CADTH
September 2016

Second-Line Pharmacotherapy for Type 2 Diabetes (Update) [DRAFT]

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TABLE OF CONTENTS

Table of Contents

ABBREVIATIONS

BMI	body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DDD	defined daily dose
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin A1c
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
MET	metformin
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
SGLT-2	sodium-glucose co-transporter-2
SU	sulfonylurea
UKPDS	United Kingdom Prospective Diabetes Study

EXECUTIVE SUMMARY

Context and Policy Issues

In 2010 and 2013, CADTH published systematic reviews and cost effectiveness analyses of second-line anti-hyperglycemic therapies added to metformin in patients with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy.[1,2] The results of these reviews indicated that there were no apparent differences in efficacy across the available drug classes, and that sulfonylureas were the most cost effective treatment option. Based on the most recent review in 2013, the Canadian Drug Expert Committee (CDEC) recommended that most patients requiring a second treatment after metformin should be prescribed a sulfonylurea.[3]

Since the 2013 review, a new antihyperglycemic drug class been introduced — sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In addition, a fourth DPP-4 inhibitor (alogliptin) as well as 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. There is therefore a need to re-evaluate the comparative clinical and cost effectiveness of second-line therapies for the treatment of patients with type 2 diabetes.

Objectives and Research Questions

The objective of this evaluation was to perform an update of CADTH's previous cost effectiveness analysis of second-line diabetes pharmacotherapy. The research question addressed in this analysis was similar to the one 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?

- Sulfonylurea
- Insulin
- DPP-4 inhibitor
- GLP-1 analogue
- SGLT-2 inhibitor

Methods

The updated pharmacoeconomic study utilized similar methodology as 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:

- 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[4]
- Treatment effect estimates were obtained from CADTH's updated systematic review and network meta-analysis.[5]
- Costs for drugs were updated to year 2016; costs for disease management and long-term diabetes complications were adjusted for inflation.

Key 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 incremental cost utility ratio (ICUR) of $38,653 per quality-adjusted life-year (QALY) gained. This was due primarily to the lower cost of agents in this drug

class compared with insulin and newer classes. The ICUR of SGLT-2 inhibitors was approximately $92,000 per QALY vs. sulfonylureas, and the ICUR of GLP-1 analogues was approximately $222,000 per QALY vs. 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 less 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 blood glucose testing. 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

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 insulin NPH was added to all non-insulin second-line treatments once HbA1c 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 and Implications for Decision or Policy Making

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 agents, hypoglycemia incidence, and the impact of hypoglycemia and weight change on quality of life.

1. Pharmacoeconomic Analysis

1.1 Objective

To update the 2013 CADTH pharmacoeconomic analysis of second-line therapies for type 2 diabetes to incorporate key agents currently approved in Canada based on the results of CADTH's updated systematic review and NMA.[5]

1.2 Methods

1.2.1 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.

1.2.2 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.[5]

1.2.3 Treatments

The comparisons in the analysis were of metformin plus sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 analogues, or insulins versus metformin alone.

1.2.4 Perspective

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

1.2.5 Efficacy and Safety

Treatment effects (HbA1c, overall hypoglycemia, weight) for the analysis were derived from the updated systematic review investigating the use of second-line antidiabetic agents in patients with inadequate glycemic control on metformin monotherapy. Where possible, estimates of efficacy for the economic analysis were obtained from the NMA of RCTs included in the systematic review.[5]

Most RCTs included in the meta-analysis were unlikely to have had adequate sample size, or been of sufficient duration, to capture incidence rates of infrequent events that may be of economic importance.[5] 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 randomized controlled trials. The baseline rates of severe hypoglycemia among patients using metformin monotherapy (0.05 per 100 patients years) and metformin plus sulfonylurea (0.9 per 100 patient years), were derived from a population-based study by Leese et al. [6]

1.2.6 [7]Time Horizon

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

1.2.7 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.[4] It is based on patient data from the United Kingdom Prospective Diabetes Study[8] and uses a wide variety of input data, including previous events, and 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.[9]

The UKPDS Outcomes Model was revised from the version of the model used in previous CADTH reports on second and third line treatments.[2] The current version includes additional risk factors such as albuminuria, heart rate, white blood cells (WBC), hemoglobin and estimated glomerular filtration rate (eGFR). eGFR and micro- or macroalbuminuria are associated in the model with several types of vascular events (e.g., MI), while WBC 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/).[4]

1.2.8 Costs

1.2.8.1 Cost of Treatments

Unit costs for drugs were obtained from the Ontario Public Drug Program (August 2016) when available. Otherwise, prices were obtained from other public drug programs (Quebec and British Columbia Drug Benefits) in Canada.[10,11] 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, insulin NPH 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% mark-up 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/day), it was assumed that patients used the average defined daily dose from the World Health Organization for each treatment. [12] 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, insulin NPH, biphasic insulin analogues, and biphasic human insulin respectively) were similar to the values used in the previous CADTH reports.

Patients using certain antidiabetic agents (i.e., insulin secretagogues, insulin) typically use more blood glucose test strips than those using other agents. 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 1). [13] A scenario analysis was conducted using the Ontario Public Drug Program reimbursement limits for blood glucose test strips (Table 2).[14] 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 mark-up was applied as test strips are not eligible for mark-up in the Ontario Public Drug Program. A scenario analysis was conducted where the cost of test strips was not considered.

Table 1: 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 (http://journal.cpha.ca/index.php/cjph/article/viewFile/4788/3120) [14]

Table 2: 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 anti-diabetes medication with high risk of causing hypoglycemia	400
Patients managing diabetes using anti-diabetes medication with low risk of causing hypoglycemia	200
Patients managing diabetes through diet/lifestyle therapy only (no insulin or anti-diabetes medications)	200

Source: Ontario Public Drug Programs (http://www.health.gov.on.ca/en/pro/programs/drugs/teststrips/bg_teststrips.aspx, Accessed October 2016)[14]

The older generation sulfonylurea, glyburide, remained the lowest daily cost second-line treatment, even with the additional cost of blood glucose test strips (Table 3). DPP-4 inhibitors, SGLT-2 inhibitors, and insulin NPH were less expensive than long-acting insulin analogues, biphasic human insulin, and GLP-1 analogues.

Table 3: 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	2000 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 µg daily	$4.41	$5.17
Basal human insulin	Insulin NPH 0.75 U per kg per day[b]	$2.54	$4.24
Long-acting insulin analogues	Insulin glargine 0.53 U per kg per day[b]	$3.78	$5.48
Biphasic human insulin	Insulin NPH 30/70 1.50 U per kg per day[b]	$4.68	$6.38

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

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.[12]

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

1.2.8.2 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 4) [15] Inpatient, outpatient, and emergency room 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.[16] 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 (HF).

Table 4: Management Costs of Long-Term Diabetes-Related Complications

Complications	First-year costs†		In subsequent years†
	Fatal	Non-Fatal	
Ischaemic 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

† Costs from the Ontario Diabetes Economic Model (ODEM)[15] inflated to 2016 Canadian dollars (C$) using the health component of the Consumer Price Index.[16]

1.2.8.3 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. [6] and NICE.[17] Management costs were based on data from the Alberta Case Costing Database (2006).[18] Because resource use was derived from the United Kingdom, 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 such, 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 5: 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 United Kingdom[6]
[c] Ontario Drug Benefit (October 2016)[19]
[d] Unit cost from Alberta[18]

1.2.9 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-dimension (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.[20] Utility weights for modelled long-term diabetes-related complications were obtained from Sullivan et al. [21,22] when available. Otherwise, utility scores were obtained from the study by Clarke et al. (2002).[20] Estimates from Clarke et al. [20] are often used in cost effectiveness studies related to diabetes interventions. However, unlike Sullivan et al. [21,22], Clarke et al. [20] 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 HRQoL. Multiple complications were assumed to have an additive effect on utility. For example, the utility of a patient who has a myocardial infarction and then an amputation would first be decremented 0.0409, and then by a further 0.28.

Table 6: 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;[21,22] therefore, they were obtained from a study by Clarke et al. [20]

There is limited evidence that examines the impact of hypoglycemia and fear of hypoglycemia on health-related quality of life. 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)[23] 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.[24] However, to assess the uncertainty associated with the effects of hypoglycemia, a sensitivity analysis was conducted where, for mild or moderate hypoglycemia, a decrement of 0.0052 was applied as published in NICE Guidance on the use of insulin glargine.[25] 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.[17]

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 agents observed in the NMA of second-line therapies.[5] 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[26], 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.

1.2.10 Handling of Uncertainty

1.2.10.1 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.

1.2.10.2 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 cost effectiveness acceptability curves 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:

Net monetary benefit = λ*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.

1.2.10.3 Threshold Analysis

Threshold analyses were also conducted for treatments which 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.

1.3 Results

1.3.1 Reference Case

From the updated analysis (Table 7), 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 ICURs) when compared with the next least costly treatment.

Table 7: 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 co-transporter 2; SU = sulfonylurea

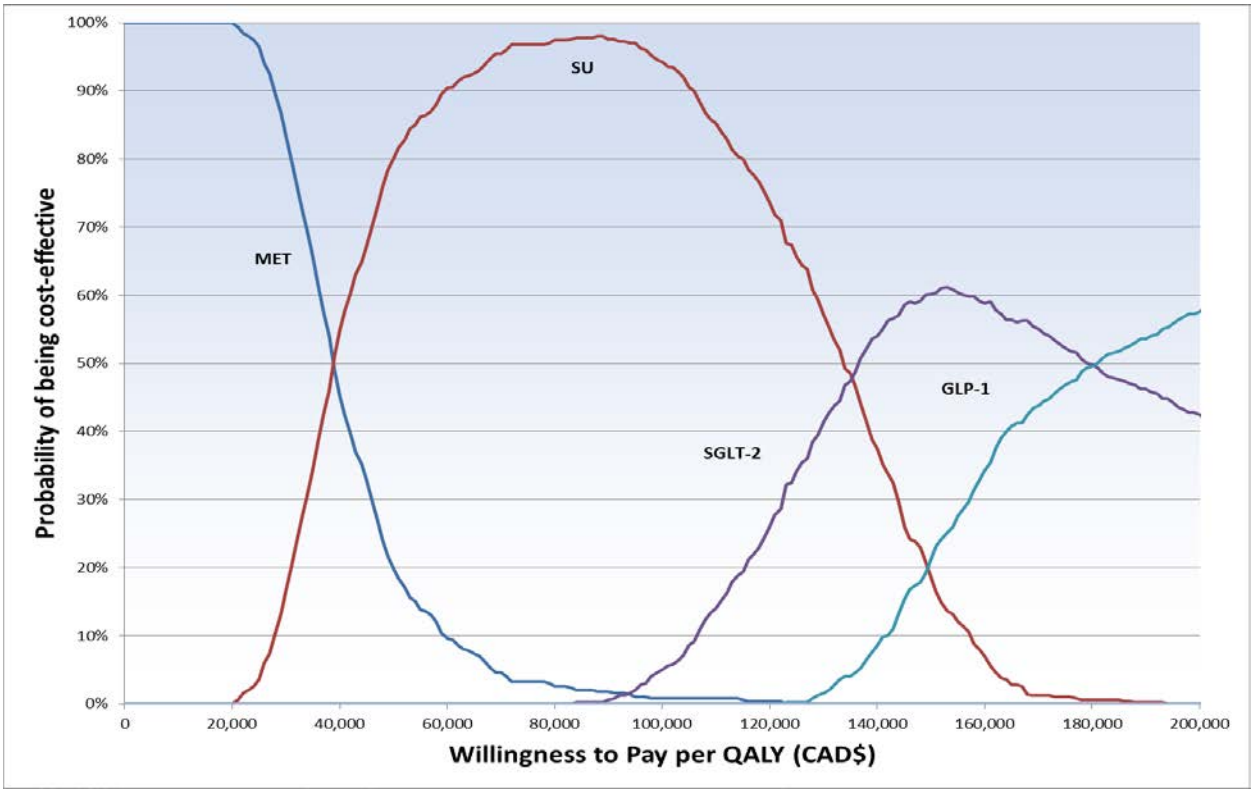
Note: A dominated strategy is associated with more costs and less benefits than the previous most effective strategy. An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore an extendedly dominated strategy produces additional gains in effectiveness 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 cost effectiveness acceptability curve (**Figure 1**) 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 1: 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 co-transporter 2; SU = sulfonylurea.

1.3.2 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 I. The following is a summary of some of the notable results from 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)[14] increased the ICUR of SU compared to MET compared with the base case, but had little to no effect on GLP-1 analogues and SGLT-2 inhibitors.

Table 8: 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	Sequential ICUR

			($/QALY)	($/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; ODB = Ontario Drug Benefit; QALY = quality-adjusted life year; SGLT-2 = sodium glucose co-transporter 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, GLP-1
[c] dominated by SGLT-2, GLP-1

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

Table 9: 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 co-transporter 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

- Using the price of the most widely utilized SU agent in Canada based on overall market share by public drug plans ($0.0931 per gliclazide 30 mg SR tablet) instead of the price for glyburide 5 mg tablet ($0.00574), the ICUR for SU compared to MET increased modestly, but there was little to no effect on GLP-1 analogues or SGLT-2 inhibitors.[27]

Table 10: Total lifetime costs, quality-adjusted life years, and incremental cost-effectiveness results using price of most widely utilized SU (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 co-transporter 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

- 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[26]) reduced the cost effectiveness of SU and GLP-1 analogues but improved the cost effectiveness of SGLT-2 inhibitors (Table 11).

Table 11: 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 co-transporter 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 following sensitivity analyses did not result in significant changes from the base case results:

- Use of 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 Curries et al. (2006).[23] Sensitivity analyses assumed a disutility of 0.0052 per mild or moderate hypoglycemic event based on the NICE Guidance on insulin analogues[25] and 0.01 per severe hypoglycemic event based on the NICE Guidance for Type-2 Diabetes.[17]
- Varying utility estimates for diabetes complications using the values from the study by Clarke et al. (2004).[20]
- Year one costs of fatal IHD and HF events were assumed to be 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 non-fatal year one costs of myocardial infarction (~52%) to the year one cost of non-fatal IHD.

- Applying the cost per mild or moderate hypoglycemic event of $93 dollars based on the study by Brod et al. (2011)[28] 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.

1.3.3 Threshold Analysis

The results of varying the unit prices of therapies considered in this analysis showed that in order to overtake SUs 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 12.

Table 12: 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 to SU
	70 %	$0.7650	$49,250	$69,780 compared to SU
	80 %	$0.5100	$30,839	$30,839 compared to MET
	90 %	$0.2550	$12,428	$12,428 compared to MET
SGLT-2 inhibitors	Reference Case	$2.6177	$100,459	$134,861 compared to SU
	10 %	$2.3559	$90,145	$118,807 compared to SU
	20 %	$2.0941	$79,831	$102,753 compared to SU
	30 %	$1.8324	$69,518	$86,701 compared to SU
	40 %	$1.5706	$59,205	$70,648 compared to SU
	50 %	$1.3089	$48,891	$54,594 compared to SU
	60 %	$1.0471	$38,577	$38,577 compared to MET
	70 %	$0.7853	$28,263	$28,263 compared to MET
	80 %	$0.5235	$17,949	$17,949 compared to MET
	90 %	$0.2618	$7,635	$7,635 compared to MET

GLP-1 analogues	Reference Case	$1.9950	$119,997	$182,263 compared to SGLT-2
	25 %	$1.4963	$89,951	$109,135 compared to SU
	50 %	$0.9975	$59,906	$67,856 compared to SU
	60 %	$0.7980	$47,887	$51,344 compared to SU
	70 %	$0.5985	$35,869	$35,869 compared to MET
	75 %	$0.4988	$29,860	$29,860 compared to MET
	80 %	$0.3990	$23,851	$23,851 compared to MET
	90 %	$0.1995	$11,832	$11,832 compared to 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 co-transporter 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.

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).[26] The unit cost of DPP-4 inhibitors would have to be 70% lower than in the reference case to overtake SU (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 13.

Table 13: 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 to SU
	70 %	$0.7650	$50,338	$50,338 compared to MET
	80 %	$0.5100	$31,521	$31,52 compared to MET
	90 %	$0.2550	$12,703	$12,703 compared to MET
SGLT-2 inhibitors	Reference Case	$2.6177	$87,109	$91,864 compared to SU
	10 %	$2.3559	$78,166	$80,928 compared to SU
	20 %	$2.0941	$69,223	$69,993 compared to MET

	30 %	$1.8324	$60,280	$60,280 compared to MET
	40 %	$1.5706	$51,337	$51,337 compared to MET
	50 %	$1.3089	$42,394	$42,394 compared to MET
	60 %	$1.0471	$33,451	$33,451 compared to MET
	70 %	$0.7853	$24,507	$24,507 compared to MET
	80 %	$0.5235	$15,564	$15,564 compared to MET
	90 %	$0.2618	$6,621	$6,621 compared to MET
GLP-1 analogues	Reference Case	$1.9950	$111,743	$222,037 compared to SGLT-2
	25 %	$1.4963	$83,764	$86,913 compared to SU
	50 %	$0.9975	$55,785	$55,785 compared to MET
	60 %	$0.7980	$44,593	$44,593 compared to MET
	70 %	$0.5985	$33,401	$33,401 compared to MET
	75 %	$0.4988	$27,806	$27,806 compared to MET
	80 %	$0.3990	$22,210	$22,210 compared to MET
	90 %	$0.1995	$11,018	$11,018 compared to 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 co-transporter 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.

2. Discussion

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.[2] The updated cost effectiveness analysis, based on the results of the updated NMA,[5] indicated that sulfonylureas remained the most cost effective second-line therapy in patients 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 HbA1C and weight were slightly larger, which narrowed the incremental effects of second line treatments, thereby 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 similar gains in glycemic control as 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 utilized. 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[15,29,30] that compared anti-diabetic treatments in the second-line setting and reported sulfonylureas as the most cost-effective second-line treatment option against 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.

2.1 Strengths and Limitations

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 endpoint (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-on 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 are attributable to second-line treatments or subsequent treatments. Due to 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 agents. 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 whereby patients were assumed to add-on neutral protamine Hagedorn (NPH) insulin as third-line therapy after predefined criteria were met (i.e., when HbA1c 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 HbA1c, these parameters could not be modified over time. As such, some elements of the scenario analysis results could not be discounted appropriately. Nevertheless, the assumed addition of NPH at an HbA1C 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.[31,32] 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.

3. Conclusions and Implications for Decision or Policy Making

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 agents, 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 agents were approved in Canada at the time, were found to be associated with a high ICUR in the updated analysis. In order 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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Appendix I: Results of Pharmacoeconomic Sensitivity Analyses

Table 14: Base case results (using cost of NPH insulin for basal insulin)

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,648	8.8369		
SU	$ 39,251	8.8784	$38,643	$38,643
SGLT-2 inhibitors	$ 49,308	8.9530	$100,459	$134,861
GLP-1 agonists	$ 55,946	8.9894	$119,997	$182,263
DPP-4 inhibitors	$ 48,859	8.8998	$178,127	Extended Dominance[a]
Basal insulin	$ 54,852	8.8898	$324,968	Dominated[b]
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; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life year; SGLT-2 = sodium glucose co-transporter 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

Table 15: Using price of a more costly and widely utilized SU ($0.0931 per gliclazide 30 mg SR tablet, instead of price for glyburide 5 mg tablet $0.0574) with ODB blood glucose test strip limits

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 36,408	8.8369		
SU	$ 39,455	8.8784	$73,417	$73,417
SGLT-2 inhibitors	$ 48,055	8.9530	$100,341	$115,325
GLP-1 agonists	$ 54,687	8.9894	$119,871	$182,113
DPP-4 inhibitors	$ 47,614	8.8998	$178,035	Extended Dominance[a]
Basal insulin	$ 54,886	8.8898	$281,615	Dominated[b]
Biphasic insulin	$ 63,753	8.9340	$349,027	Dominated[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; ICUR = incremental cost utility ratio; MET = metformin; ODB = Ontario Drug Benefit; QALY = quality-adjusted life year; SGLT-2 = sodium glucose co-transporter 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, GLP-1

[c] dominated by SGLT-2, GLP-1

Table 16: Lower disutility for mild or moderate hypoglycemia (-0.0052 instead of -0.014) based on NICE Guidance on insulin analogues

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,648	8.8388		
SU	$ 39,251	8.8824	$36,733	$36,733
SGLT-2 inhibitors	$ 49,308	8.9549	$100,441	$138,839
GLP-1 agonists	$ 55,946	8.9913	$119,974	$182,221
DPP-4 inhibitors	$ 48,859	8.9017	$178,102	Extended Dominance[a]
Basal insulin	$ 54,852	8.8965	$298,188	Dominated[b]
Biphasic insulin	$ 63,719	8.9407	$255,897	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 co-transporter 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 GLP-1, SGLT-2

Table 17: Lower disutility for severe hypoglycemia (-0.01 instead of -0.047) based on NICE Guidance for Type-2 Diabetes

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,648	8.8371		
SU	$ 39,251	8.8822	$35,539	$35,539
SGLT-2 inhibitors	$ 49,308	8.9532	$100,457	$141,746
GLP-1 agonists	$ 55,946	8.9896	$119,994	$182,259
DPP-4 inhibitors	$ 48,859	8.9000	$178,124	Extended Dominance[a]
Basal insulin	$ 54,852	8.9369	$172,423	Dominated[b]
Biphasic insulin	$ 63,719	8.9812	$180,893	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 co-transporter 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 SGLT-2

[c] dominated by GLP-1

Table 18: Lower disutility for hypoglycemia (-0.0052 for mild and moderate; -0.01 for severe hypoglycemia)

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,648	8.8390		
SU	$ 39,251	8.8863	$33,917	$33,917
SGLT-2 inhibitors	$ 49,308	8.9551	$100,439	$146,148
GLP-1 agonists	$ 55,946	8.9915	$119,971	$182,217
DPP-4 inhibitors	$ 48,859	8.9019	$178,099	Extended Dominance[a]
Basal insulin	$ 54,852	8.9435	$164,580	Dominated[b]
Biphasic insulin	$ 63,719	8.9879	$175,085	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 co-transporter 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 SGLT-2

[c] dominated by GLP-1

Table 19: Utility estimates for diabetes complications from Clarke et al.(2004)

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,648	8.7058		
SU	$ 39,251	8.7474	$38,561	$38,561
SGLT-2 inhibitors	$ 49,308	8.8302	$93,724	$121,422
GLP-1 agonists	$ 55,946	8.8639	$115,749	$197,121
DPP-4 inhibitors	$ 48,859	8.7735	$165,693	Extended Dominance[a]
Basal insulin	$ 54,852	8.7630	$300,671	Dominated[b]

Biphasic insulin	$ 63,719	8.8076	$256,172	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 co-transporter 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

Table 20: A cost for mild or moderate hypoglycemia ($93 per event instead of zero cost) based on Brod et al. (2011)

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,668	8.8369		
SU	$ 39,294	8.8784	$39,192	$39,192
SGLT-2 inhibitors	$ 49,328	8.9530	$100,461	$134,558
GLP-1 agonists	$ 55,966	8.9894	$119,998	$182,263
DPP-4 inhibitors	$ 48,879	8.8998	$178,128	Extended Dominance[a]
Basal insulin	$ 54,922	8.8898	$325,916	Dominated[b]
Biphasic insulin	$ 63,789	8.9340	$269,015	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 co-transporter 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

Table 21: Base case results using cost of insulin glargine for basal insulin

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 37,648	8.8369		
SU	$ 39,251	8.8784	$38,643	$38,643
SGLT-2 inhibitors	$ 49,308	8.9530	$100,459	$134,861
GLP-1 agonists	$ 55,946	8.9894	$119,997	$182,263
DPP-4 inhibitors	$ 48,859	8.8998	$178,127	Extended Dominance[a]
Basal insulin	$ 60,109	8.8898	$424,272	Dominated[b]
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 co-transporter 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, GLP-1

[c] dominated by SGLT-2, GLP-1

Table 22: Base case results using costs for fatal events for ischemic heart disease and heart failure

Treatment	Costs	QALYs	ICUR (vs. Metformin monotherapy)	Sequential ICUR
MET	$ 38,107	8.8369		
SU	$ 39,732	8.8784	$39,177	$39,177
SGLT-2 inhibitors	$ 49,768	8.9530	$100,468	$134,578

GLP-1 agonists	$ 56,393	8.9894	$119,919	$181,906
DPP-4 inhibitors	$ 49,360	8.8998	$178,795	Extended Dominance[a]
Basal insulin	$ 55,321	8.8898	$325,156	Dominated[b]
Biphasic insulin	$ 64,180	8.9340	$268,519	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 co-transporter 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