPP-4	MET+SUL	1.73 (0.58 to 5.09)
MET+SGLT-2		1.18 (0.53 to 2.70)
MET+SGLT-2	MET+DPP-4	0.67 (0.21 to 2.31)
Random-effect model	Residual deviance	22.74 vs. 32 data points
	Deviance information criteria	109.921

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Total Number of Fracture Events

A total of 13 RCTs[28,37,44,48,55,67,99,110,134,136,138,159,174] reported the number of fractures but no data for the associated person-time-at-risk, and as a result analysis was not possible. Data were not available for GLP-1 agonists or basal or biphasic insulin.

Mortality

All-Cause Mortality

There were 47 RCTs[14-16,28,30,37,44,45,48,52,55,59,61,74,99,110,112,115,134,138,141,143,145,146,149,154,157,159,162,165-167,174-176,181-183,187-189,199,212,221,222,232,253] (N = 30,333) that reported all-cause mortality. Data were available for all drug classes except biphasic insulin, and only one study of basal insulin reported this outcome. The NMA model for all-cause mortality was not robust due to the low event rate and the large number of zero events in the data set (34 of the 47 RCTs reported zero deaths in one [n = 16 RCTs] or all study arms [n = 18 RCTs]).

A pairwise meta-analysis comparing DPP-4 inhibitors with sulfonylurea found no difference in the relative risk of all-cause mortality (odds ratio [OR] 1.19; 95% confidence interval [CI], 0.65 to 2.17). No other direct estimates could be estimated.

In the RCTs not included in the quantitative analyses, 19 RCTs[28,37,44,45,59,74,115,141,162,165,167,176,181,183,189,212,222,232] reported zero events in one or both[55] treatment arms. No RCTs of insulin reported this outcome. One study comparing GLP-1 inhibitors with basal insulin[59] reported zero deaths in both study arms.

Eight RCTs compared metformin monotherapy with an SGLT-2 inhibitor.[15,44,45,112,145,221,232,253] Of these, one RCT[145] reported one death in the metformin monotherapy arm (n = 137) and zero events in the SGLT-2 arm (n = 135). Three RCTs[112,221,253] reported one death each in the SGLT-2 arm (n = 551) and zero events in the metformin monotherapy arms (n = 367).

Five RCTs compared metformin monotherapy with a GLP-1 agonist.[14,55,61,74,167] Of these, two reported zero deaths.[74,167] One RCT[61] reported that two deaths occurred in the metformin monotherapy arm (n = 160) and three occurred in the GLP-1 agonist arm (n = 322). Two trials each reported one death in the GLP-1 agonist group[14,55] (n = 606) and zero deaths in the metformin group.

Fourteen trials compared metformin monotherapy with a DPP-4 inhibitor.[14,28,30,55,110,115,141,157,162,165,174,181,183,253] Of these, 11 reported zero events in either arm.[14,28,55,110,115,141,162,165,181,183,253] Of the remaining RCTs, two reported one death each in the metformin monotherapy arm,[157,174] and one[30] reported one death in the DPP-4 inhibitor group (n = 46).

Cardiovascular Mortality

There were 34 RCTs[14,15,28,30,37,44,45,48,59,74,99,105,110,115,134,138,141,143,145,149,157,162,167,174-176,181-183,188,189,212,222,232] (N = 17,282) that reported cardiovascular mortality. Data were available for all drug classes with the exception of biphasic insulin. The NMA model for cardiovascular mortality was not robust due to the low event rate and the large number of zero events in the data set (30 of the 34 RCTs reported zero deaths in one or all study arms). No RCTs compared metformin monotherapy with a sulfonylurea.

A pairwise meta-analysis comparing DPP-4 inhibitors with sulfonylurea found no difference in the relative risk of cardiovascular mortality (OR 1.84; 95% CI, 0.66 to 5.12). No other direct estimates could be estimated.

Of the included RCTs, 21 reported zero cardiovascular deaths in any treatment group.[15,28,37,44,45,59,74,105,115,141,143,145,162,167,176,181,183,189,212,222,232]

Six RCTs[15,44,45,59,145,232] compared metformin monotherapy with an SGLT-2 inhibitor; no cardiovascular deaths were reported.

Twelve RCTs compared metformin monotherapy with a DPP-4 inhibitor.[14,28,30,105,110,115,141,157,162,174,181,183] Of these, zero deaths occurred in either treatment arm in nine RCTs.[14,28,105,110,115,141,162,181,183] Two RCTs[157,174] reported zero cardiovascular deaths in the DPP-4 inhibitor group (n = 468) and a single cardiovascular death in the metformin monotherapy group (n = 273). One small RCT[30] reported one death in the DPP-4 inhibitor group (n = 46) and none in the metformin monotherapy group (n = 47).

Three RCTs compared metformin monotherapy with a GLP-1 agonist.[14,74,167] Two RCTs[74,167](n = 4,585 and n = 1,979) reported zero deaths in either arm, while one RCT[14] reported that a single participant in the GLP-1 agonist group died (n = 304) while zero deaths occurred in those taking metformin monotherapy (n = 177).

Heart Failure

Heart Failure

There were 15 RCTs[16,44,55,99,109,110,125,138,154,165,166,175,189,199,225] (N = 10,876) that reported heart failure. Data were not available for all drug classes except the GLP-1 agonists and insulins. The NMA model for cardiovascular mortality was not robust due to the low event rate and the large number of zero events in the data set (eight of the 15 RCTs reported zero events in one or all study arms). No RCTs involved an insulin product.

A pairwise meta-analysis comparing DPP-4 inhibitors with sulfonylurea found no difference in the risk of heart failure (OR 1.35; 95% CI, 0.48 to 3.82). No other direct estimates could be made.

In the RCTs reporting heart failure as an outcome, four reported zero events in either treatment arm.[44,109,110,225] One RCT comparing metformin monotherapy with a sulfonylurea[55] reported a single event in the sulfonylurea group (n = 307).

Two RCTs compared metformin monotherapy with an SGLT-2 inhibitor.[44,109] A 16-week RCT[44] reported zero heart-failure events, while a 12-week RCT[109] reported one case of heart failure in the SGLT-2 inhibitor arm (n = 193) and zero in the metformin monotherapy arm (n = 65).

Four RCTs compared metformin monotherapy with a DPP-4 inhibitor.[55,109,110,165] Of these, two[109,110] reported zero cases of heart failure, while two RCTs[55,165] each reported one case of heart failure in the DPP-4 inhibitor group (n = 509) and zero in the metformin monotherapy group (n = 205).

Hospitalization for Heart Failure

No studies reported hospitalizations for heart failure in the reference case.

Stroke

Fatal Stroke

There were 27 RCTs[14,15,24,28,37,44,45,59,74,105,110,115,134,138,143,162,167,174-176,181-183,188,189,222,232] (N = 11,978) that reported fatal stroke. The NMA model for fatal stroke was not robust due to the low event rate and the large number of zero events in the data set (all RCTs reported zero events in one [four RCTs] or all study arms [23 RCTs]). Pairwise meta-analysis was not possible. Data were not available for any of the insulins.

In the four RCTs[14,134,138,175] reporting a single fatal stroke event in one study arm, fatal stroke events were as follows:

- in the sulfonylurea arm in two RCTs of DPP-4 inhibitors added to metformin (N = 1,892)
- in the TZD arm of a single RCT comparing sulfonylurea and TZD added to metformin (N = 595)
- in the GLP-1 agonist arm of a single RCT comparing metformin monotherapy with DPP-4 inhibitors and GLP-1 agonists (N = 796).

Nonfatal Stroke

Ten RCTs[48,98,99,105,110,134,138,143,176,181] reported nonfatal stroke (N = 7,821). Data were not available for any of the insulins. The NMA model for nonfatal stroke was not robust due to the low event rate and the large number of zero events in the data set (six of 11 RCTs reported zero events in one study arm). All RCTs included DPP-4 inhibitors. No studies included insulins, SGLT-2 inhibitors, or GLP-1 agonists added to metformin monotherapy.

A pairwise meta-analysis comparing DPP-4 inhibitors with sulfonylurea found no difference in the risk of heart failure (OR 2.46; 95% CI, 0.97 to 6.26). No other direct estimates could be made.

Four RCTs[98,105,110,181] compared metformin monotherapy with a DPP-4 inhibitor. In these RCTs, nonfatal strokes were reported as follows:

- a single nonfatal stroke in the metformin arm of one RCT[110] (n = 129), with zero events in the metformin arm of the other three RCTs[98,105,181]
- four events in the DPP-4 inhibitor arm of three RCTs (N = 526), with zero events in the DPP-4 inhibitor arm of the remaining RCT (n = 129).

One RCT comparing DPP-4 inhibitors with GLP-1 agonists reported one event in the DPP-4 inhibitor group (n = 166) and zero events in the GLP-1 agonist arm (n = 160).

Transient Ischemic Attack

There were 14 RCTs[16,33,37,48,52,55,99,112,130,138,145,159,163,176,181,253] that reported transient ischemic attack (TIA). Two RCTs,[130,163] one comparing basal insulin (zero TIAs reported) with bolus insulin (single TIA reported), and the other comparing basal insulin (single TIA reported) with a GLP-1 agonist (zero TIAs reported), were disconnected from the NMA. When continuity corrections were applied, the NMA model for TIA was not robust due to the low event rate and the large number of zero events in the data set (all RCTs reported zero events in one [eight RCTs] or all study arms [two RCTs]).

The NMA for the reference case (N = 10,389) was robust when two RCTS[55,253] with zero events in both study arms were removed. A single RCT[33] comparing meglitinides with metformin monotherapy was removed to improve the robustness of the NMA model (zero events reported in the metformin arm, one event in the meglitinide arm) (Table 24). When

sulfonylurea and SGLT-2 and DPP-4 inhibitors were compared with metformin monotherapy and each other in the reference-case NMA, no significant differences in the odds of TIA were found.

Table 24: Transient Ischemic Attack — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	0.96 (0.13 to 6.13)
MET+DPP-4		0.62 (0.09 to 4.15)
MET+SGLT-2		0.69 (0.12 to 3.56)
MET+DPP-4	MET+SUL	0.67 (0.23 to 1.69)
MET+SGLT-2		0.73 (0.14 to 3.43)
MET+SGLT-2	MET+DPP-4	1.13 (0.22 to 5.28)
Random-effects model	Residual deviance	22.14 vs. 30 data points
	Deviance information criteria	104.55

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; vs. = versus.

Pancreatitis

A total of 15 RCTs[16,28,37,48,55,61,74,99,110,135,143,149,163,222,241] reported patients with pancreatitis (N = 9,238). The NMA model for pancreatitis was not robust due to the low event rate and the large number of zero events in the data set (14 of 15 RCTs reported zero events in one [five RCTs] or all study arms [nine RCTs]). Pairwise meta-analysis was also not possible. There were no studies of biphasic insulin, and only one study reported use of basal insulin.

One RCT[55] compared metformin monotherapy with a sulfonylurea: zero events were reported. Two RCTs[55,110] compared metformin with a DPP-4 inhibitor, and two RCTs[61,74] compared metformin with a GLP-1 agonist. Zero events were reported in all treatment groups. One study comparing basal insulin with a GLP-1 agonist reported a single case of pancreatitis in the GLP-1 agonist group (n = 36) and none in the insulin group (n = 33).

Additional cases of pancreatitis were reported in the RCTs as follows:

- three cases in the sulfonylurea arm of one RCT[48] (n = 869) and one case in the sulfonylurea arm of one RCT (n = 41)
- one case each in the DPP-4 inhibitor arm of two RCTs (n = 1,654)[48,99]
- one case each in the GLP-1 agonist arm of two RCTs (n = 475)[149,163]
- one case in the TZD arm of one RCT (n = 43).[241]

Cancer

Pancreatic Cancer

A total of five RCTs[16,44,99,134,149] reported pancreatic cancer while on treatment (N = 3,961) The NMA model for pancreatic cancer was not robust due to the low event rate and the large number of zero events in the data set (14 of 15 RCTs reported zero events in one [five RCTs] or all study arms [nine RCTs]). Pairwise meta-analysis was not possible. Included studies compared sulfonylureas (one event), GLP-1 agonists (one event), SGLT-2 inhibitors (zero events), and DPP-4 inhibitors (three events) added to a metformin background

therapy. Only one study compared an intervention with metformin monotherapy (zero events).

Bladder Cancer

Six RCTs[16,44,48,55,138,145] reported bladder cancer (N = 4,605) as an outcome. The NMA model for bladder cancer was not robust due to the low event rate and the large number of zero events in the data set. (All RCTs reported zero events in one or all study arms.) Pairwise meta-analysis was not possible.

All three RCTs[16,48,138] that reported bladder cancer events compared sulfonylurea with a DPP-4 inhibitor. All events were singular and occurred in the DPP-4 inhibitor study arms. One RCT[55] comparing metformin monotherapy with sulfonylurea and DPP-4 inhibitors reported zero events in all study arms. Two RCTs[44,145] comparing metformin monotherapy with SGLT-2 inhibitors also reported zero events in all study arms.

Ketoacidosis

A total of two RCTs[48,253] reported ketoacidosis events in the reference case.[48,253] The NMA model for ketoacidosis was not robust due to the low number of studies, the low event rate, and the number of zero events in the data set. (All RCTs reported zero events in one or all study arms.) Pairwise meta-analysis was not possible.

In one RCT[48] comparing sulfonylurea with DPP-4 inhibitors, a single event was reported in the DPP-4 inhibitor arm (n = 1,747). In the second RCT,[253] there were zero ketoacidosis events in the three study arms (metformin and DPP-4 and SGLT-2 inhibitors).

Other: Cardiovascular Health

Unstable Angina

A total of 17 RCTs[16,48,52,55,99,107,110,138,143,145,159,165,170,174,181,189,253] reported unstable angina as an outcome, and 14 RCTs were included in the reference-case NMA (N = 11,676).

Three RCTs[107,189] were removed from the analysis to improve the robustness of the NMA model. Both RCTs were the only studies to report basal insulin and meglitinides and had zero events in one arm. A single unstable angina event was reported in the meglitinide arm of one RCT (compared with sulfonylurea with zero events, n = 213), and two events were reported in the basal insulin arm of the second RCT (compared with DPP-4 inhibitor with zero events, n = 501). One RCT[110] comparing metformin monotherapy with added TZD and DPP-4 inhibitors reported zero events for all treatments.

When sulfonylurea and SGLT-2 and DPP-4 inhibitors added to metformin were compared with metformin monotherapy and with each other in the reference-case NMA, no significant differences in the odds of unstable angina were found (Table 25).

Table 25: Unstable Angina — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
MET+SUL	MET	0.94 (0.24 to 3.56)
MET+DPP-4		0.98 (0.32 to 3.10)
MET+SGLT-2		0.81 (0.15 to 3.58)
MET+DPP-4	MET+SUL	1.08 (0.43 to 2.93)

Treatment	Reference	OR (95% CrI)
MET+SGLT-2		0.88 (0.22 to 3.20)
MET+SGLT-2	MET+DPP-4	0.80 (0.18 to 3.64)
Random-effects model	Residual deviance	24.26 vs. 29 data points
	Deviance information criteria	107.69

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; MET = metformin; , OR = odds ratio; SGLT-2 = sodium-glucose cotransporter2; SUL = sulfonylurea; vs. = versus.

Hospitalization for Unstable Angina

A single study of a sulfonylurea compared with a DPP-4 inhibitor on top of a metformin background reported hospitalization for unstable angina.[99] In this RCT, three participants in each treatment group were admitted to hospital for unstable angina (SUL: n = 775; DPP-4: n = 776).

Nonfatal Myocardial Infarction

Eleven RCTs[28,37,48,99,110,136,138,182,186,189,199] reported nonfatal MI (N = 8,010). Data were not available for any of the insulins. The NMA model for nonfatal MI was not robust due to the low event rate and the large number of zero events in the data set (nine of 11 RCTs reported zero events in one [seven RCTs] or all study arms [two RCTs]). Eight of the RCTs included DPP-4 inhibitors. No studies reported insulins.

A pairwise meta-analysis comparing DPP-4 inhibitors with sulfonylurea found no difference in the odds of nonfatal MI (OR 1.35; 95% CI, 0.63 to 2.92). No other direct estimates could be made.

Two RCTs[110,136] reported zero events during the study. Thirty-one nonfatal MIs were reported among the other RCTs. These events were reported as follows:

- in the DPP-4 inhibitor arms of four RCTs[28,48,99,138] (12 events, n = 2,156)
- in the sulfonylurea arms of four RCTs[48,99,182,189] (17 events, n = 2,329)
- in the SGLT-2 inhibitor arm of one RCT[37] (one event, n = 179)
- in the GLP-1 inhibitor arm of one RCT[186] (one event, n = 36)
- no events were reported in participants taking metformin monotherapy.

Fatal Myocardial Infarction

Forty-six RCTs[14-16,24,26,28,29,37,38,40,42,44,45,51,58,59,74,99,105,110,115,138,140,141,143,145,156,162,164,167,172-174,176,181-183,188,189,192,200,204,210,212,222,232] (N = 18,730) reported either fatal MIs or zero deaths (inferred as zero fatal MIs). In total, 12 participants experienced a fatal MI (0.06%). The NMA model for fatal myocardial infarction was not robust due to low event rate and the large number of zero events in the data set (all RCTs reported zero events in at least one [12 RCTs] or all study arms [34 RCTs]). Pairwise meta-analysis was not possible.

Data were available for all drug classes, including basal and biphasic insulin (two RCTs), one comparing GLP added to metformin with basal insulin as an add-on to metformin[58] (zero events, N = 319) and another[192] comparing sulfonylurea plus metformin with biphasic insulin added to metformin (one event, N = 222)].

Coronary Revascularization

Only one RCT[28] reported a single coronary revascularization procedure in a comparison of metformin monotherapy with a DPP-4 inhibitor (saxagliptin). The event was described as follows: “a 100% right coronary artery ostial occlusion with collateralization was noted, and the 80%–90% proximal left circumflex artery lesion was treated with percutaneous transluminal coronary angioplasty and a stent.” The patient resumed medication (DPP-4 inhibitor) and completed the study.

Major Adverse Cardiovascular Events

A total of two RCTs[28,48] reported the cardiovascular composite of major adverse cardiovascular events (MACEs). The composite was composed of three outcomes: cardiovascular mortality, nonfatal MI, and nonfatal stroke. The NMA model for MACE was not robust due to the low number of studies, low event rate, and the presence of zero events in the data set.

One RCT[28] of metformin monotherapy compared with a DPP-4 inhibitor (n = 160) reported one MACE outcome in the DPP-4 inhibitor arm. The study was powered for the primary efficacy outcome of A1C, and treatment duration was 12 weeks. A second RCT[48] (n = 1,747), also powered for a primary efficacy outcome of A1C, compared sulfonylurea with a DPP-4 inhibitor for 104 weeks. A total of 11 MACE events occurred in the sulfonylurea arm, and 11 events in the DPP-4 inhibitor arm.

Results: Research Question 2 — Cardiovascular Trials

Selection of Primary Studies

After removal of duplicates, a total of 22,238 citations were identified in the literature search. Of these, 18,294 citations were excluded, based on titles and/or abstracts. Full-text articles of the remaining 3,944 citations were assessed. For research question 2, 66 articles representing 17 unique RCTs[91,257-272] were included in the systematic review (with 48 companion publications[12,159,171,180,273-316]). Of these, three were study protocols,[91,257,270] one was a single study without usable data,[261] and two were clinical trial registry records[271,272] of a completed RCT that did not report study results. A complete list of included studies is available in Appendix 3.

Study Characteristics

The systematic review of cardiovascular trials included 17 unique RCTs. Of these, three were reported as protocols only.[91,257,270] One study[267] compared the effects of prandial and basal glycemic control on cardiovascular outcomes after acute MI. The CANVAS RCT reported only biomarker data or an interim analysis, with the goal of reporting long-term cardiovascular outcomes in a future publication.[261]

Characteristic and outcome data were extracted from 11 RCTs.[258-260,263-266,268,269,292,317] All were double-blind, with the exception of one trial,[269] and all were funded by a pharmaceutical company. The sample size ranged from 304 participants[265] to 16,492.[264] The threshold baseline A1C level for inclusion in the trials was typically 6.5%, although some used a threshold as low as 6.0%. The upper A1C bound for inclusion was between 9.0% and 11.0% One study did not report the A1C criteria for inclusion (population was

described as “inadequate control”).[265] The mean baseline duration of diabetes ranged from 5.6 years[265] to 13.4 years;[292] one study did not report the duration of diabetes.[290]

The included RCTs enrolled patients on varying background therapies, and pragmatically allowed for continuation of whatever the existing background therapy was at baseline. Background therapy was not specified in one RCT.[263] No subgroups based on background therapies could be elucidated from the data presented. In general, participants added the study intervention to their existing therapy. Background therapies were no treatment (i.e., patients were drug-naive and started the study intervention); monotherapy (patients were taking a single antidiabetic medication or insulin and added the study intervention to that therapy); dual therapy; and combinations of more than two therapies. Monotherapy was predominantly metformin or insulin, and dual therapy predominantly metformin plus a sulfonylurea or insulin. In many cases, the RCTs reported only “combinations of oral antidiabetic drugs” or “insulin with an oral antidiabetic drug.” Little or no data were available for the baseline proportions of background therapy for the enrolled participants. For example, Home et al.[159] enrolled patients who were taking metformin or sulfonylurea, while Green et al.[260] enrolled patients taking metformin, sulfonylurea, insulin, or a TZD, alone or in combination (see Appendix 6 for further detail).

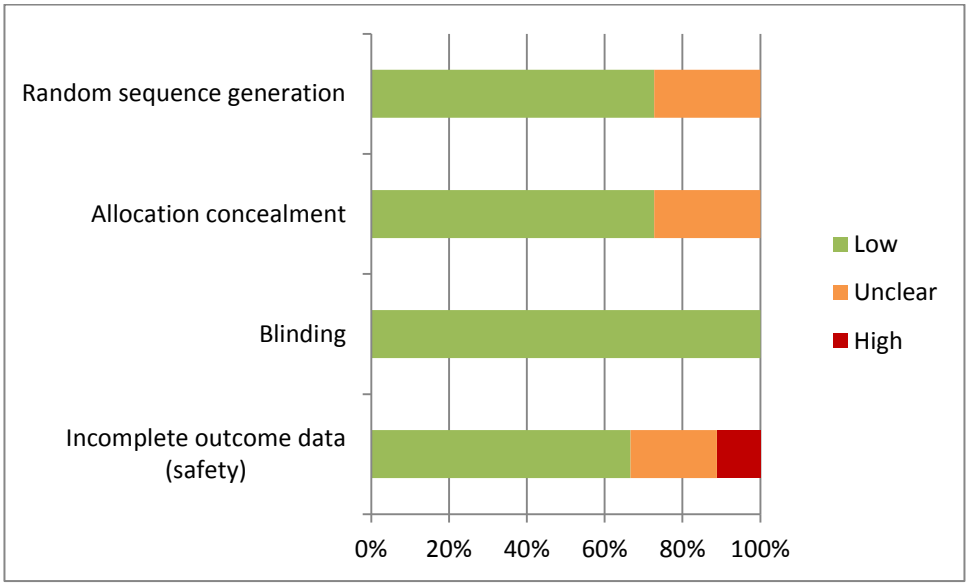
Most studies enrolled participants at high-risk of cardiovascular events[262,290] or with cardiovascular disease.[258,260,263-266,268] One study excluded participants with a presence or history of cardiovascular disease[159] (Appendix 7).

The percentage of men in the studies ranged from 52%[269] to 78%.[265] The mean age of participants was between 58.8 (standard deviation [SD] 8.3)[269] and 65.5 (SD 8.0).[260] The percentage of current smokers ranged between 11%[260] and 18%;[292] one study did not report smoking status (ID4794). Mean BMI was between 25.2 (SD3.0)[265] and 32.5 (SD 6.3).[262]

Risk of Bias

Most of the included RCTs were at overall low ROB. A total of 72% of RCTs were judged to be at low ROB for random-sequence generation and allocation concealment. As all of the outcomes of interest were considered objective, all RCTs were judged to be at low ROB for outcome assessment. Most trials were judged to be at low ROB (67%) for incomplete outcome data. One RCT (11%) was judged to be at high ROB because of early termination because of an increased number of cardiovascular events (composite outcome: cardiovascular death, hospitalization or emergency department visit for heart failure) in the pioglitazone group (ID4794); about 60% of patients completed the trial (six months of treatment), but it was unclear whether the patients who discontinued were followed up for additional outcomes. Two trials[258,263] (22%; ID1901, ID791) were judged to have an unclear ROB for outcome data because, in the first trial, it was unclear whether all patients were followed for outcome assessment after discontinuation of the study drug and, in the second trial, the flow of patients through the trial was not reported. (Figure 3).

Figure 3: Summary of Risk of Bias Assessment for RCTs Reporting Cardiovascular Outcomes



Other Limitations

While carrying out the ROB assessments, reviewers noted that there were some limitations that should be noted in the cardiovascular RCTs, including the use of outcome definitions that may deviate from what would be considered standard (EMPA-REG OUTCOME), lack of control for type I error (LEADER and EMPA-REG OUTCOME, exploratory analyses were not adjusted for), and the fact that most of the RCTs were funded and conducted by manufacturers. Other concerns include the following:

- Protocol amendments were made after an interim analysis (EMPA-REG OUTCOME).
- A number of participants censored in the LEADER study completed or discontinued the study before having an outcome after their last visit, and there is concern that missed events occurring after that visit were not included.

Data Synthesis

NMAs were conducted for 13 outcomes for the reference case of class-level comparisons (Table 26 and Table 27). Intra-class (individual drug) and dose-level comparisons were not possible given the limited number of studies. NMA results presented in Tables 26 and 27 represent all available interventions included for each outcome. As in research question 1, if additional drugs (e.g., sulfonylurea, TZD) were reported, they were included in each network and are also reported. Although the index node for the NMAs is called “placebo,” standard of care involved a variety of background treatments, and results should be considered in the context of this limitation.

Table 26: Summary of NMA Outcomes and Model Selection for Cardiovascular Outcomes

Outcome	Network Meta-Analysis	Network Meta-Analysis Model	Descriptive
Major adverse cardiovascular events	Y	Normal likelihood, identity link, treatment difference	–
Cardiovascular mortality	Y	Normal likelihood, identity link, treatment difference	–
All-cause mortality	Y	Normal likelihood, identity link, treatment difference	–
Hospitalization for heart failure	Y	Normal likelihood, identity link, treatment difference	–
Total adverse events	Y	Binomial likelihood, Logit link	–
Severe hypoglycemia	Y	Binomial likelihood, Logit link	–
Nonsevere hypoglycemia	–	–	Y
Nocturnal hypoglycemia	–	–	Y
Severe adverse events	Y	Binomial likelihood, Logit link	–
Pancreatic cancer	Y	Binomial likelihood, Logit link	–
Bladder cancer	Y	Binomial likelihood, Logit link	–
Withdrawals due to adverse events	Y	Binomial likelihood, Logit link	–
Renal adverse events	Y	Binomial likelihood, Logit link	–
Urogenital adverse events	–	–	Y
Pancreatitis	Y	Binomial likelihood, Logit link	–
Fractures	Y	Binomial likelihood, Logit link	–
Ketoacidosis	Y	Binomial likelihood, Logit link	–

Y = yes.

The choice of these outcomes for NMA was based on clinical relevance, and the sufficiency of the data available to derive robust and consistent network models. Due to limitations in the data reported, only study-level summary measures log hazard ratios were available for four outcomes (MACEs, cardiovascular mortality, all-cause mortality, and hospitalizations for heart failures). In this case, a normal distribution for the continuous measure of treatment effect (log hazard ratio) was assumed, and a normal likelihood with identity link model was applied on the treatment difference-log hazard ratio. For the other dichotomous outcomes, a binomial likelihood with logit link model was used for the Bayesian NMAs. WinBUGs software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian NMA. Both fixed- and random-effects NMAs were conducted. Inconsistency between direct evidence and indirect evidence cannot be assessed for all cardiovascular NMAs, as there is no closed loop in the network.

For each outcome, the point estimates and 95% credible intervals (odds ratio for dichotomous outcome or hazard ratio for time-to-event outcome) from the NMA of the reference case were estimated using Markov chain Monte Carlo methods and reported, comparing each drug class.

Table 27: Reference Rates for the Index Node and Sample Sizes for Analysis Populations — NMA for Cardiovascular RCTs

Outcome	Number of RCTs Included in Reference Case NMA (N)	Reference Rate for Placebo[a] OR (95% CrI)	Sample Size (N)
Dichotomous Outcomes, OR (95% CrI)			
Major adverse cardiovascular events	5	Only HR available	50,410
Cardiovascular mortality	6	Only HR available	30,439
All-cause mortality	8	Only HR available	66,311
Hospitalization for heart failure	5	Only HR available	51,246
Total adverse events	3	0.80 (0.79 to 0.81)	19,395
Withdrawals due to adverse events	6	0.080 (0.075 to 0.085)	26,848
Serious adverse events	6	0.35 (0.35 to 0.36)	31,219
Severe hypoglycemia	8	0.0097 (0.0083 to 0.01121)	66,163
Renal adverse events	5	0.06 (0.023 to 0.029)	45,752
Pancreatitis	5	0.0025 (0.0019 to 0.0032)	51,951
Bone fractures	3	0.026 (0.023 to 0.030)	25,614
Pancreatic cancer	6	0.0014 (0.0007 to 0.0020)	56,398
Bladder cancer	3	0.0022 (0.0013 to 0.0033)	19,025

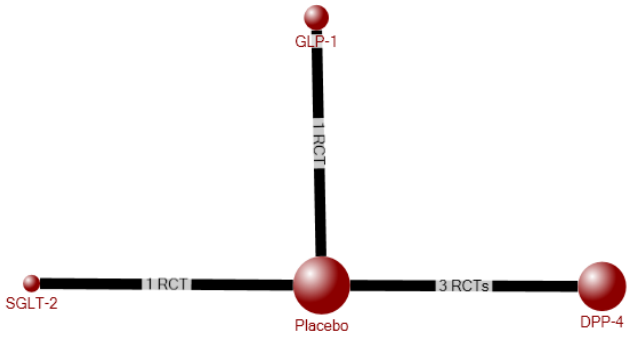
CrI = credible interval; NMA = network meta-analysis; OR = odds ratio; RCT = randomized controlled trial.

[a] Reference rates for outcomes analyzed using study-level hazard ratios could not be calculated. For dichotomous outcomes, the reference rate is the baseline probability of achieving an outcome in the metformin arm. It was generated directly from the NMA model. The baseline was calculated by using the mean log odds ratio (LOR) of the outcome in the metformin arm averaged over all studies in which it was used. Given this assumed baseline (log odds of outcome in the metformin arm), the NMA model added the LORs relative to the metformin arm to this baseline to get the absolute probability of achieving an outcome in the other treatment arms. For continuous outcome, the reference is the mean with standard deviation of outcome in the metformin arm and was generated directly from the NMA model by averaging over all studies in which metformin arm was used. Given this estimated mean in the metformin arm, the NMA model added the mean difference relative to the metformin arm to this reference mean to get the absolute mean of outcome in the other treatment arm.

Major Adverse Cardiovascular Events

A total of five RCTs[259,260,262-264] (N = 50,410) reported the cardiovascular composite of MACE and were included the NMA (Figure 4). The composite was composed of three outcomes: cardiovascular mortality, nonfatal MI, and nonfatal stroke. Data were available for SGLT-2 (one RCT[259]) and DPP-4 inhibitors (three RCTs[260,263,264]), GLP-1 agonists (one RCT[262]) and placebo (Figure 4).

Figure 4: Treatment Network for Major Adverse Cardiovascular Events



Consistency could not be checked. The results of the random-effects NMA model for all available treatment class comparisons are presented in Table 28. Compared with placebo and with each other, none of the selected classes significantly lowered the risk of MACEs.

Table 28: Major Adverse Cardiovascular Events — Hazard Ratios for All Class Comparisons

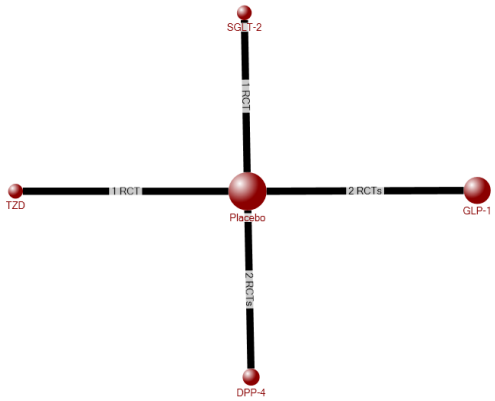
Treatment	Reference	HR (95% CrI)
DPP-4	Placebo	0.99 (0.68 to 1.45)
SGLT-2		0.86 (0.46 to 1.67)
GLP-1		0.87 (0.45 to 1.65)
SGLT-2	DPP-4	0.87 (0.41 to 1.88)
GLP-1		0.88 (0.41 to 1.83)
GLP-1	SGLT-2	1.01 (0.39 to 2.46)
Random-effects model	Total residual deviance	4.053 vs. 5 data points
	Deviance information criteria	–9.193

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; SGLT-2 = sodium-glucose cotransporter; vs. = versus -2.

Cardiovascular Mortality

A total of six RCTs[159,258,259,262-264] (N = 30,439) reported cardiovascular mortality and were included in the reference-case analysis (Figure 5). Data were available for SGLT-2 inhibitors (one RCT[259]), TZD (one RCT[159]), DPP-4 (two RCTs[263,264]) and GLP-1 agonists (two RCTs[258,262]), and placebo.

Figure 5: Treatment Network for Cardiovascular Mortality



Consistency could not be checked. The results of the random-effects NMA model for all available treatment class comparisons are presented in Table 29. Compared with placebo and with each other, none of the selected classes significantly lowered the risk of cardiovascular mortality.

Three RCTs[258,260,268] reported cardiovascular mortality outcomes but could not be included in the NMA, as the effect estimates were not comparable with those used in the analysis.

Table 29: Cardiovascular Mortality — Hazard Ratios for All Class Comparisons

Treatment	Reference	HR (95% CrI)
DPP-4	Placebo	0.97 (0.33,2.68)
SGLT-2		0.58 (0.14,2.55)
GLP-1		0.86 (0.30,2.47)
TZD		0.83 (0.20,3.73)
SGLT-2	DPP-4	0.60 (0.10,3.72)
GLP-1		0.89 (0.22,4.03)
TZD		0.86 (0.15,5.27)
GLP-1	SGLT-2	1.48 (0.25,8.94)
TZD		1.42 (0.18,11.65)
TZD	GLP-1	0.96 (0.15,6.20)
Random-effects model	Total residual deviance	6.063 vs. 6 data points
	Deviance information criteria	–2.803

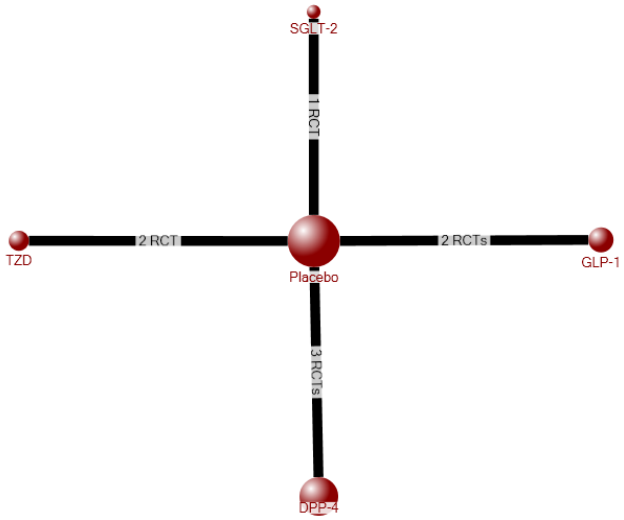
CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; vs. = versus.

All-Cause Mortality

A total of eight RCTs[159,258-260,262-264,266] (N = 66,311) reported all-cause mortality and were included in the reference-case analysis (Figure 6). Data were available for SGLT-2 inhibitors

(one RCT[259]), TZD (two RCTs[159,266]), DPP-4 inhibitors (three RCTs[260,263,264]), GLP-1 agonists (two RCTs[258,262]), and placebo.

Figure 6: Treatment Network for All-Cause Mortality



Consistency could not be checked. The results of the random-effects NMA model for all available treatment class comparisons are presented in Table 30. Compared with placebo, DPP-4 inhibitors, and SGLT-2 inhibitors reduced the risk of all-cause mortality. None of the other treatments reduced the risk of all-cause mortality.

Table 30: All-Cause Mortality — Hazard Ratios for All Class Comparisons

Treatment	Reference	HR (95% CrI)
DPP-4	Placebo	1.02 (0.83 to 1.20)
SGLT-2		**0.67 (0.47 to 0.95)**
GLP-1		0.89 (0.71 to 1.12)
TZD		0.91 (0.71 to 1.16)
SGLT-2	DPP-4	**0.66 (0.45 to 0.99)**
GLP-1		0.87 (0.67 to 1.19)
TZD		0.90 (0.67 to 1.24)
GLP-1	SGLT-2	1.32 (0.89 to 2.03)
TZD		1.36 (0.90 to 2.09)
TZD	GLP-1	1.03 (0.74 to 1.42)
Random-effects model	Total residual deviance	7.678 vs. 8 data points
	Deviance information criteria	–10.022

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; vs. = versus.

Note: Bolded values indicate statistically significant results.

Hospitalizations for Heart Failure

A total of five RCTs[258-260,262,264] (N = 51,246) reported hospitalizations for heart failure and were included in the reference-case analysis. Data were available for SGLT-2 (one RCT[259]) and DPP-4 inhibitors (two RCTs[260,264]), GLP-1 agonists (two RCTs[258,262]), and placebo.

Consistency could not be checked. The results of the random-effects NMA model for all available class comparisons are presented in Table 31. Compared with placebo and with each other, none of the selected classes significantly lowered the risk of hospitalizations for heart failure. It is unclear how multiple hospitalizations for individuals were handled by the individual RCTs, as only hazard ratios were available for analysis, not individual event counts and person-time.

Table 31: Hospitalization for Heart Failure — Hazard Ratios for All Available Class Comparisons

Treatment	Reference	HR (95% CrI)
DPP-4	Placebo	1.13 (0.43 to 2.93)
SGLT-2		0.68 (0.18 to 2.75)
GLP-1		0.91 (0.35 to 2.40)
SGLT-2	DPP-4	0.60 (0.12 to 3.35)
GLP-1		0.80 (0.21 to 3.13)
GLP-1	SGLT-2	1.34 (0.24 to 6.86)
Random-effects model	Total residual deviance	5.03 vs. 5 data points
	Deviance information criteria	–3.26

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; SGLT-2 = sodium-glucose cotransporter-2; vs. = versus

One RCT[268] reported hospitalizations for heart failure but could not be included in the NMA, as the effect estimates were not comparable with those used in the analysis. In the study, hospitalization or emergency department visits for heart failure were 50% higher in the pioglitazone group (30 hospitalizations) when compared with the glyburide group (15 hospitalizations).

Total Adverse Events

A total of three RCTs reported total adverse events[259,263,317] (811,1901, LEADER) (N = 19,395) and were included in the NMA.

Consistency could not be checked. The results of the random-effects NMA model for all available class comparisons are presented in Table 32. Compared with placebo and with each other, none of the classes significantly increased or decreased odds of an adverse event.

Table 32: Total Adverse Events — Odds Ratios for All Available Class Comparisons

Treatment	Reference	OR (95% CrI)
DPP-4	Placebo	1.08 (0.40 to 2.85)
SGLT-2		0.86 (0.33 to 2.33)
GLP-1		1.07 (0.41 to 2.97)
SGLT-2	DPP-4	0.80 (0.20 to 3.36)
GLP-1		1.00 (0.25 to 4.11)
GLP-1	SGLT-2	1.24 (0.31 to 5.02)
Random-effects model	Residual deviance	6.006 vs. 6 data points
	Deviance information criteria	59.719

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; vs. = versus

A single RCT of sulfonylurea compared with pioglitazone (4,794) (n = 518) could not be included in the NMA, as it did not share a common comparator with the other RCTs and was disconnected from the network of treatments. Total adverse events in both treatment groups were comparable (74.0% and 74.6%).

Severe Hypoglycemia

A total of eight RCTs reported severe hypoglycemia[258-260,263,264,266,269,294] (N = 66,133) and were included in the reference-case NMA. The percentage of participants with a severe hypoglycemic event ranged from 0.3%[269] to 3.3%.[259]

Consistency could not be checked. The results of the random-effects NMA model for all available class comparisons are presented in Table 33. Compared with placebo, GLP-1 agonists resulted in significantly less risk of severe hypoglycemia but TZDs resulted in a significantly increased risk. There was a significantly lower risk of severe hypoglycemia with GLP-1 agonists relative to DPP-4 inhibitors. TZD significantly increased risk of severe hypoglycemic events relative to both DPP-4 inhibitors and GLP-1 agonists, but did not significantly differ in risk from SGLT-2 inhibitors.

Table 33: Severe Hypoglycemia — Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
DPP-4	Placebo	1.18 (0.91 to 1.54)
SGLT-2		0.82 (0.45 to 1.47)
GLP-1		**0.71 (0.49 to 0.99)**
TZD		**2.05 (1.11 to 3.98)**
SGLT-2		0.69 (0.36 to 1.33)
GLP-1	DPP-4	**0.60 (0.38 to 0.92)**
TZD		1.74 (0.89 to 3.51)
GLP-1	SGLT-2	0.87 (0.43 to 1.70)
TZD		**2.52 (1.07 to 5.98)**
TZD	GLP-1	**2.89 (1.44 to 6.24)**

Treatment	Reference	OR (95% CrI)
Random-effects model	Residual deviance	13.86 vs. 16 data points
	Deviance information criteria	114.457

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; vs. = versus.

Note: Bolded values indicate statistically significant results.

Nonsevere Hypoglycemia

A single RCT[264] comparing saxagliptin with placebo reported nonsevere hypoglycemia. The event was reported as minor hypoglycemia, defined as the "presence of symptoms but the patient recovered without assistance within 30 minutes after ingestion of carbohydrates." The authors reported that 12.5% (1,028/8,212) of patients in the placebo arm and 14.2% (1,172/8,280) patients in the saxagliptin arm experienced minor hypoglycemia.

Nocturnal Hypoglycemia

No studies reported nocturnal hypoglycemia.

Severe Adverse Events

A total of six RCTs[258,259,263,266,268,317] reported severe adverse events (N = 31,219) and were included in the reference-case NMA. The percentage of people with serious adverse events ranged between 18%[268] and 50%.[259]

Consistency could not be checked. The results of the random-effects NMA model for all available treatment class comparisons are presented in Table 34. Compared with placebo and with each other, none of the selected classes significantly differed in the risk of severe adverse events.

Table 34: Severe Adverse Events — Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
SUL	Placebo	0.81 (0.37 to 1.77)
DPP-4		0.92 (0.58 to 1.47)
SGLT-2		0.94 (0.58 to 1.50)
GLP-1		0.95 (0.68 to 1.33)
TZD		0.92 (0.57 to 1.49)
DPP-4	SUL	1.13 (0.46 to 2.83)
SGLT-2		1.15 (0.46 to 2.85)
GLP-1		1.17 (0.50 to 2.72)
TZD		1.13 (0.61 to 2.11)
SGLT-2	DPP-4	1.02 (0.52 to 1.97)
GLP-1		1.03 (0.58 to 1.81)
TZD		0.99 (0.51 to 1.94)
GLP-1	SGLT-2	1.02 (0.57 to 1.83)
TZD		0.98 (0.50 to 1.96)

Treatment	Reference	OR (95% CrI)
TZD	GLP-1	0.96 (0.54 to 1.73)
Random-effects model	Residual deviance	11.8 vs. 12 data points
	Deviance information criteria	117.501

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; vs. = versus.

Pancreatic Cancer

Six RCTs reported pancreatic cancer outcomes[258,260,263,264,269,294] (N = 56,398) and were included in the reference-case analysis. Data were not available for all drug classes, including SGLT-2 inhibitors.

Consistency of the network could not be checked. The results of the random-effects NMA model for all class comparisons are presented in Table 35. Relative to placebo, TZD significantly decreased the risk of pancreatic cancer. When the classes were compared, TZD also significantly decreased the risk of pancreatic cancer relative to GLP-1 agonists.

Table 35: Pancreatic Cancer — Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
DPP-4	Placebo	0.53 (0.19 to 1.46)
GLP-1		1.09 (0.34 to 3.10)
TZD		**0.13 (0.01 to 0.75)**
GLP-1	DPP-4	2.04 (0.44 to 9.01)
TZD		0.24 (0.02 to 1.89)
TZD	GLP-1	**0.12 (0.01 to 0.97)**
Random-effects Model	Residual Deviance	16.92 vs. 12 data points
	Deviance Information Criteria	64.97

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; OR = odds ratio; TZD = thiazolidinediones; vs. = versus.

Bladder Cancer

Three RCTs[259,266,269] comparing TZD and GLP-1 agonists with placebo reported bladder cancer outcomes. Consistency could not be checked. The results of the random-effects NMA model for all available treatment class comparisons are presented in Table 36. Compared with placebo and with each other, none of the selected classes significantly increased the risk of cardiovascular mortality.

Interpretation of these results are limited given the small number of RCTs reporting this outcome.

Table 36: Bladder Cancer — Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
GLP-1	Placebo	1.25 (0.44 to 3.78)
TZD		1.86 (0.75 to 4.67)
TZD	GLP-1	1.50 (0.36 to 5.84)
Random-effects model	Residual deviance	5.652 vs. 6 data points
	Deviance information criteria	35.228

CrI = credible interval; GLP-1 = glucagon-like peptide-1 receptor agonist, OR = odds ratio; TZD = thiazolidinediones; vs. = versus.

Withdrawals Due to Adverse Events

Six RCTs[258,263,265,266,268,294] reported withdrawals due to adverse events (N = 26,848) and were included in the reference-case analysis. Rates ranged from 3.2% to 11.4%. Data were not available for all drug classes, including SGLT-2 inhibitors.

Consistency of the network could not be checked. The results of the random-effects NMA model for all class comparisons are presented in Table 37. Compared with placebo and with each other, none of the classes significantly increased or decreased withdrawals due to adverse events.

Table 37: Withdrawals Due to Adverse Events — Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
MET	Placebo	0.33 (0.05 to 1.76)
SUL		0.67 (0.21 to 1.98)
DPP-4		0.97 (0.50 to 1.87)
GLP-1		1.49 (0.96 to 2.39)
TZD		1.19 (0.60 to 2.28)
SUL	MET	2.01 (0.58 to 8.24)
DPP-4		2.95 (0.48 to 20.04)
GLP-1		4.54 (0.81 to 29.39)
TZD		3.63 (0.76 to 18.98)
DPP-4	SUL	1.44 (0.40 to 5.54)
GLP-1		2.23 (0.70 to 7.77)
TZD		1.78 (0.73 to 4.54)
GLP-1	DPP-4	1.54 (0.70 to 3.54)
TZD		1.23 (0.48 to 3.11)
TZD	GLP-1	0.80 (0.34 to 1.72)
Random-effects model	Residual deviance	12.14 vs. 12 data points
	Deviance information criteria	99.864

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; MET = metformin; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SUL = sulfonylurea; TZD = thiazolidinediones; vs. = versus.

Renal Adverse Events

Five RCTs[259,260,263,264,294] reported renal adverse events (renal failure, renal dialysis, renal "abnormality," nephropathy). The count of renal adverse events at any time during the study and the total number of participants who experienced at least one renal adverse event over that same time period were extracted. Analysis could not be conducted for count outcome, and the NMA for the participants who experienced at least one renal adverse event was not robust.

Urogenital Adverse Events

The EMPA-REG OUTCOME study was the only RCT to report urogenital adverse events.[259] Study authors reported "events consistent with urinary tract infections" for 18.1% (423/2,333) of patients in the placebo group, 18.2% (426/2,345) in the empagliflozin 10 mg daily group, and 17.8% (416/2,342) in the empagliflozin 25 mg daily group.

Pancreatitis

Five RCTs[258,260,263,264,317] reported pancreatitis outcomes and were included in the reference-case NMA. The results of the random-effects NMA model for all class comparisons are presented in Table 38. Consistency of the network could not be checked. None of the treatments increased risk of pancreatitis relative to placebo or to each other.

Table 38: Pancreatitis — Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
DPP-4	Placebo	1.60 (0.97 to 2.66)
GLP-1		0.73 (0.37 to 1.39)
GLP-1	DPP-4	0.45 (0.20 to 1.03)
Random-effects model	Residual deviance	7.972 vs. 10 data points
	Deviance information criteria	59.869

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; OR = odds ratio; vs. = versus.

Fractures

A total of three RCTs[259,264,269] reported fracture outcomes and were included in the reference-case analysis. Consistency of the network could not be checked. The results of the random-effects NMA model for selected class comparisons are presented in Table 39. Based on the limited evidence available, none of the classes significantly increased the risk of bone fractures when compared with placebo or with each other in the NMA. Based on the limited evidence available, none of the classes significantly increased fracture risk when compared with placebo or with each other in the NMA. Fracture events were not considered recurrent events for analysis.

Table 39: Bone Fractures — Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI)
DPP-4	Placebo	1.00 (0.39 to 2.47)
SGLT-2		0.95 (0.37 to 2.48)
TZD		1.39 (0.50 to 3.65)

Treatment	Reference	OR (95% CrI)
SGLT-2	DPP-4	0.96 (0.24 to 3.67)
TZD		1.39 (0.35 to 5.24)
TZD	SGLT-2	1.46 (0.36 to 5.60)
Random-effects model	Residual deviance	6.002 vs. 6 data points
	Deviance information criteria	50.27

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter 2, TZD = thiazolidinediones; vs. = versus.

Ketoacidosis

The EMPA-REG OUTCOME study was the only RCT to report ketoacidosis.[259] Study authors reported that less than 0.1% (1/2,333) of patients in the placebo group, 0.1% (3/2,345) in the empagliflozin 10 mg daily group, and less than 0.1% (1/2,342) in the empagliflozin 25 mg daily group experienced ketoacidosis.

Pharmacoeconomic Analysis

Objective

To update the 2013 CADTH pharmacoeconomic analysis of second-line therapies for type 2 diabetes to incorporate key drugs currently approved in Canada; the update is based on the results of CADTH's updated systematic review and NMA.

Methods

Type of Economic Evaluation

Cost-utility analyses comparing alternative second-line therapies in adults with type 2 diabetes experiencing inadequate glycemic control with metformin monotherapy.

Target Population

Adults with type 2 diabetes inadequately controlled with metformin monotherapy. When available, baseline characteristics of simulated patients were derived from RCTs included in the systematic review and NMA.

Treatments

The analysis compared metformin alone with metformin plus sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 analogues, or insulins.

Perspective

The analysis was conducted from the perspective of the Canadian publicly funded health care system.

Efficacy and Safety

Treatment effects (A1C, overall hypoglycemia, weight) for the analysis were derived from the updated systematic review investigating the use of second-line antidiabetic drugs in patients with inadequate glycemic control on metformin monotherapy. If possible, estimates of efficacy for the economic analysis were obtained from the NMA of RCTs included in the systematic review.

Most RCTs included in the meta-analysis were unlikely to have had adequate sample size, or to have been of sufficient duration, to capture incidence rates of infrequent events that may be of economic importance. This includes severe hypoglycemia in patients using insulin secretagogues or insulin. Rather than pool results from smaller RCTs, event rates and treatment effects for these events were derived from large observational studies and RCTs. The baseline rates of severe hypoglycemia among patients using metformin monotherapy (0.05 per 100 patient-years) and metformin plus sulfonylurea (0.9 per 100 patient-years) were derived from a population-based study by Leese et al.[318]

Time Horizon

A 40-year (i.e., patient lifetime) time horizon was used for the reference-case analysis.[318]

Modelling

The latest version of the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (version 2.0, May 2015) was used to forecast long-term diabetes-related complications and cost consequences for each treatment class. The UKPDS Outcomes Model is a computer simulation model developed by the University of Oxford Diabetes Trial Unit, for estimating the impact of health interventions for people with type 2 diabetes over an extrapolated lifetime.[1] It is based on patient data from the United Kingdom Prospective Diabetes Study[319] and uses a wide variety of input data, including previous events. It is capable of accounting for changes in the levels of some risk factors (such as blood glucose level, blood pressure, lipid levels, and smoking status) over time. The UKPDS has been well-validated through comparison of its predictions with results reported in published clinical and epidemiological studies.[320]

The UKPDS Outcomes Model was revised from the version of the model used in previous CADTH reports on second- and third-line treatments.[321] The current version includes additional risk factors, such as:

- albuminuria and estimated glomerular filtration rate, which are associated in the model with several types of vascular events (e.g., MI);
- heart rate;
- hemoglobin; and
- white blood cell count, which is associated with a wide range of complications (e.g., MI, stroke, blindness, amputation, and renal failure).

More information on the UKPDS Outcomes Model can be found at http://www.dtu.ox.ac.uk/outcomesmodel/.[1]

Costs

Cost of Treatments

Unit costs for drugs were obtained from the Ontario Public Drug Program (August 2016), if available. Otherwise, prices were obtained from other public drug programs (Quebec and British Columbia Drug Benefits) in Canada.[322,323] For the reference-case analysis, the price of the lowest-cost alternative was applied for each drug class (i.e., price of generic glyburide for sulfonylureas, neutral protamine Hagedorn (NPH) insulin for basal insulin, biphasic human insulin for biphasic insulin, linagliptin for DPP-4 inhibitors, exenatide for GLP-1 analogues, and empagliflozin for SGLT-2 inhibitors) plus a 8.00% markup and $8.83 pharmacy fee per 90-day supply. With the exception of metformin, for which we assumed the use of maximal doses (2,000 mg daily), it was assumed that patients used the average DDD from the World Health Organization for each treatment.[324] The doses for insulin products (0.53 U/kg, 0.75 U/kg, 1.2 U/kg, and 1.5 U/kg for long-acting insulin analogues, NPH insulin, biphasic insulin analogues, and biphasic human insulin, respectively) were similar to the values used in the previous CADTH reports.

Patients using certain antidiabetic drugs (i.e., insulin secretagogues, insulin) typically use more blood glucose test strips than those using other drugs. For the reference-case analysis, average daily utilization of blood glucose test strips for each drug class was derived from a utilization study in Ontario (Table 40).[325] A scenario analysis was conducted using the Ontario Public Drug Program reimbursement limits for blood glucose test strips (Table 41).[326] A cost of $0.729 per test strip (as listed in the Ontario Public Drug Program) plus a pharmacy fee of $8.83 per 100 test strips was applied. No markup was applied, as test strips are not eligible for markup in the Ontario Public Drug Program. A scenario analysis was conducted in which the cost of test strips was not considered.

Table 40: Mean Daily Utilization of Blood Glucose Test Strips in 2008 by Seniors in the Ontario Public Drug Program, by Type of Pharmacotherapy

Therapy	Daily Use	Standard Deviation
Insulin	2.08	1.71
Hypoglycemia-inducing oral glucose-lowering drugs	1.16	0.94
Non–hypoglycemia-inducing oral glucose-lowering drugs	0.94	1.19

Source: Gomes et al. [326]

Table 41: Ontario Public Drug Programs Reimbursement of Blood Glucose Test Strips

Diabetes Treatment	Number of Blood Glucose Testing Strips Allowed Within a 365-Day Period
Patients managing diabetes with insulin	3,000
Patients managing diabetes with antidiabetes medication with high risk of causing hypoglycemia	400
Patients managing diabetes using antidiabetes medication with low risk of causing hypoglycemia	200
Patients managing diabetes through diet/lifestyle therapy only (no insulin or antidiabetes medications)	200

Source: Ontario Public Drug Programs (http://www.health.gov.on.ca/en/pro/programs/drugs/teststrips/bg_teststrips.aspx, accessed October 2016)[326]

The older-generation sulfonylurea, glyburide, remained the lowest daily cost second-line treatment, even with the additional cost of blood glucose test strips (Table 42). DPP-4 inhibitors, SGLT-2 inhibitors, and NPH insulin were less expensive than long-acting insulin analogues, biphasic human insulin, and GLP-1 analogues.

Table 42: Average Daily Cost of Treatments With and Without the Cost of Blood Glucose Test Strips

Treatment	Assumed Doses	Daily Treatment Cost Without Test Strips[a]	Daily Treatment Cost With Test Strips
Metformin	2,000 mg daily	$0.29	$1.06
Sulfonylureas	Glyburide 10 mg daily	$0.22	$1.17
DPP-4 inhibitors	Linagliptin 5 mg daily	$2.85	$3.62
SGLT-2 inhibitors	Empagliflozin 10 mg daily	$2.92	$3.69
GLP-1 analogues	Exenatide 20 mcg daily	$4.41	$5.17
Basal human insulin	NPH insulin 0.75 U/kg per day[b]	$2.54	$4.24
Long-acting insulin analogues	Insulin glargine 0.53 U/kg per day[b]	$3.78	$5.48
Biphasic human insulin	NPH insulin 30/70 1.50 U/kg per day[b]	$4.68	$6.38

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

Note: Total daily costs for insulins are based on assumed body weight of 87 kg (derived from RCTs included in systematic review).

[a] The cost of the lowest-cost alternative was applied for each drug class, plus a 10% markup and $8.83 pharmacy fee per 90-day supply. It was assumed that patients used the average DDD from the World Health Organization for each treatment.[324]

[b] CADTH Optimal Use Report on Second-line Pharmacotherapy for Type-2 Diabetes — Update (Volume 3, Issue 1A, July 2013).[321]

Costs Due to Long-Term Diabetes Complications

Resource utilization and costs associated with managing long-term diabetes-related complications were obtained from the Ontario Ministry of Health and Long-term Care (2006) (Table 43).[327] Inpatient, outpatient, and emergency department visits, prescription drug claims, long-term care, and home care costs for managing diabetes-related complications were included in the model. Costs were inflated to 2016 Canadian dollars using the Health Component of the Canadian Consumer Price Index.[328] The average annual cost for patients without diabetes-related complications who were using metformin was $2,075. A scenario analysis was conducted to assume costs for fatal first-year events of ischemic heart disease (IHD) and heart failure.

Table 43: Management Costs of Long-Term Diabetes-Related Complications

Complications	First-year Costs[a]		In Subsequent Years[a]
	Fatal	Nonfatal	
Ischemic heart disease	N/A	$6,094	$3,519
Myocardial infarction	$10,212	$19,472	$3,045
Heart failure	N/A	$17,813	$4,994
Stroke	$9,610	$26,523	$3,680
Amputation	N/A	$41,143	$5,635
Blindness	N/A	$3,258	$2,322
Renal failure	N/A	$26,398	$11,981

[a] Costs from the Ontario Diabetes Economic Model[327] inflated to 2016 Canadian dollars (C$) using the health component of the Consumer Price Index.[328]

Costs Due to Hypoglycemic Episodes

For the reference case, it was assumed that episodes of mild to moderate hypoglycemia had no impact on health service resource use. Resource utilization associated with managing a severe hypoglycemic episode was based on Leese et al.[318] and National Institute for Health and Care Excellence (NICE).[329] Management costs were based on data from the Alberta Case Costing Database (2006).[330] Because resource use was derived from the UK, the information used in the previous analysis was presented to diabetes experts for verification. In general, they felt the resource utilization data were reasonable, although the percentage of patients receiving glucagon was thought to be higher than that in Canada. As a result, the average cost of a severe hypoglycemic episode may be overestimated, potentially biasing results against therapies that are associated with an increased risk of hypoglycemia (e.g., insulin).

Table 44: Cost of Severe Hypoglycemic Events

Resource Use	Unit Cost[a]	% Receiving[b]	Weighted
Glucagon	$77.72[c]	90	$74.91
Consultation with ambulance services only[d]	$674	34	$229.29
Consultation with primary/emergency care only[d]	$226	7	$15.83
Consultation with both primary/emergency care and ambulance service	$901	52	$468.26
Direct or indirect hospital admission[d]	$4,834	28	$1,353.52
Total			**$2,141.81**

[a] Costs updated and inflated to 2016 Canadian dollars.

[b] Data from the UK.[318]

[c] Ontario Drug Benefit (October 2016).[331]

[d] Unit cost from Alberta.[330]

Valuing Outcomes

The primary outcome measure in the analysis was the quality-adjusted life-year (QALY), which captures both quantity and quality of life. Patients with type 2 diabetes were assumed to have a EuroQol 5-Dimensions questionnaire (EQ-5D) score of 0.785, based on a study in which the EQ-5D health status questionnaire was used to survey 3,192 patients still participating in the UKPDS in 1997.[332] Utility weights for modelled long-term diabetes-

related complications were obtained from Sullivan et al.[333,334] if available. Otherwise, utility scores were obtained from the study by Clarke et al. (2002).[332] Estimates from Clarke et al.[332] are often used in cost-effectiveness studies related to diabetes interventions. However, unlike Sullivan et al.,[333,334] Clarke et al.[332] did not control for non–diabetes-related complications or other confounding variables such as income, education, ethnicity, and number of comorbidities, all of which may impact health-related quality of life (HRQoL). Multiple complications were assumed to have an additive effect on utility. For example, the utility of a patient who has an MI and then an amputation would first be decremented by 0.0409, and then by a further 0.28.

Table 45: Utility Decrements Associated With Modelled Diabetic Complication Health States

Complication	Utility Decrement (Year 1)	Utility Decrement in Subsequent Years (Year ≥ 2)
Ischemic heart disease	–0.0412	–0.0240
Myocardial infarction	–0.0409	–0.0120
Heart failure	–0.0635	–0.0180
Stroke	–0.0524	–0.0400
Amputation[a]	–0.28	–0.28
Blindness	–0.0498	–0.0498
Renal failure[a]	–0.2630	–0.2630

[a] Utility decrements were not available from the US catalogue;[333,334] therefore, they were obtained from a study by Clarke et al.[332]

There is limited evidence that examines the impact of hypoglycemia and fear of hypoglycemia on HRQoL. For the reference-case analysis, patients experiencing mild to moderate hypoglycemia were assumed to have a reduction in HRQoL of 0.014 per event, while those having a severe hypoglycemic episode were subjected to an HRQoL decrement of 0.047. These decrements were derived from the study by Currie et al. (2006)[335] that modelled the fear of hypoglycemia in patients with type 2 diabetes based on severity and frequency of hypoglycemic events. Upon reviewing the available literature, the decrements reported in Currie et al. (2006) appear to lie within the range of published disutilities associated with minor and major hypoglycemic events.[336] However, to assess the uncertainty associated with the effects of hypoglycemia, a sensitivity analysis was conducted in which, for mild or moderate hypoglycemia, a decrement of 0.0052 was applied, as published in NICE guidance on the use of insulin glargine.[337] For severe hypoglycemia, a decrement of 0.01 per event was applied in sensitivity analysis, as reported in the NICE guidelines on the management of patients with type 2 diabetes.[329]

A utility decrement for weight gain in the primary economic analysis was not applied. Most widely cited studies derive such estimates from much larger weight differences (i.e., 13 kg to 30 kg), and it is unclear whether these can be applied in a proportional manner to the smaller weight differences between drugs observed in the NMA of second-line therapies. It is also uncertain whether these utility decrements are sustained over time. A sensitivity analysis was performed based on data presented in the NICE obesity guidelines,[338] which assumed a utility decrement of 0.00195 per unit increase in BMI. This utility decrement was applied to each year of the simulation based on the estimated BMI for each treatment.

Handling of Uncertainty

Univariate Sensitivity Analyses

Univariate sensitivity analyses were conducted to explore the impact of variation in model inputs and assumptions. Parameters varied in sensitivity analyses were selected based on findings from the previous analysis, and in light of the magnitude of differences in results between previous and updated clinical reviews. Therefore, not all parameters tested in the previous analysis were reassessed.

Cost-Effectiveness Acceptability Curves

A non-parametric bootstrapping method, consisting of 500 bootstrap iterations of 100 patients each with each patient simulated through the model for 10,000 loops (i.e., Monte Carlo trials), was used to estimate the mean quality-adjusted life expectancy and lifetime costs for each treatment arm. Costs and effectiveness for each treatment, as derived from the 500 bootstrap iterations, were plotted as cost-effectiveness acceptability curves (CEACs) to convey the inherent uncertainty in the reference case results. Net benefits CEACs were generated based on the proportion of bootstrap iterations with the highest net monetary benefit across a range of willingness-to-pay thresholds, according to the following formula:

$$\text{Net monetary benefit} = \lambda * E - C$$

where λ = decision-maker's willingness to pay per QALY gained; E = total QALYs for each treatment; C = total lifetime cost of each treatment.

Threshold Analysis

Threshold analyses were also conducted for treatments that were not cost-effective in the base case, to determine the minimal price reductions required for each of those classes to become the second-line treatment strategy with the most favourable cost-effectiveness results in comparison with other second-line treatment strategies.

Results

Reference Case

From the updated analysis (Table 46), sulfonylureas were associated with the lowest total lifetime costs ($39,251), while use of biphasic insulin was associated with the highest lifetime costs ($63,753). Cost-effectiveness estimates were largely driven by the difference in prices of treatments. Sulfonylureas were associated with the most favourable cost-effectiveness estimate, with an incremental cost of $38,643 per QALY gained when compared with metformin monotherapy. Other active treatments were associated with unfavourable cost-effectiveness estimates (i.e., they were dominated, extendedly dominated, or demonstrated very high incremental cost-utility ratios (ICURs) when compared with the next least-costly treatment.

Table 46: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results From the Updated Reference-Case Analysis

Treatment	Cost	QALYs	ICUR vs. MET ($/QALY)	Sequential ICUR ($/QALY)
MET	$ 37,648	8.8369	NA	NA
MET + SU	$ 39,251	8.8784	$38,643	$38,643
MET + SGLT-2 inhibitors	$ 49,308	8.9530	$100,459	$134,861
MET + GLP-1 analogues	$ 55,946	8.9894	$119,997	$182,263
MET + DPP-4 inhibitors	$ 48,859	8.8998	$178,127	Extended dominance[a]
MET + Basal insulins	$ 54,852	8.8898	$324,968	Dominated[b]
MET + Biphasic insulins	$ 63,719	8.9340	$268,496	Dominated[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; NA = not applicable; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

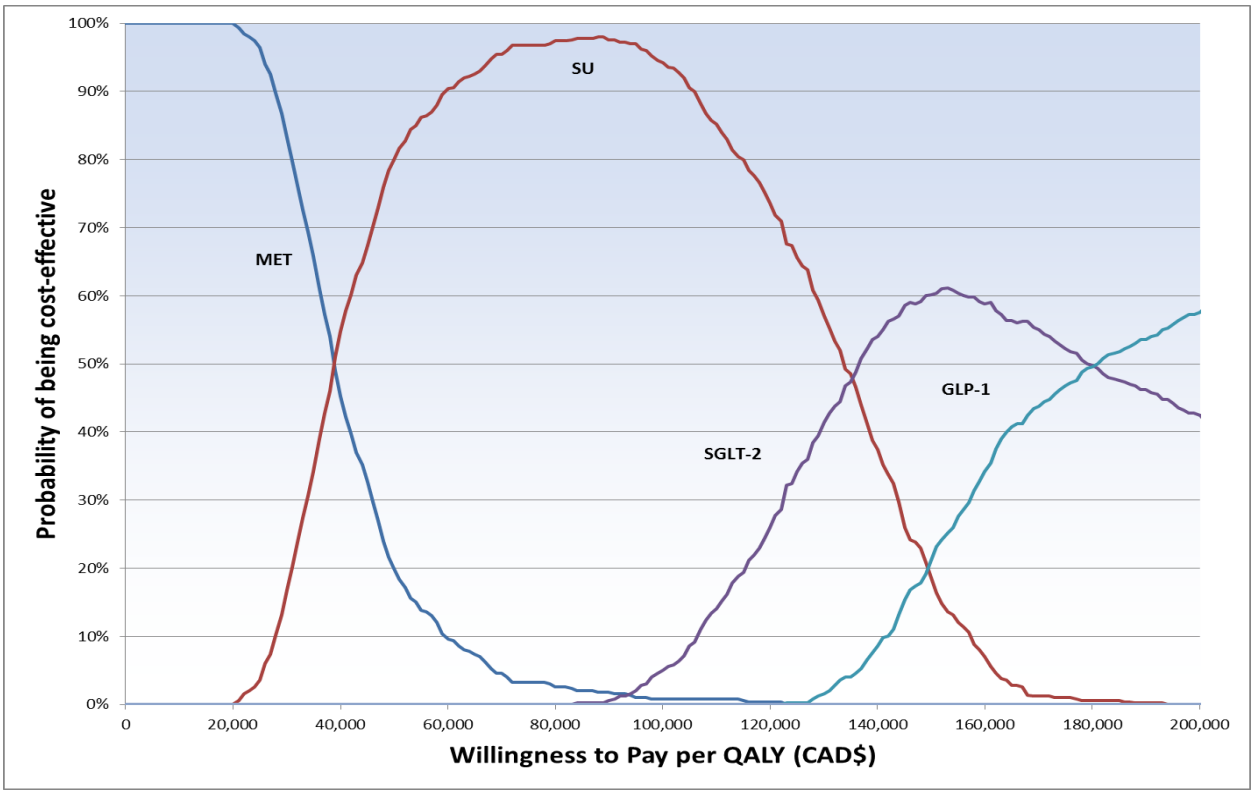
[a] Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1.

[b] Dominated by DPP-4, SGLT-2.

[c] Dominated by SGLT-2, GLP-1.

The cost-effectiveness acceptability curve (Figure 7) shows that addition of a sulfonylurea to metformin had the highest probability of being cost-effective at willingness-to-pay thresholds of between $39,000 and $135,000 per QALY. SGLT-2 inhibitors had the highest likelihood of being cost-effective at thresholds of between $136,000 and $180,000 per QALY. When the willingness-to-pay threshold exceeds $180,000 per QALY, GLP-1 analogues become the most cost-effective treatment overall.

Figure 7: Cost-Effectiveness Acceptability Curve for the Reference-Case Analysis



GLP-1 = glucagon-like peptide-1 analogue; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Sensitivity Analyses

The results of sensitivity analyses indicated that sulfonylureas added to metformin remained the most cost-effective option. Full results from the sensitivity analyses are provided in Appendix 15. The following is a summary of some of the notable results from the sensitivity analyses.

Applying the Ontario Drug Benefit annual reimbursement limits for blood glucose test strips ($400/year for patients using antihyperglycemic medications with high hypoglycemic risk, $200/year for patients using medications with low glycemic risk)[326] increased the ICUR of sulfonylureas compared with metformin compared with the base case, but had little to no effect on GLP-1 analogues and SGLT-2 inhibitors.

Table 47: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results Using Ontario Drug Benefit Reimbursement Limits on Test Strips

Treatment	Cost	QALYs	ICUR vs. MET ($/QALY)	Sequential ICUR ($/QALY)
MET	$ 36,408	8.8369		
MET + SU	$ 39,131	8.8784	$65,600	$65,600
MET + SGLT-2 inhibitors	$ 48,055	8.9530	$100,341	$119,675
MET + GLP-1 analogues	$ 54,687	8.9894	$119,871	$182,113
MET + DPP-4 inhibitors	$ 47,614	8.8998	$178,035	Extended Dominance[a]
MET + Basal insulins	$ 54,886	8.8898	$349,027	Dominated[b]
MET + Biphasic insulins	$ 63,753	8.9340	$281,615	Dominated[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

[a] Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1.

[b] Dominated by DPP-4, SGLT-2, GLP-1.

[c] Dominated by SGLT-2, GLP-1.

Excluding the costs associated with blood glucose test strip use improved the cost-effectiveness of sulfonylureas compared with metformin but had little to no effects on GLP-1 analogues and SGLT-2 inhibitors.

Table 48: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results With Price of Blood Glucose Test Strips Removed

Treatment	Costs	QALYs	ICUR vs. MET ($/QALY)	Sequential ICUR ($/QALY)
MET	$ 34,533	8.8369		
MET + SU	$ 35,367	8.8784	$20,103	$20,103
MET + SGLT-2 inhibitors	$ 46,158	8.9530	$100,164	$144,718
MET + GLP-1 analogues	$ 52,782	8.9894	$119,681	$181,883
MET + DPP-4 inhibitors	$ 45,729	8.8998	$177,897	Extended Dominance[a]
MET + Basal insulin	$ 47,681	8.8898	$248,350	Dominated[b]
MET + Biphasic insulin	$ 56,519	8.9340	$226,431	Dominated[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

[a] Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1.

[b] Dominated by DPP-4, SGLT-2.

[c] Dominated by SGLT-2, GLP-1.

Using the price of the most widely utilized sulfonylurea in Canada based on overall market share by public drug plans ($0.0931 per gliclazide 30 mg slow release [SR] tablet) instead of the price for glyburide 5 mg tablet ($0.00574), the ICUR for sulfonylureas compared with metformin increased modestly, but there was little to no effect on GLP-1 analogues or SGLT-2 inhibitors.[339]

Table 49: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results Using Price of Most Widely Utilized Sulfonylurea (Gliclazide 30 mg SR, $0.0931/tablet)

Strategy	Cost	QALYs	ICUR vs. MET ($/QALY)	Sequential ICUR ($/QALY)
MET	$ 37,648	8.8369		
MET + SU	$ 39,365	8.8784	$41,383	$41,383
MET + SGLT-2 inhibitors	$ 49,308	8.9530	$100,459	$133,335
MET + GLP-1 analogues	$ 55,946	8.9894	$119,997	$182,263
MET + DPP-4 inhibitors	$ 48,859	8.8998	$178,127	Extended dominance[a]
MET + Basal insulin	$ 54,852	8.8898	$324,968	Dominated[b]
MET + Biphasic insulin	$ 63,719	8.9340	$268,496	Dominated[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

[a] Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1.

[b] Dominated by DPP-4, SGLT-2.

[c] Dominated by SGLT-2, GLP-1.

Assuming a quality-of-life reduction due to weight gain (utility decrement of 0.00195 per unit increase in BMI, as per NICE obesity guidelines[338]) reduced the cost-effectiveness of sulfonylureas and GLP-1 analogues but improved the cost-effectiveness of SGLT-2 inhibitors (Table 50).

Table 50: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results Assuming a Utility Decrement of 0.00195 Per Unit Increase in BMI

Strategy	Cost	QALYs	ICUR vs. MET ($/QALY)	Sequential ICUR ($/QALY)
MET	$ 37,648	8.8191		
MET + SU	$ 39,251	8.8435	$65,765	$65,765
MET + SGLT-2 inhibitors	$ 49,308	8.9530	$87,109	$91,864
MET + GLP-1 analogues	$ 55,946	8.9829	$111,743	$222,037
MET + DPP-4 inhibitors	$ 48,859	8.8807	$182,063	Extended Dominance[a]
MET + Basal insulin	$ 54,852	8.8498	$560,703	Dominated[b]
MET + Biphasic insulin	$ 63,719	8.8926	$354,672	Dominated[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

[a] Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1.

[b] Dominated by DPP-4, SGLT-2.

[c] Dominated by SGLT-2, GLP-1.

The following sensitivity analyses did not result in significant changes from the base-case results:

- Using lower disutility values associated with mild, moderate, and severe hypoglycemia: The base-case analysis assumed that disutilities of 0.014 and 0.047 per event would be applied for patients with mild/moderate or severe hypoglycemia, respectively, based on the study by Currie et al. (2006).[335] Sensitivity analyses assumed a disutility of 0.0052 per mild or moderate hypoglycemic event based on the NICE Guidance on insulin analogues[337] and 0.01 per severe hypoglycemic event based on the NICE Guidance for type 2 diabetes.[329]
- Varying utility estimates for diabetes complications using the values from the study by Clarke et al. (2004).[320]
- Assuming year one costs of fatal IHD and heart failure events were zero in the base-case analysis (as Canadian data were not available to inform these costs). An assumption was made to include a cost for these events by applying the proportion of fatal to nonfatal year one costs of MI (~52%) to the year one cost of nonfatal IHD.
- Applying a cost per mild or moderate hypoglycemic event of $93 dollars based on the study by Brod et al.,[340] in contrast to the base-case assumption of no costs associated with mild or moderate hypoglycemic events.
- Assuming the price of insulin glargine (Lantus) for basal insulin rather than the price of insulin NPH.

Threshold Analysis

The results of varying the unit prices of therapies considered in this analysis showed that, in order to overtake sulfonylureas as the most favourable second-line treatment strategy, the unit cost of DPP-4 inhibitors would have to be 80% lower than in the reference case (resulting in an ICUR of $30,846 per QALY gained relative to metformin monotherapy). When price reductions less than 70% were modelled, DPP-4 inhibitors remained extendedly

dominated. For SGLT-2 inhibitors, a 60% reduction in unit price would be necessary for this class to be the most cost-effective treatment option (for an ICUR of $38,586 per QALY gained relative to metformin monotherapy). For GLP-1 analogues, a 70% reduction in unit price would be necessary for this class to be the most cost-effective treatment option (for an ICUR of $35,879 per QALY gained relative to metformin monotherapy). The full results of the threshold analysis are presented in Table 51.

Table 51: Threshold Analysis for DPP-4 Inhibitors, SGLT-2 Inhibitors, and GLP-1 Analogues as Second-Line Treatments

Class	Price Reduction	New Unit Price	ICUR ($/QALY) (vs. Metformin Monotherapy)	Sequential ICUR ($/QALY)
DPP-4 inhibitors	Reference case	$2.5500	$178,127	Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1
	10%	$2.2950	$159,716	
	20%	$2.0400	$141,305	
	30%	$1.7850	$122,893	
	40%	$1.5300	$104,482	Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, SU and GLP-1
	50%	$1.2750	$86,071	Subject to extended dominance through SU and SGLT-2, SU and GLP-1
	60%	$1.0200	$67,660	$123,825 compared with SU
	70%	$0.7650	$49,250	$69,780 compared with SU
	80%	$0.5100	$30,839	$30,839 compared with MET
	90%	$0.2550	$12,428	$12,428 compared with MET
SGLT-2 inhibitors	Reference case	$2.6177	$100,459	$134,861 compared with SU
	10%	$2.3559	$90,145	$118,807 compared with SU
	20%	$2.0941	$79,831	$102,753 compared with SU
	30%	$1.8324	$69,518	$86,701 compared with SU
	40%	$1.5706	$59,205	$70,648 compared with SU
	50%	$1.3089	$48,891	$54,594 compared with SU
	60%	$1.0471	$38,577	$38,577 compared with MET
	70%	$0.7853	$28,263	$28,263 compared with MET
	80%	$0.5235	$17,949	$17,949 compared with MET
	90%	$0.2618	$7,635	$7,635 compared with MET
GLP-1 analogues	Reference case	$1.9950	$119,997	$182,263 compared with SGLT-2
	25%	$1.4963	$89,951	$109,135 compared with SU
	50%	$0.9975	$59,906	$67,856 compared with SU
	60%	$0.7980	$47,887	$51,344 compared with SU
	70%	$0.5985	$35,869	$35,869 compared with MET
	75%	$0.4988	$29,860	$29,860 compared with MET
	80%	$0.3990	$23,851	$23,851 compared with MET
	90%	$0.1995	$11,832	$11,832 compared with MET

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter 2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

An additional threshold analysis was conducted for the scenario in which a disutility for weight gain is included based on the NICE obesity guidelines (0.00195 per BMI unit increase).[338] The unit cost of DPP-4 inhibitors would have to be 70% lower than in the reference case to overtake sulfonylureas (resulting in an ICUR of $50,338 per QALY gained relative to metformin monotherapy). When price reductions less than 60% were modelled, DPP-4 inhibitors remained extendedly dominated. For SGLT-2 inhibitors, a 30% reduction in unit price would be necessary for this class to be the most cost-effective treatment option (for an ICUR of $60,280 per QALY gained relative to metformin monotherapy). For GLP-1 analogues, a 50% reduction in unit price would be necessary for this class to be the most cost-effective treatment option (for an ICUR of $55,785 per QALY gained relative to metformin monotherapy). The full results of the threshold analysis are presented in Table 52.

Table 52: Threshold Analysis for DPP-4 Inhibitors, SGLT-2 Inhibitors, and GLP-1 Analogues as Second-Line Treatments Assuming a Utility Decrement of 0.00195 Per Unit Increase in BMI

Class	Price Reduction	New Unit Price	ICUR ($/QALY) (vs. Metformin monotherapy)	Sequential ICUR ($/QALY)
DPP-4 inhibitors	Reference case	$2.5500	$182,064	Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, MET and GLP-1, SU and GLP-1
	10%	$2.2950	$163,246	
	20%	$2.0400	$144,428	
	30%	$1.7850	$125,609	
	40%	$1.5300	$106,791	Subject to extended dominance through MET and SGLT-2, SU and SGLT-2, SU and GLP-1
	50%	$1.2750	$87,973	Subject to extended dominance through MET and SGLT-2, SU and SGLT-2
	60%	$1.0200	$69,156	$71,379 compared with SU
	70%	$0.7650	$50,338	$50,338 compared with MET
	80%	$0.5100	$31,521	$31,52 compared with MET
	90%	$0.2550	$12,703	$12,703 compared with MET
SGLT-2 inhibitors	Reference case	$2.6177	$87,109	$91,864 compared with SU
	10%	$2.3559	$78,166	$80,928 compared with SU
	20%	$2.0941	$69,223	$69,993 compared with MET
	30%	$1.8324	$60,280	$60,280 compared with MET
	40%	$1.5706	$51,337	$51,337 compared with MET
	50%	$1.3089	$42,394	$42,394 compared with MET
	60%	$1.0471	$33,451	$33,451 compared with MET
	70%	$0.7853	$24,507	$24,507 compared with MET
	80%	$0.5235	$15,564	$15,564 compared with MET
	90%	$0.2618	$6,621	$6,621 compared with MET
GLP-1	Reference	$1.9950	$111,743	$222,037 compared with SGLT-2

Class	Price Reduction	New Unit Price	ICUR ($/QALY) (vs. Metformin monotherapy)	Sequential ICUR ($/QALY)
analogues	case			
	25%	$1.4963	$83,764	$86,913 compared with SU
	50%	$0.9975	$55,785	$55,785 compared with MET
	60%	$0.7980	$44,593	$44,593 compared with MET
	70%	$0.5985	$33,401	$33,401 compared with MET
	75%	$0.4988	$27,806	$27,806 compared with MET
	80%	$0.3990	$22,210	$22,210 compared with MET
	90%	$0.1995	$11,018	$11,018 compared with MET

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter 2; SU = sulfonylurea; vs. = versus.

Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

Discussion

The objective of this review was to conduct an update of CADTH's 2013 systematic review and NMAs of diabetes pharmacotherapy for patients with diabetes inadequately controlled with metformin monotherapy. In addition, the number of outcomes studied was expanded, and a second review question was added to systematically review pharmacotherapy for patients who are at high risk for cardiovascular complications.

For the first research question, the literature search identified 107 additional RCTs that were incorporated into the 2013 CADTH review, increasing the total number to 175 unique RCTs. For the second research question, a total of 17 unique RCTs reporting populations at high risk for cardiovascular complications of diabetes were examined in-depth.

Interpretation of Systematic Review Results

Patients Inadequately Controlled on Metformin

Results from the systematic review align with other class-level systematic reviews and meta-analyses that have assessed the comparative efficacy of antidiabetes drugs in patients with inadequate glycemic control on metformin monotherapy, although this review includes significantly more RCTs and examines many more clinical outcomes and adverse events.[341,342] Results also support current clinical practice guidelines for this patient population by DC. Similar to the previous CADTH review and other systematic reviews of oral antidiabetes drugs, there remained a lack of conclusive evidence regarding the effects of various therapies on the long-term complications of diabetes.

Regarding glycemic control, the updated NMA demonstrated that all of the drug classes of interest resulted in statistically significant reductions in A1C relative to metformin monotherapy, with few statistically significant differences between any of the active treatments. The effect estimates showed that sulfonylurea and GLP-1 analogues significantly decreased A1C compared with DPP-4 inhibitors (–0.30%).

When looking at patient weight, GLP-1 analogues and SGLT-2 inhibitors significantly decreased body weight compared with metformin monotherapy and the other treatment options. As expected, effect estimates showed significantly increased weight from insulin and sulfonylurea. The evidence for BMI was insufficient to find any differences among the treatments.

Reductions in systolic blood pressure were seen with SGLT-2 inhibitors and GLP-1 analogues compared with metformin monotherapy, sulfonylurea, and DPP-4 inhibitors. All treatments improved diastolic blood pressure compared with metformin monotherapy, with the SGLT-2 inhibitors showing superiority over the rest of the drug classes of interest when compared in the NMA. While not approved as antihypertensive drugs, the evidence shows that some of the drugs studied may have capabilities to lower blood pressure.

Changes in LDL and HDL cholesterol may impact short and long-term patient outcomes and overall risk for cardiovascular disease. In this review, the NMA showed small but statistically significant increases in the mean difference in the relative change from baseline for LDL cholesterol, and similar increases in the mean difference in the relative change from baseline for HDL cholesterol with SGLT-2 inhibitors added to metformin. The clinical significance of these findings has not been investigated, and the impact on patients, given the small increase in both “bad” and “good” cholesterol, remains unclear.

The NMA analysis of total adverse events and withdrawals due to adverse events showed no significant differences among the effect estimates across drug classes, with the exception of GLP-1 analogues and insulins (basal and biphasic). Although this review analyzed total number of adverse events, we did not examine the type of individual adverse events commonly reported in the RCTs. It is well documented, however, that gastrointestinal adverse events are commonly reported with the GLP-1 analogues, and hypoglycemia is common with the insulins. Both classes are additionally known for irritation, redness, or itchiness at the injection site. No differences across the treatment classes were seen when serious adverse effects were analyzed in the NMA.

Effect estimates from the NMA show a significant increase in nonsevere hypoglycemia with sulfonylureas and both basal and biphasic insulin when compared with metformin monotherapy (range 3.18 to 7.59 for the odd ratios). These differences are maintained when sulfonylurea and insulins are compared with the other treatment classes in the NMA, although basal insulin shows significantly fewer nonsevere hypoglycemia events when compared with sulfonylurea indirectly (OR 0.42). Given that recent literature has suggested that preventing hypoglycemia is as important, or more important, for disease management and long-term prognosis, than tight glycemic control, these results may be considered clinically relevant when weighing treatment choices following failure of metformin monotherapy.

Urinary tract and genital infections are a particular concern with the SGLT-2 inhibitors, as their mechanism of action may lead to glycosuria (excretion of glucose into the urine), a well-recognized risk factor for genital infections. In the current review, RCT data were available only for sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors compared with metformin monotherapy. Effect estimates produced through the NMA do not show a statistically significant increase in the odds of a urogenital adverse event with the SGLT-2 inhibitors when compared with metformin monotherapy and DPP-2 inhibitors. These events were noted in the Health Canada summary of regulatory decision, and the increase for this

outcome may be driven by an increase in genital infections, although this was not investigated in this review and the mechanism leading to genital infection is still not completely understood.

None of the treatment classes significantly increased or decreased renal adverse events, although the NMA was limited by the large number of RCTs reporting zero events, making results difficult to interpret conclusively.

Most RCTs included in this review were not adequately powered (by size or duration) to ascertain differences in long-term complications of type 2 diabetes. Given the paucity of data available in this review, no significant differences between the treatment classes were found.

Treatment strategies for patients with type 2 diabetes must consider more than glycemic control and must take individual requirements for treatment into consideration. This review has identified some risks that may partially offset benefits for some treatments and effect estimates varied across both treatment classes and outcomes. Choice of treatment must be considered in context with recommendations and guidelines in mind.

Patients at High Risk for Cardiovascular Events

There are clear correlations between type 2 diabetes and the long-term health impacts related to heart disease, premature death, and cardiovascular complications. Until recently, there has been neutral evidence supporting any benefit to patients in terms of long-term cardiovascular outcomes following pharmacologic treatment. This review considers RCTs assessing the cardiovascular safety of GLP-1 agonists (ELIXA and LEADER), DPP-4 inhibitors (SAVOR-TIMI 53, EXAMINE, and TECOS), and SGLT-2 inhibitors (EMPA-REG OUTCOME). Evidence from both the EMPA-REG OUTCOME and LEADER RCTs has led to changes in practice. Following publication of the EMPA-REG OUTCOME study, DC produced 2016 interim guidance suggesting that patients who are not meeting their glycemic targets and who have clinical cardiovascular disease be treated with an SGLT-2 inhibitor with proven cardiovascular benefit. The LEADER study, published more recently in June 2016, produced similar changes in DC guidelines (November 2016).

Results from both the LEADER and EMPA-REG OUTCOME studies individually showed a statistically significant end point for the cardiovascular composite MACE (when all uncategorized deaths were considered to be cardiovascular deaths); however, these results were not maintained in the NMA when combined with other studies reporting this outcome. When the individual outcomes that make up MACE were analyzed separately in the RCTs, there were no statistically significant findings, which was supported by the results of the NMA in this review. Due to the small number of studies in the network (time-to-event via hazard ratios), we are unable to investigate inconsistency, heterogeneity, and the impact of the network geometry on the effect estimates produced. As there are limitations of the study data and disagreement between the RCT evidence and the NMA, data from future studies may provide an opportunity to investigate these outcomes further.

The NMA for all-cause mortality showed a statistically significant reduction in all-cause mortality with the SGLT-2 inhibitors when compared with placebo and with DPP-4 inhibitors. These results are consistent with the findings of previous meta-analyses[343] and may indicate a protective effect in patients taking SGLT-2 inhibitors. Further evidence development may be required to confirm this outcome, but results look promising.

Concerns over hospitalizations for heart failure with the DPP-4 inhibitors have been noted, but no statistically significant increases were noted with any of the treatments included in the NMA compared with placebo or with each other (SGLT-2 inhibitors, DPP-4 inhibitors, GLP-1 analogues).

Severe hypoglycemia was significantly reduced when the GLP-1 analogues were compared with placebo and with DPP-4 inhibitors, but neutral when compared with SGLT-2 inhibitors. No significant increases in other severe adverse events were found. A limited number of RCTs reported both bladder and pancreatic cancer, and no increases were seen the GLP-1 analogues (bladder, pancreatic cancer) or DPP-4 inhibitors (pancreatic cancer). Given the small number of RCTs reporting cancer outcomes, results should be interpreted with caution.

Many of the large RCTs looking at cardiovascular outcomes were powered for cardiovascular safety outcomes, and limitations in the reporting of many efficacy outcomes (e.g., A1C) meant that results for many outcomes of interest could not be used in this review. Assessment of the noted cardiovascular benefits in context with other outcomes related to glycemic control are therefore not possible. Although it was not possible to consider the data from the recent large clinical trials (e.g., EMPA-REG-OUTCOME and LEADER) in the NMA for research question 1, results showed benefit in the high-risk populations studied. Treatment options for patients at high risk for cardiovascular disease should consider these study results in context with the results from the NMA.

Interpretation of Pharmacoeconomic Results

The reference-case results of the 2013 CADTH report on the cost-effectiveness of second-line treatments indicated that sulfonylureas were associated with the most favourable cost-effectiveness estimate, with an incremental cost of $8,445 per QALY gained relative to metformin monotherapy.[321] The updated cost-effectiveness analysis, based on the results of the updated NMA, indicated that sulfonylureas remained the most cost-effective second-line therapy in patients with diabetes inadequately controlled on metformin monotherapy, despite higher rates of hypoglycemia and weight gain relative to newer oral antidiabetic drugs. The results of the updated NMA differed from the 2013 analysis in that the effects of metformin monotherapy on A1C and weight were slightly larger, which narrowed the incremental effects of second-line treatments, resulting in lower QALY gains and increased ICUR values. Similar to the previous analysis, the favourable cost-effectiveness results for sulfonylureas were attributable to the following:

- low price relative to other classes of drugs
- minimal differences in glycemic control between drug classes, resulting in small differences in predicted complication rates and QALY gains
- low absolute risk of severe hypoglycemia requiring health care resource use.

A large number of sensitivity analyses were performed to examine robustness of the results to changes in model inputs and assumptions. In all instances, sulfonylureas remained the most cost-effective strategy.

The SGLT-2 inhibitors, GLP-1 analogues, and DPP-4 inhibitors were among the classes with the least favourable cost-effectiveness results, largely driven by their high cost and gains in glycemic control similar to those of less costly drug classes. The cost-effectiveness

results for SGLT-2 inhibitors, GLP-1 analogues, and DPP-4 inhibitors were robust even in the optimistic scenarios when higher disutilities for weight gain were used. Threshold analyses revealed that significant unit price reductions would be necessary in order to displace sulfonylureas as the most cost-effective second-line therapy.

The results of the reference case are aligned with previous CADTH analyses[327,344,345] that compared antidiabetic treatments in the second-line setting and reported sulfonylureas as the most cost-effective second-line treatment option compared with DPP-4 inhibitors and GLP-1 analogues. Economic analyses that included SGLT-2 inhibitors as a second-line treatment option were not available at the time of this review.

Strengths and Limitations

Clinical Review

Strengths and limitations of this review were similar to those reported in previous CADTH reviews. The updated systematic review was conducted according to a protocol specified in advance, using standard approaches for identification of evidence, data abstraction, quality assessment, and analysis. By conducting an NMA, both direct and indirect estimates of effect were captured, and results are reported in a manner that is practical for health care professionals and decision-makers. Results from the NMA were generally consistent with those from direct pairwise comparisons across all outcomes, a finding that adds validity to the analysis. Sensitivity analyses were conducted to explore methodological heterogeneity. The consistency of these results with the reference-case analysis demonstrates the robustness of the findings.

Similar to the previous CADTH review, there are limitations related to the available evidence, and these limitations warrant discussion. First, the population of interest for the systematic review consisted of patients with diabetes inadequately controlled with first-line metformin monotherapy who required a second-line drug; but most identified trials included patients who might have received various antidiabetes drugs before the use of metformin monotherapy. Second, for populations inadequately controlled on metformin, there was little evidence for the effect of second-line drugs on long-term diabetes-related complications. Hence, comparative efficacy on such outcomes must be inferred from A1C, a surrogate with some important limitations, particularly with respect to the prediction of macrovascular outcomes. Unfortunately, there is little high-quality evidence associating reductions in major morbidity or premature death with reductions in A1C. As well, rates of severe hypoglycemia and other identified adverse events of interest were low, potentially limiting any meaningful comparisons between treatments.

The reference case for the NMA was conducted by grouping drugs into classes (e.g., sulfonylureas, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 analogues) — an approach that requires the important assumption that drugs within a particular drug class are similar enough to pool, and that class effects are significant. The individual drug NMA was conducted to investigate the similarity of effect sizes within each drug class; the results suggested that the effects are similar within the classes, supporting the decision to conduct the class-level analysis. The decision to pool NPH insulin with long-acting insulin analogues (i.e., insulin glargine and insulin detemir) into a single “basal insulin” class may have limitations given the different pharmacodynamics profiles of insulin glargine and insulin detemir; however, given the paucity of evidence for these drugs in many of the outcomes of interest, splitting them into separate classes may have impacted the robustness of the NMA.

CADTH previously reported that a prior assessment of long-acting insulin analogues found little or no difference between NPH insulin and insulin glargine for A1C (weighted mean difference [WMD] = –0.05%; 95% CI, –0.13% to 0.04%) or NPH insulin and insulin detemir (WMD = 0.13%; 95% CI, 0.03% to 0.22%).[147,148] These findings were noted in the previous CADTH review for second-line therapies and suggest that it is appropriate to pool these drugs into a single "basal insulin" class for the purposes of this NMA.

For research question 1, we were unable to include the results from emerging trials reporting clinically important outcomes (e.g., EMPA-REG OUTCOME and LEADER) in the NMA. The high-risk populations eligible for these studies included treatment-naive and treatment-experienced participants who may have been on one or more unspecified background therapies in addition to the intervention during the study. Limited reporting of both the population characteristics and outcomes restricted our availability to evaluate transitivity assumptions for the NMA, and data for participants with diabetes inadequately controlled on metformin could not be extracted from the entirety of the study population. For example, a number of patients in the standard-of-care arm of the EMPA-REG OUTCOME study were treated with background therapies also included as comparators in the NMA. As a result, data from these studies could not be considered in the economic evaluation, as only NMA results from research question 1 informed the analyses. In addition, it was difficult to comprehensively elucidate the comparative microvascular effects of the drug classes, given the heterogeneity in outcome reporting and definitions. This limited our capacity to investigate nephroprotective effects.

Although we conducted a complete ROB assessment using the Cochrane Collaboration Tool, our assessment assumed outcomes were objective, and there are limitations to this approach. For example, we are aware that the FDA Endocrinologic and Metabolic Drugs Advisory Committee cited a lack of clarity in the cardiovascular mortality outcome definition and the "nonassessible deaths" reported in the EMPA-REG OUTCOME trial.

The limited number of studies meeting the eligibility requirements for research question 2 restricted our capacity to comprehensively evaluate individual and class effects through the Bayesian NMA. In addition, the trials were powered for individual comparisons for the MACE outcome, but not for the individual components in the outcome. Clinical studies continue to emerge, and further evidence development will improve the robustness of the NMA analyses for this patient population at high risk of cardiovascular events with inadequately controlled diabetes. Positive results from the individual SUSTAIN-6 trial for the GLP-1 agonist semaglutide were published in November 2016, after the NMA results from this review were finalized, and additional findings are expected by 2019 for other GLP-1 drugs and for SGLT-2 and DPP-4 inhibitors.

While the newer drugs show promise in high-risk populations, there remains a paucity of long-term evidence for the safety and effectiveness of these medications as second-line therapy for those with diabetes inadequately controlled on metformin alone.

Pharmacoeconomic Review

With respect to limitations of the pharmacoeconomic analysis, it should be noted that the UKPDS model does not explicitly incorporate a number of diabetes-related morbidities (e.g., peripheral neuropathy and ulceration). Furthermore, some complications are represented as a single end point (e.g., blindness and end-stage renal disease) in the model rather than intermediate states (e.g., retinopathy and nephropathy) that may themselves be associated

with reduced HRQoL. Since a reduced incidence of these outcomes and the resulting benefits in terms of HRQoL and reduced treatment costs are not captured, use of the UKPDS model may result in slight overestimation of incremental cost-effectiveness ratios. However, the impact of this factor on cost-effectiveness estimates is likely negligible, given the minimal differences in glycemic control across drug classes.

Type 2 diabetes is a chronic, progressive disease that usually requires augmentation of antidiabetic therapy over time. Modelling changes in treatment over time is challenging with any model, including the UKPDS Outcomes Model. There is uncertainty about which treatments patients will add or switch to after inadequate control on second-line therapy. Furthermore, when patients use multiple treatments over time, it is difficult to assess whether benefits over a lifetime are attributable to second-line treatments or subsequent treatments. Because of these considerations, it was assumed in the reference case that patients remained on their respective second-line therapy over their expected lifetime, without adding or switching to subsequent drugs. This approach is admittedly not reflective of clinical practice, given the progressive nature of diabetes. The effect of this assumption was tested in the 2013 CADTH report, but not in this updated evaluation, through a scenario analysis in which patients were assumed to add NPH insulin as third-line therapy after predefined criteria were met (i.e., when A1C level reached or surpassed 9.0%). However, to conduct this analysis within the UKPDS model, the weight and hypoglycemia inputs had to be front-loaded (i.e., applied in year one) because, unlike A1C, these parameters could not be modified over time. As a result, some elements of the scenario analysis results could not be discounted appropriately. Nevertheless, the assumed addition of NPH at an A1C value of 9% did not appear to alter the reference-case results in direction or magnitude in the 2013 analysis. In the future, if the UKPDS model is updated to enable more seamless integration of changes in treatment sequences over time, reanalysis may be warranted.

Another limitation of the UKPDS model is its inability to account for potential cardiovascular benefits of SGLT-2 inhibitors and GLP-1 analogues beyond those due to improved glycemic control. The EMPA-REG OUTCOME and LEADER trials demonstrated that empagliflozin and liraglutide, respectively, lowered the rate of cardiovascular outcomes and death in patients with pre-existing cardiovascular disease, likely through mechanisms other than improved glycemic control.[259,262] Such benefits are not accounted for in the current analysis; therefore, the true cost-effectiveness of the SGLT-2 inhibitor and GLP-1 analogue classes may be more attractive than suggested by the estimated ICURs.

With respect to the inputs used in the analysis, there was considerable uncertainty regarding the disutility associated with insulin use, weight changes, and hypoglycemia. In the absence of sound data for these inputs, conservative estimates were used for the reference-case analysis but were tested in sensitivity analyses. The results were robust to variations in these parameters (i.e., SUs remained the most cost-effective alternative), primarily due to the large difference in drug costs between SUs and newer classes such as SGLT-2 inhibitors and DPP-4 inhibitors. However, should these cost differences be narrower than the list prices suggest (e.g., as a result of price negotiations), uncertainty regarding the disutilities associated with hypoglycemia and weight gain may have greater importance in determining the most cost-effective second-line therapy. This was reflected in the threshold analyses conducted using an optimistic scenario of higher disutility with weight gain, in which only a 30% reduction in the cost of SGLT-2 inhibitors would result in this class surpassing sulfonylureas as the most cost-effective second-line treatment strategy.

Conclusions and Implications for Decision or Policy-Making

Results from the systematic review align with other class-level systematic reviews and meta-analyses that have assessed the comparative efficacy of antidiabetes drugs in patients with inadequate glycemic control on metformin monotherapy, although this review includes significantly more RCTs and examines many more clinical outcomes and adverse events. Results also support current clinical practice guidelines for this patient population by Diabetes Canada. Similar to the previous CADTH review and other systematic reviews on oral antidiabetes drugs, there remained a lack of conclusive evidence regarding the effects of various therapies on the long-term complications of diabetes.

There are clear correlations between type 2 diabetes and the long-term health impacts related to heart disease, premature death, and cardiovascular complications. Many of the large cardiovascular outcome RCTs were powered for cardiovascular safety outcomes yet limited in the reporting of many other efficacy outcomes. As a result, it is difficult to place the noted cardiovascular benefits in context with other outcomes related to glycemic control. Although it was not possible to consider the data from the recent large clinical trials (e.g., EMPA-REG OUTCOME and LEADER) in the NMA for research question 1, results show benefit in the high-risk populations studied. Treatment options for patients at high risk for cardiovascular disease should consider these study results in context with the results from the NMA.

The results of the updated cost-effectiveness analysis comparing second-line treatments for type 2 diabetes after inadequate control with metformin monotherapy were congruent with the results of the previous analysis. Sulfonylureas added to metformin represented the most cost-effective second-line therapy, a finding that was robust in numerous sensitivity analyses. These results were primarily driven by the low cost of sulfonylureas relative to other drugs, marginal differences in glycemic control and long-term complications between sulfonylureas and other drugs, and the expected low absolute risk of severe hypoglycemic episodes requiring health care resource use. SGLT-2 inhibitors, which could not be considered in the previous analysis since no drugs were approved in Canada at the time, were found to be associated with a high ICUR in the updated analysis. To surpass the sulfonylureas as the most cost-effective second-line therapy, reductions in cost of 60% or more would be required for this class while DPP-4 inhibitors and GLP-1 analogues would require reductions of 70% or more. Because of the lack of adequate clinical data, there was considerable uncertainty surrounding some of the key drivers in the economic analysis. These included the disutilities associated with insulin use, weight change, and hypoglycemia, and the incidence of hypoglycemia across various treatments.

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