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New Drugs for Type 2 Diabetes: Second-Line Therapy — Recommendations Report

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Abbreviations

A1C	glycated hemoglobin
CDA	Canadian Diabetes Association
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
CrI	credible interval
DPP-4	dipeptidyl peptidase-4
EQ-5D	EuroQol 5-Dimensions questionnaire
GLP-1	glucagon-like peptide-1
HDL	high-density lipoprotein
ICUR	incremental cost-utility ratio
LDL	low-density lipoprotein
MACE	major adverse cardiac events
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SGLT-2	sodium-glucose cotransporter-2
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study

Background

CADTH previously completed an Optimal Use Report in 2010 and a subsequent update in 2013 on drug therapies for second- and third-line treatment of type 2 diabetes. Since 2013, several new drugs and a new medication class (sodium-glucose cotransporter-2 [SGLT-2] inhibitors) have been released on the market in Canada. During the same period, CADTH Common Drug Review has provided multiple recommendations in technology assessments of individual drugs for type 2 diabetes. Given the evolving landscape of the treatment of type 2 diabetes, an update of the previous review has been undertaken. This document provides the draft recommendations for second-line drug treatments for type 2 diabetes based on this update.

Table 1: Drugs Included in the Clinical Review

Drug Class	Drugs
DPP-4 inhibitor	Alogliptin; Alogliptin/metformin
	Linagliptin; Linagliptin/metformin
	Saxagliptin; Saxagliptin/metformin
	Sitagliptin; Sitagliptin/metformin
SGLT-2 inhibitor	Canagliflozin; Canagliflozin/metformin
	Dapagliflozin; Dapagliflozin/metformin
	Empagliflozin; Empagliflozin/metformin
Sulfonylurea	Chlorpropamide
	Gliclazide
	Glimepiride
	Glyburide
	Tolbutamide
Thiazolidinedione	Pioglitazone
	Rosiglitazone
Meglitinide	Nateglinide
	Repaglinide
Alpha-glucosidase inhibitor	Acarbose
GLP-1 analogue	Dulaglutide
	Exenatide
	Exenatide extended-release
	Liraglutide
	Albiglutide
Bolus insulin	Insulin aspart
	Insulin glulisine
	Insulin lispro
	Insulin, regular
	Insulin, pork
Basal insulin	Insulin, NPH
	Insulin, pork
	Insulin detemir
	Insulin glargine
Biphasic insulin	Insulin regular/insulin, NPH
	Insulin lispro/lispro protamine
	Insulin aspart/aspart protamine

DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; SGLT-2 = sodium-glucose cotransporter-2.

CADTH Canadian Drug Expert Committee Values and Preferences

CADTH Canadian Drug Expert Committee (CDEC) considered the needs and concerns of patients, as represented in the feedback received from Diabetes Canada (formerly the Canadian Diabetes Association), as well as the available clinical and economic evidence. Based on evidence that the efficacy of treatments is similar across drug classes, CDEC identified the values of safety and the efficient use of health care resources as particularly important in making its recommendation for a second-line agent for the treatment of adults with type 2 diabetes. In considering the patients' perspectives, CDEC noted patients' concerns about the risk of weight gain and hypoglycemia that can be associated with some diabetes treatments, including sulfonylureas.

CDEC noted that patients prefer an individualized approach to therapy and access to all available treatments. However, this preference needs to be balanced with the total cost-effectiveness associated with different diabetes treatments. CDEC noted that ensuring the efficient use of limited health care resources and promoting the sustainability of public drug programs is of great importance to Canadians.

Stakeholder Feedback

CDEC highly valued the input from stakeholders throughout the process of developing these recommendations. Over the course of the review, stakeholders were invited to provide feedback on the protocol, the draft science reports, and the draft recommendations. At each stage, CDEC listened to feedback from clinical experts, the patient group, manufacturers, and jurisdictions, and it incorporated this feedback into each step of the process. As a result of stakeholder feedback, among other modifications to the scope and review, analyses of weight gain and hypoglycemia were conducted to better inform the committee about these issues of concern to patient groups. The recommendations provided in this document reflect the input received by CADTH at all steps of the process.

Policy Question

What is/are the preferred second-line agent(s) to consider for the treatment of adults with type 2 diabetes with inadequate glycemic control on metformin monotherapy?

Recommendation

Recommendation 1

For patients with type 2 diabetes and without established cardiovascular disease, CDEC recommends that a sulfonylurea be added to metformin for adults inadequately controlled on metformin alone.

Reasons for Recommendation

1. The results of the clinical review and a network meta-analysis (NMA) demonstrated that all classes of antidiabetes drugs were associated with similar efficacy for improving glycated hemoglobin (A1C) in adults with diabetes inadequately controlled with metformin alone (mean differences from baseline ranged from −0.58% for dipeptidyl peptidase-4 [DPP-4] inhibitors to −0.94% for biphasic insulin). No class demonstrated any clear clinical superiority over sulfonylureas for any safety or efficacy outcome.
2. The CADTH pharmacoeconomic evaluation demonstrated that sulfonylureas are the most cost-effective second-line treatment option for adults with diabetes inadequately controlled on metformin alone. For a base case representing a typical Canadian patient with diabetes, sulfonylureas were associated with an incremental cost-utility ratio (ICUR) of $38,643 per quality-adjusted life-year (QALY) gained compared with metformin alone. Compared with metformin monotherapy, the ICURs for the other drug classes, when added to metformin, were SGLT-2 inhibitors ($100,459), glucagon-like peptide-1 (GLP-1) analogues ($119,997), DPP-4 inhibitors ($178,127), basal insulins ($324,968), and biphasic insulins ($268,496).

Of Note

- The CADTH therapeutic review was conducted using a rigorous systematic review methodology. The clinical review focused on data from randomized controlled trials (RCTs), as these studies were considered to offer the best available evidence for making comparisons within and across drug classes. Although the systematic review included a large number of studies (i.e., 175 unique RCTs), CDEC noted limitations with the available evidence, including insufficient data regarding the comparative efficacy of second-line treatment options for reducing the risk of clinically important long-term outcomes, such as major cardiovascular events, and the unknown impact of bias in individual trials included in the NMAs. Despite these limitations, the NMA conducted using results from 84 trials was robust, as efficacy and safety outcomes analyzed were consistent with direct pairwise comparisons.
- CDEC noted that the clinical trial data suggest that, among all patients with diabetes, clinically meaningful hypoglycemic events are rare across all drug classes, with low absolute rates of severe hypoglycemia reported. Weight gain associated with treatment involving sulfonylureas is relatively small (i.e., approximately 2 kg). CDEC reviewed several sensitivity analyses of the cost-utility analyses completed to evaluate increased impacts of weight gain and hypoglycemia on the reported ICURs and treatment rankings. These adjustments to utility scores were based on values that well exceeded estimates found in the literature.

Sulfonylureas remained the most cost-effective treatment option for most of these analyses.

- CDEC noted that the 2012 “American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults” states that two sulfonylureas, chlorpropamide and glyburide, should be avoided in elderly patients because of the risk of prolonged hypoglycemia (high-quality evidence; strong recommendations). The 2013 Diabetes Canada Clinical Practice Guidelines (DC Guidelines) recommend that sulfonylureas be used with caution in elderly patients because of the risk of hypoglycemia (Grade D, Level 4). Should a sulfonylurea be used, DC recommends that elderly patients should receive half of the dose that would be used when initiating treatment for a younger patient, and any subsequent increase in the dosage should be gradual (Grade D, consensus). DC also notes the potential increase in hypoglycemia with glyburide and recommends that gliclazide and glimepiride be used as alternatives.4 The 2016 American Diabetes Association Standards of Medical Care in Diabetes (ADA Guidelines) include similar statements regarding the need for caution when using insulin secretagogues in older adults. CDEC also noted that chlorpropamide, one of the less favourable sulfonylureas, is being discontinued in the Canadian market and may not be available after mid-2017.
- CDEC noted that inadequate glycemic control should be based on a glycemic target that has been individualized for the patient.

Recommendation 2

For adults with type 2 diabetes and established cardiovascular disease, CDEC recommends that therapy be considered in accordance with CDEC recommendations for individual drugs that have been reviewed specifically for this indication.

Reasons for Recommendation

1. Data regarding the comparative long-term efficacy and safety of different classes of second-line antidiabetes drugs on clinically important complications of diabetes, particularly cardiovascular outcomes, are currently sparse and of limited quality. Similarly, there are limited long-term safety data regarding the adverse events associated with long-term use of antidiabetes drugs from different classes. However, CDEC noted that data in patients at high risk for a cardiovascular event are emerging. CDEC noted that, in most cases, the gaps in evidence and limitations of the existing evidence are too large to support a specific drug-class recommendation based on these data. The committee recognized that this review is based on data available up to June 2016, and that relevant data will continue to be published over the next four to five years; these data may impact these recommendations.

2. CDEC has previously provided recommendations regarding the use of empagliflozin for patients at high risk of cardiovascular events, if evidence was sufficient to support this recommendation. Empagliflozin is the only drug at the time of this recommendation to have a specific indication from Health Canada for the prevention of cardiovascular death. CDEC continues to endorse the reimbursement of empagliflozin for this specific population until more evidence becomes available to comprehensively evaluate all drug classes for patients with diabetes and established cardiovascular disease.

Of Note

- CDEC reviewed the cardiovascular outcome data extensively. The available current trials that assess major cardiovascular events as a primary outcome have several limitations, leading to gaps in the evidence. Not all drugs of interest have been subjected to trials that assessed their long-term safety on cardiovascular outcomes. Most trials were designed as safety trials, and primarily designed to assess harm, which affects the outcomes that were evaluated in the trials. The trials enrolled a heterogeneous group of patients, including those with varying risks and histories of cardiovascular disease, and varying background antidiabetes treatments. Data were not available to specifically assess the new classes of drugs for type 2 diabetes for all patients with type 2 diabetes, including those without cardiovascular disease. Because of these limitations, along with a high level of uncertainty in the outputs of the NMA, the committee was not able to comment beyond the existing recommendations provided to date for some drugs.
- CDEC discussed the validity of the economic model used in light of emerging cardiovascular outcome data included in this review. The committee felt that the United Kingdom Prospective Diabetes Study (UKPDS) model continues to be the best available model for this assessment, as data from the UKPDS trial remain the seminal data to inform the role of early intensive glycemic control for all patients with type 2 diabetes. Given the gaps in evidence, this model can comprehensively evaluate all drug treatments available. However, CDEC also noted that, in future reviews, as more cardiovascular outcome data become available for more drugs, CADTH should explore modification to this model or alternative models that might more effectively incorporate these data.

Summary of the Evidence

Research Questions

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 agent: sulfonylurea, insulin, DPP-4 inhibitor, GLP-1 analogue, or 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: insulin, DPP-4 inhibitor, GLP-1 analogue, or SGLT-2 inhibitor?
3. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative cost-effectiveness of using a drug from one of the following classes as second-line agent: sulfonylurea, insulin, DPP-4 inhibitor, GLP-1 analogue, or SGLT-2 inhibitor?

Patient Considerations

Diabetes Canada provided the only patient submission for consideration in this therapeutic review. Information in Diabetes Canada's submission was gathered through a series of surveys involving individuals living with type 2 diabetes. Patients expressed frustration with having to cope with diabetes, a condition that negatively impacts all areas of their lives. Patients and their caregivers experience these impacts in their daily activities, work, travel, and social life. It was noted that a high proportion of the survey respondents have advanced diabetes and experience a range of complications and/or comorbidities. These include neuropathy, foot complications, cardiovascular disease, eye problems or loss of vision, kidney complications, pancreatitis, skin ulcers, erectile dysfunction, and amputations. Patients noted that there is stigma associated with diabetes that can create considerable mental stress for patients and lead to depression.

With respect to the available therapeutic drugs for diabetes, the patient group indicated that patients are a heterogeneous group and that treatment needs to be individualized. Treatment regimens should be selected based on a patient's clinical profile, goals for treatment, individual preferences, and tolerance. Specifically, patients are looking for new medications that will address five key areas: maintaining blood glucose at satisfactory levels, avoiding weight gain, reducing hypoglycemic events, reducing adverse effects, and reducing costs. Patients noted that weight gain is a source of complications and comorbidities for those living with diabetes. They noted that weight gain can be a side effect of many medications that are used to treat diabetes.

Clinical Evidence

Research Question 1

Clinical evidence was selected systematically according to a predefined protocol.[1] 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 that did not investigate or report outcomes of interest were included in the systematic review, but were not summarized in the clinical report.

The systematic review identified 175 unique RCTs that evaluated the efficacy and/or safety of the antidiabetes drugs in participants whose diabetes was inadequately controlled on metformin monotherapy.[2] Of these, 166 reported outcomes that were of interest for this review. 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. A total of 37 outcomes were extracted, including A1C, weight and body mass index, blood pressure, cholesterol, overall or severe hypoglycemia, and important long-term cardiovascular outcomes (major adverse cardiovascular events [MACE], cardiovascular mortality, hospitalization for heart failure, and all-cause mortality). The RCTs were used for a mixed treatment comparison that comprised NMAs for 18 outcomes for the

reference case of drug-class comparisons. A summary of the key efficacy and safety results is provided in Table 2.

Glycemic Control

Relative to metformin monotherapy, all of the selected classes significantly reduced mean difference in the change from baseline for A1C (range −0.58% to −0.94%). 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).

Body Weight

Relative to metformin monotherapy, sulfonylureas and basal insulins 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 statistically 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 statistically significant reductions in mean body weight relative to sulfonylureas (range −1.9 kg to −4.3 kg). SGLT-2 inhibitors and GLP-1 agonists also resulted in statistically significant reductions in mean body weight relative to DPP-4 inhibitors (70 RCTs).

Blood Pressure

SGLT-2 inhibitors and GLP-1 agonists added to metformin resulted in a statistically 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). Relative to metformin monotherapy, all treatments added to metformin, except sulfonylureas, resulted in significantly lower mean differences in the change from baseline for diastolic blood pressure (26 RCTs). When the classes were compared, SGLT-2 inhibitors added to metformin statistically significantly lowered the mean difference in the change from baseline for diastolic blood pressure relative to sulfonylureas and DPP-4 inhibitors.

Hypoglycemia

Only sulfonylureas increased the risk of severe hypoglycemia when compared with metformin monotherapy (odds ratio [OR] 6.40; 95% confidence interval [CI], 2.24 to17.51; 48 RCTs). When compared with each other, GLP-1 agonists and SGLT-2 and DPP-4 inhibitors statistically significantly reduced the risk of severe hypoglycemia relative to sulfonylureas. Compared with metformin monotherapy, the odds of nonsevere hypoglycemia were higher with sulfonylureas and with basal and biphasic insulin (67 RCTs). When the classes were compared, all classes except biphasic insulin significantly reduced odds of nonsevere hypoglycemia relative to sulfonylureas. 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. The data were insufficient to evaluate risk factors for severe hypoglycemia such as age.

Mortality

The NMA models for all-cause mortality (47 RCTs; N = 30,333) and cardiovascular mortality (34 RCTs; N = 17,282) were not robust due to the low event rate and the large number of zero events in the data sets. Pairwise meta-analyses comparing DPP-4 inhibitors with sulfonylureas did not find a significant difference in all-cause mortality (OR 1.19; 95% CI, 0.65 to 2.17). For the same comparison, the OR for cardiovascular mortality was not statistically significantly different (OR 1.84; 95% CI, 0.66 to 5.12). No other direct estimates could be calculated.

Adverse Events (Table 2)

Compared with metformin monotherapy and with each other, none of the classes statistically significantly increased or decreased odds of serious adverse events (66 RCTs). Relative to metformin monotherapy, sulfonylureas, DPP-4 inhibitors, and basal insulin, GLP-1 agonists were the only class added to metformin to statistically significantly increase the odds of withdrawals due to adverse events (70 RCTs). Biphasic insulin significantly increased the odds of withdrawals due to adverse events relative to basal insulin. Compared with metformin monotherapy, GLP-1 agonists and basal or biphasic insulin significantly increased the total number of adverse events. Basal and biphasic insulin was associated with a statistically significant increase in total adverse events compared with all other classes. GLP-1 agonists significantly increased total adverse events when compared with DPP-4 and SGLT-2 inhibitors (57 RCTs).

Cholesterol

SGLT-2 inhibitors added to metformin resulted in statistically significant increases in the mean difference in the change from baseline for low-density lipoprotein (LDL) cholesterol relative to metformin alone and significant increases relative to DPP-4 inhibitors (31 RCTs). SGLT-2 inhibitors added to metformin resulted in statistically significant increases in mean difference in the change from baseline for high-density lipoprotein (HDL) cholesterol relative to metformin alone, and relative to sulfonylureas, DPP-4 inhibitors, and GLP-1 agonists added to metformin (36 RCTs).

Heart Failure

The NMA for heart failure (15 RCTs; N = 10,876) 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). A pairwise meta-analysis comparing DPP-4 inhibitors with sulfonylureas did not find a significant difference in heart failure (OR 1.35; 95% CI, 0.48 to 3.82). No other direct estimates could be calculated.

Stroke and Transient Ischemic Attack

The NMA models for fatal stroke and nonfatal stroke were not robust due to the low event rate and the large number of zero events in the data set. Pairwise meta-analysis was also not possible. When sulfonylureas, 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 transient ischemic attack were found (14 RCTs; N = 10,389).

Pancreatitis

The NMA model for pancreatitis (15 RCTs; N = 9,238) 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 [n = five RCTs] or all [n = nine RCTs] study arms). Pairwise meta-analysis was also not possible.

Urogenital Adverse Events

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 (21 RCTs).

Fractures

Compared with metformin monotherapy and each other, none of the classes added to metformin significantly increased or decreased the odds of fracture (15 RCTs). Data were not available for GLP-1 agonists or for basal or biphasic insulin.

Unstable Angina

When sulfonylureas and SGLT-2 and DPP-4 inhibitors added to metformin were compared with metformin monotherapy and each other in the reference-case NMA, no significant differences in the odds of unstable angina were found (14 RCTs; N = 11,676).

Table 2: Key Efficacy and Safety Results From the Network Meta-Analyses

End Point	RCTs	Drug Class + Metformin Versus Metformin Alone					
		Sulfonylurea	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 Analogue	Basal Insulin	Biphasic Insulin
Continuous end points, MD (95% CrI)							
A1C (%)	84	–0.70 (–0.83 to –0.58)	–0.58 (–0.68 to –0.48)	–0.67 (–0.84 to –0.49)	–0.88 (–1.05 to –0.71)	–0.85 (–1.16 to –0.53)	–0.94 (–1.41 to –0.48)
Weight (kg)	70	2.11 (1.59 to 2.63)	0.18 (–0.22 to 0.58)	–2.21 (–2.75 to –1.67)	–1.44 (–2.07 to –0.81)	2.76 (1.56 to 4.01)	2.91 (0.85 to 5.04)
Systolic BP	29	0.28 (–1.54 to 2.06)	-1.04 (–2.34 to 0.22)	-4.06 (–5.24 to –2.89)	–2.79 (–4.57 to –1.07)	1.01 (–3.04 to 5.16)	0.15 (–5.62 to 5.93)
LDL-C (mmol/L)	31	0.06 (–0.09 to 0.20)	–0.02 (–0.12 to 0.08)	0.14 (0.02 to 0.27)	–0.02 (–0.17 to 0.13)	–0.18 (–0.47 to 0.11)	NA
HDL-C (mmol/L)	36	–0.02 (–0.06 to 0.01)	–0.01 (–0.03 to 0.02)	0.06 (0.03 to 0.09)	–0.02 (–0.06 to 0.02)	–0.02 (–0.09 to 0.06)	0.03 (–0.05 to 0.11)
Binary end points, OR (95% CrI)							
Severe hypoglycemia	48	6.40 (2.24 to 17.51)	0.91 (0.34 to 2.41)	0.61 (0.13 to 2.36)	1.80 (0.63 to 5.96)	3.08 (0.65 to 27.65)	3.36 (0.33 to 91.77)
Nonsevere hypoglycemia	67	7.59 (5.25 to 11.22)	0.77 (0.55 to 1.10)	1.00 (0.62 to 1.58)	0.75 (0.46 to 1.25)	3.18 (1.73 to 5.80)	6.92 (3.34 to 14.52)
Total AEs	57	1.14 (0.99 to 1.32)	0.97 (0.87 to 1.08)	1.03 (0.88 to 1.21)	1.38 (1.12 to 1.68)	2.20 (1.47 to 3.33)	2.32 (1.42 to 3.79)
SAEs	66	0.96 (0.76 to 1.21)	0.91 (0.72 to 1.15)	1.11 (0.83 to 1.51)	1.05 (0.71 to 1.51)	1.48 (0.63 to 3.74)	1.73 (0.42 to 8.43)
WDAEs	70	0.74 (0.51 to 1.11)	0.78 (0.56 to 1.09)	1.00 (0.61 to 1.66)	1.81 (1.12 to 2.99)	0.33 (0.07 to 1.40)	3.27 (0.41 to 54.86)
Urogenital AEs	21	1.02 (0.69 to 1.49)	1.23 (0.90 to 1.72)	1.06 (0.70 to 1.58)	1.17 (0.59 to 2.27)	0.87 (0.07 to 6.51)	NA
Fractures	15	1.15 (0.35 to 3.89)	2.02 (0.63 to 6.75)	1.35 (0.48 to 4.20)	NA	NA	NA
TIAs	14	0.96 (0.13 to 6.13)	0.62 (0.09 to 4.15)	0.69 (0.12 to 3.56)	NA	NA	NA

A1C = glycated hemoglobin; AEs = adverse events; BP = blood pressure; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; SAEs = serious adverse events; SGLT-2 = sodium-glucose cotransporter-2; TIA = transient ischemic attack; WDAEs = withdrawals due to adverse events.

Research Question 2

The systematic review of cardiovascular trials included 17 unique RCTs.[2] Most studies enrolled participants at high risk of cardiovascular events or with cardiovascular disease. The included RCTs enrolled patients on varying background therapies and pragmatically allowed for continuation of whatever the existing background therapy was at baseline. Background therapies were no treatment (i.e., they were drug-naive and starting the study intervention); monotherapy (they 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. There were limited data regarding proportions of background therapy for the enrolled participants.

NMAs were conducted for 13 outcomes for the reference case of class-level comparisons. A summary of the key efficacy and safety results is provided in Table 2.

Major Adverse Cardiovascular Events

The MACE end point was composed of three outcomes: cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Data were insufficient to conclude that any of the selected classes lowered the risk of MACE when compared with placebo or with each other (five RCTs; N = 50,410).

Mortality

SGLT-2 inhibitors reduced the risk of all-cause mortality when compared with placebo (OR 0.67; 95% CI, 0.47 to 0.95) or DPP-4 inhibitors (OR 0.66; 95% credible interval [CrI], 0.45 to 0.99). Data were insufficient to conclude that any other treatments reduced the risk of all-cause mortality (eight RCTs; N = 66,311). None of the selected classes significantly lowered the risk of cardiovascular mortality when compared with placebo or with each other (six RCTs; N = 30,439).

Hospitalizations for Heart Failure

Data were insufficient to conclude that any of the selected classes significantly lowered the risk of hospitalizations for heart failure when compared with placebo or with each other (five RCTs; N = 51,246). The individual RCTs report only hazard ratios for analysis, and not individual event counts and person-years, therefore limiting the ability to comprehensively evaluate these data.

Adverse Events

Compared with placebo or with each other, none of the classes significantly increased or decreased odds of an adverse event (three RCTs; N = 19,395), serious adverse events (six RCTs; N = 31,219), or withdrawals due to adverse events (six RCTs; N = 26,848).

Severe Hypoglycemia

GLP-1 agonists were associated with a significantly reduced risk of severe hypoglycemia compared with placebo but with a significantly increased risk

compared with TZDs (eight RCTs; N = 66,163). There was a significantly lower risk of severe hypoglycemia with GLP-1 agonists relative to DPP-4 inhibitors. TZDs 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.

Cancer

Relative to placebo, TZDs significantly decreased the risk of pancreatic cancer (0.13; 95% CrI, 0.01 to 0.75). When the classes were compared, TZD also significantly decreased the risk of pancreatic cancer relative to GLP-1 agonists (OR 0.13; 95% CrI, 0.01 to 0.75) (six RCTs; N = 56,398). Compared with placebo and with each other, none of the selected classes significantly increased the risk of bladder cancer (three RCTs; N = 19,025).

Pancreatitis

Neither DPP-4 inhibitors (OR 1.60; 95% CI, 0.97 to 2.66) nor GLP-1 analogues (OR 0.73; 95% CI, 0.37 to 1.39) increased the risk of pancreatitis relative to placebo or to each other (five RCTs; N = 51,951).

Fractures

Based on the limited evidence available (three RCTs; N = 25,614), none of the classes significantly increased fracture risk when compared with placebo or with each other in the NMA.

Table 3: Key Efficacy and Safety Results From the Network Meta-Analyses

End Point	RCTs	Drug Class versus Existing Therapy					
		TZD	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 Analogue	Sulfonylurea	Metformin
OR (95% CrI)							
MACE	5	NA	0.99 (0.68 to 1.45)	0.86 (0.46 to 1.67)	0.87 (0.45 to 1.65)	NA	NA
Cardiovascular mortality	6	0.83 (0.20 to 3.73)	0.97 (0.33 to 2.68)	0.58 (0.14 to 2.55)	0.86 (0.30 to 2.47)	NA	NA
All-cause mortality	8	0.91 (0.71 to 1.16)	1.02 (0.83 to 1.20)	0.67 (0.47 to 0.95)	0.89 (0.71 to 1.12)	NA	NA
Hospitalization for HF	5	NA	1.13 (0.43 to 2.93)	0.68 (0.18 to 2.75)	0.91 (0.35 to 2.40)	NA	NA
Total AEs	3	NA	1.08 (0.40 to 2.85)	0.86 (0.33 to 2.33)	1.07 (0.41 to 2.97)	NA	NA
WDAEs	6	1.19 (0.60 to 2.28)	0.97 (0.50 to 1.87)	NA	1.49 (0.96 to 2.39)	0.67 (0.21 to 1.98)	0.33 (0.05 to 1.76)
SAEs	6	0.92 (0.57 to 1.49)	0.92 (0.58 to 1.47)	0.94 (0.58 to 1.50)	0.95 (0.68 to 1.33)	0.81 (0.37 to 1.77)	NA
Severe hypoglycemia	8	2.05 (1.11 to 3.98)	1.18 (0.91 to 1.54)	0.82 (0.45 to 1.47)	0.71 (0.49 to 0.99)	NA	NA
Pancreatitis	5	NA	1.60 (0.97 to 2.66)	NA	0.73 (0.37 to 1.39)	NA	NA
Bone fractures	3	1.39 (0.50 to 3.65)	1.00 (0.39 to 2.47)	0.95 (0.37 to 2.48)	NA	NA	NA
Pancreatic cancer	6	0.13 (0.01 to 0.75)	0.53 (0.19 to 1.46)	NA	1.09 (0.34 to 3.10)	NA	NA
Bladder cancer	3	1.86 (0.75 to 4.67)	NA	NA	1.25 (0.44 to 3.78)	NA	NA

AEs = adverse events; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HF = heart failure; MACE = major adverse cardiovascular events; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; SAE = serious adverse event; SGLT-2 = sodium/glucose cotransporter 2; WDAE = withdrawal due to adverse events.

Economic Evidence

Research Question 3

Since the 2013 CADTH review of second-line antihyperglycemic therapies, a new antihyperglycemic drug class has been introduced — SGLT-2 inhibitors. In addition, a fourth DPP-4 inhibitor (alogliptin) and a third GLP-1 analogue (dulaglutide) have been introduced, and new data on the impact on cardiovascular outcomes of newer drug classes have been published. For this update, the same approach was taken to evaluate the comparative clinical and cost-effectiveness of second-line therapies for the treatment of patients with type 2 diabetes, using updated information. In addition to including the new class of antidiabetes drugs, an updated UKPDS Outcomes Model (version 2.0) was used, as well as updated costs for treatments, disease management, and long-term diabetes complications.

The research question addressed in this analysis was similar to that in the original evaluation: 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: sulfonylureas; insulin, DPP-4 inhibitors, GLP-1 analogues, and SGLT-2 inhibitors?

The economic analysis used the UKPDS Outcomes Model[3] to forecast the cumulative incidence of diabetes-related complications during a 40-year time horizon as well as associated costs for six treatment classes added to metformin as second-line therapy (sulfonylureas, basal insulin, biphasic insulin, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 analogues). For each treatment strategy, inputs for predictive risk factors in the model, such as A1C, body mass index, and body weight were informed by the results of the systematic review and NMA.[2]

Unit costs for drugs were obtained from the Ontario Public Drug Program (December 2016) when available. Otherwise, prices were obtained from other public drug programs (Quebec and British Columbia) in Canada.[4-6] The lowest-cost alternative for each class of drugs was used in the primary economic analysis plus a 10.00% markup and $8.83 pharmacy fee per 90-day supply. For metformin, however, the maximum dose (2,000 mg per day) was used, based on the average defined daily dose from the World Health Organization for each treatment.[7] The doses for insulin products for long-acting insulin analogues (0.53 U/kg), neutral protamine Hagedorn insulin (0.75 U/kg), biphasic insulin analogues (1.2 U/kg), and biphasic human insulin (1.5 U/kg) were based on the values used in the previous CADTH reports obtained from patient sample in British Columbia (Dr. Marshall Dahl, University of British Columbia: unpublished data, 2008) (Table 4).

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).[8] 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. For the reference case, it was assumed that episodes of mild to moderate hypoglycemia had no impact on

health care resource use. Resource use associated with managing a severe hypoglycemic episode was based on Leese et al.[9] and National Institute for Health and Care Excellence (NICE).[10] Management costs were based on data from the Alberta Case Costing Database (2006).[11]

Patients with diabetes mellitus monitor the concentration of glucose in the blood by performing self-testing periodically using blood glucose test strips. For some patients using certain antidiabetes drugs (i.e., insulin secretagogues, insulin), the utilization of blood glucose test strips is higher than in those patients 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.[12]

The primary outcome measure in the analysis was the QALY, which captures both quantity and quality of life. Patients with type 2 diabetes were assumed to have a EuroQol 5-Dimensions (EQ-5D) questionnaire score of 0.785, based on a study in which the EQ-5D questionnaire was used to survey 3,192 patients participating in the UKPDS in 1997.[13] Utility weights for modelled long-term diabetes-related complications were obtained from Sullivan et al.,[14,15] when available. Otherwise, utility scores were obtained from the study by Clarke et al. (2002).[13] Multiple complications were assumed to have an additive effect on utility.

Table 4: Average Daily Cost of Treatments With and Without the Cost of Blood Glucose Test Strips

Treatment	Assumed Doses	Daily Treatment Cost [a]	Daily Treatment Cost (Test Strips Included)[b]
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 per kg per day	$2.54	$4.24
Long-acting insulin analogues	Insulin glargine 0.53 U per kg per day	$3.78	$5.48
Biphasic human insulin	NPH insulin 30/70 1.50 U per kg per day	$4.68	$6.38

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; SGLT-2 = sodium-glucose transporter-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 defined daily dose from the World Health Organization for each treatment with the exception of metformin, for which the use of maximal doses (2,000 mg per day) was assumed.[7]
[b] Average test strip use, by type of pharmacotherapy, was obtained from an analysis of the Ontario Public Drug Program.[4] A cost of $0.729 per test strip plus a pharmacy fee of $8.83 per 100 test strips was applied.

For the reference-case analysis, it was assumed that drugs within a drug class yield similar estimates of effects; that differences in weight gain among treatments do not confer advantages in terms of quality of life; that patients remain on their second-line therapies over their remaining lifetime; and that DPP-4 inhibitors, GLP-1 analogues, and SGLT-2 inhibitors are not associated with any adverse events. In terms of hypoglycemia, it was assumed that mild to moderate hypoglycemic episodes are associated with a transient reduction in quality of life, while severe hypoglycemic episodes

are associated with a chronic reduction in quality of life. Finally, it was assumed that insulin injections are not associated with a reduction in quality of life.

In the reference-case analysis, the addition of a sulfonylurea to metformin monotherapy was associated with the most favourable cost-effectiveness estimate compared with metformin monotherapy, with an incremental cost per QALY gained of $38,643 relative to metformin alone (Table 5). Other active treatments were associated with unfavourable cost-effectiveness estimates (i.e., they were dominated, extendedly dominated, or demonstrated high ICURs) when compared with the next least costly treatment. Cost-effectiveness results were robust to variation in most model inputs and assumptions. Probabilistic analyses found that sulfonylureas had the highest probability of being the most cost-effective second-line treatment option for willingness-to-pay thresholds between $39,000 and $135,000 per QALY gained.

Table 5: 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; ICUR = incremental cost-utility ratio; MET = metformin; NA = not applicable; QALY = quality-adjusted life-year; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea.
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 results of sensitivity analyses indicated that sulfonylurea added to metformin remained the most cost-effective option. The key drivers of the results included:

- Applying the Ontario Drug Benefit annual reimbursement limits for blood glucose test strips (400 per year for patients using antihyperglycemic medications with high hypoglycemic risk, 200 per year for patients using medications with low glycemic risk).16 This increased the ICUR of sulfonylureas compared with metformin compared with the base case to $65,600 per QALY, but had little effect on GLP-1 analogues and SGLT-2 inhibitors.
- Excluding the costs associated with the use of blood glucose test strips improved the cost-effectiveness of sulfonylureas compared with metformin but had little to no effect on GLP-1 analogues and SGLT-2 inhibitors.

- 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 ($0.0574), the ICUR for sulfonylureas compared with metformin increased modestly, but there was little to no effect on GLP-1 analogues or SGLT-2 inhibitors.17
- Assuming a quality-of-life reduction due to weight gain (utility decrement of 0.00195 per unit increase in body mass index, per NICE obesity guidelines)18 reduced the cost-effectiveness of sulfonylureas and GLP-1 analogues and improved the cost-effectiveness of SGLT-2 inhibitors.

Other sensitivity analyses that did not result in significant changes from the base-case results included using lower disutility values with mild, moderate, and severe hypoglycemia; varying utility estimates for diabetes complications; assuming no costs in year one of fatal ischemic heart disease and heart failure events; and applying the cost per mild or moderate hypoglycemic event.

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 the classes to become the second-line treatment strategy with the most favourable cost-effectiveness results in comparison with other second-line treatment strategies. In order to displace 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); SGLT-2 inhibitors would have to be 60% lower (for an ICUR of $38,586 per QALY gained relative to metformin monotherapy); and GLP-1 analogues would have to be 70% lower (for an ICUR of $35,879 per QALY gained relative to metformin monotherapy).

An additional threshold analysis was conducted for a scenario in which a disutility for weight gain is included based on the NICE obesity guidelines (0.00195 per unit increase in body mass index).[18] The unit cost of DPP-4 inhibitors would have to be 70% lower than in the reference case to displace sulfonylureas; SGLT-2 inhibitors would have to be 30% lower; and GLP-1 analogues would have to 50% lower.

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 were added as part of this update, were found to be associated with a high ICUR of more than $100,000 per QALY. To displace sulfonylureas as the most cost-effective second-line therapy, price reductions of 60% or more would be required for SGLT-2 inhibitors, while DPP-4 inhibitors and GLP-1 analogues would require price reductions of 70% or more.

Limitations of the Evidence

Clinical Evidence for Research Question 1

There were several limitations of the available evidence from the systematic review of second-line treatment options for type 2 diabetes. The majority of the studies identified in the systematic literature search enrolled patients who were using varied and unspecified antidiabetes drugs at baseline (i.e., they were not specifically using metformin monotherapy at baseline). In accordance with CADTH's review protocol, these studies could not be incorporated into the NMAs, which reduced the overall number of studies that could be used to estimate the comparative efficacy and safety of the different drug classes.

The included RCTs generally had a moderate risk of bias; however, at least 20% of the studies were considered to be at a high risk of bias. Common limitations with the published studies included poor reporting of the following: randomization and allocation processes; protocol definitions used for outcomes evaluated in the studies (e.g., hypoglycemia); details regarding dosage and duration of background metformin therapy; and lack of clarity regarding the use of a true intention-to-treat analysis. Several RCTs used an A1C threshold of 6.5% to define adequate control that differs from the threshold commonly used in Canadian practice (7.0%).

With respect to the ability to conduct analyses on clinically important end points, there was little evidence for long-term diabetes-related complications from studies investigating the efficacy of second-line drugs for patients with diabetes that was inadequately controlled with metformin monotherapy. Similarly, there was limited ability to perform NMA for many of the outcomes of interest due to low events rates within the individual studies.

Clinical Evidence for Research Question 2

Due to the small number of studies in the networks, it was not possible to investigate inconsistency, heterogeneity, and the impact of the network geometry on the effect estimates that were derived from the NMAs. As there were 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. Also, given the small number of RCTs in some of the networks (e.g., cancer outcomes), the results should be interpreted with caution.

Economic Evidence

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 small differences in glycemic control across drug classes. Another limitation of the UKPDS model is its inability to directly 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.[19,20] Due to uncertainty with the limited evidence available on cardiovascular effects, the model was considered insufficient as a basis to directly incorporate these estimates within the model (as opposed to modelling the effects on surrogate outcomes with long-term effects on cardiovascular outcomes). Such benefits were not accounted for in the current analysis; therefore, the true cost-effectiveness of the SGLT-2 inhibitor and GLP-1 agonist may not be fully captured.

There was 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 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. The results remained robust in the analyses, with sulfonylureas remaining the most cost-effective treatment strategy, followed by SGLT-2 inhibitors and GLP-1 analogues.

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. A scenario analysis in which an insulin rescue dose was applied at A1C levels of 9% and higher resulted in sulfonylureas becoming less costly than metformin, thereby dominating metformin. SGLT-2 inhibitors and GLP-1 analogues were still associated with ICURs above $100,000 per QALY, while DPP-4 inhibitors and insulins were subjected to dominance and extended dominance.

Discussion Points

Efficacy and Safety

- Across all outcomes, the efficacy and safety results that were derived from the NMAs were highly consistent with those from the direct pairwise comparisons. CDEC noted that consistency between the direct and indirect estimates of effect adds validity to the analysis.
- CDEC noted that, since not all drugs have cardiovascular outcome data, the generalizability of findings to support a conclusion of class effects of new drugs for type 2 diabetes is not possible at this time.
- CDEC discussed the risk of hypoglycemia with sulfonylureas as a limitation to achieving optimal control on a sulfonylurea, as well as the impact of hypoglycemia on patients' quality of life. CDEC considered patient input that described the challenges of managing hypoglycemia, particularly in the elderly. Trials included in the NMA reviewed by CDEC reported low rates of hypoglycemia, but included low numbers of very

elderly patients. Most trials did not report hypoglycemia specifically in this subgroup, limiting any analysis that could be done with this population. CDEC also noted that there is a lack of robust evidence available to estimate the effect of hypoglycemia on health-related quality of life.

Cost-Effectiveness

- CDEC discussed the more recent cardiovascular outcome trials published and how they could inform the economic model or necessitate the development of an entirely new model. CDEC noted that the data mainly include patients with a longer duration of diabetes and at high risk of cardiovascular events, which represents only a subgroup of patients with type 2 diabetes, as defined by the policy question for this therapeutic review. The review is intended to provide a recommendation for all patients with type 2 diabetes, including those who have been recently diagnosed and those with lower risks of cardiovascular disease. CDEC also noted that not all drugs have cardiovascular outcome data, precluding the ability to model comparative effectiveness of all drugs.
- Based on patient and stakeholder feedback, CDEC explored sensitivity analyses on the impact of weight gain and hypoglycemia on the existing cost-utility ratios and recognized that the ranking of treatments would be unlikely to change based on available utility values for weight gain and hypoglycemia.
- CDEC also noted that the model did not fully capture some adverse effects of newer drug classes (e.g., urogenital infections or ketoacidosis with SGLT-2 inhibitors).
- CDEC noted that publicly available prices were used in the economic analysis, which may not reflect any confidential agreements member jurisdictions may have to lower the cost of these drugs.

Research Gaps

- CDEC noted that the major research gap remains the absence of cardiovascular outcome data for all drugs included in this review, as well as a lack of comparative data evaluating the efficacy and safety of new drugs for type 2 diabetes.
- CDEC also noted that elderly patients have not been extensively evaluated in the included RCTs; thus, this population's tolerance of sulfonylureas in regard to hypoglycemia could not be comprehensively explored in this therapeutic review.

Committee Members

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, Dr. Harindra Wijeysundera.

Two external clinical experts who are practising endocrinologists participated in the discussion, but did not vote on the recommendations.

Regrets

None

Conflicts of Interest

None

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