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CADTH Therapeutic Review

Economic Evaluation: Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and Sulfonylurea Combination Therapy

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Supporting Informed Decisions

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ABBREVIATIONS

A1C	glycosylated hemoglobin
BMI	body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CHF	congestive heart failure
CI	confidence interval
DPP-4	dipeptidyl peptidase-4
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
MTC	mixed treatment comparison
NPH	neutral protamine Hagedorn
OR	odds ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study

EXECUTIVE SUMMARY

Background

Type 2 diabetes mellitus is a progressive metabolic disease that causes significant morbidity and mortality worldwide. Clinical practice guidelines recommend metformin as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions. Many guidelines recommend the addition of a sulfonylurea when metformin monotherapy is insufficient; however, they lack specific recommendations regarding which agents are optimal when metformin and sulfonylurea combination therapy is inadequate. We therefore conducted an economic evaluation to examine the comparative cost-effectiveness of third-line antidiabetes pharmacotherapies in the management of patients with type 2 diabetes that is inadequately controlled on metformin and sulfonylurea combination therapy.

Methods

A cost-effectiveness analysis was conducted comparing four treatment classes as third-line therapy in the management of type 2 diabetes among patients who are inadequately controlled on metformin and sulfonylurea combination therapy. In addition to placebo, the four classes added to metformin and sulfonylurea combination therapy were: basal insulin (i.e., insulin neutral protamine Hagedorn [NPH] or long-acting insulin analogues), biphasic insulin (i.e., regular human insulin, insulin aspart, and insulin lispro), thiazolidinediones (TZDs) (i.e., rosiglitazone or pioglitazone), and dipeptidyl peptidase (DPP)-4 inhibitors (i.e., sitagliptin). The price of the lowest cost alternative was applied for each drug class. It was assumed that patients used the average defined daily dose from the World Health Organization for each treatment. The doses for insulin products were obtained from a convenience sample of patients with type 2 diabetes in British Columbia[1] The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model[2] was used to forecast long-term diabetes-related complications and cost consequences for each treatment class. The impact of each treatment regimen on risk factors, such as glycosylated hemoglobin (A1C), body mass index (BMI), and body weight, was based on the results of a Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review and mixed treatment comparison meta-analysis.[1] Based on patient attributes and control of risk factors, the cumulative incidence of diabetes-related complications was forecasted over a 40-year time horizon using equations from UKPDS 68.[2] The following other adverse events were also considered: overall hypoglycemia, severe hypoglycemia, and congestive heart failure.

This economic evaluation took the perspective of a Canadian ministry of health. Costs from published Canadian sources and provincial drug formularies were incorporated within the model. Utility decrements were applied for diabetes-related complications[3,4] and hypoglycemia.[5,6] Both costs and quality-adjusted life-years (QALYs) were discounted at a rate of 5%. Sensitivity analyses were performed to examine the robustness of results to variation in model inputs and assumptions.

Key Results and Interpretation

The average daily cost of insulin NPH ($3.60) was comparable with generic pioglitazone ($3.40) and DPP-4 inhibitors ($3.81) when the additional cost of blood glucose test strips was included. Long-acting insulin analogues ($4.69), rosiglitazone ($5.92), the lowest cost biphasic human insulin ($5.45), and biphasic insulin analogue ($5.98) were among the more expensive treatments.

In the reference case analysis, the addition of insulin NPH to metformin and sulfonylurea combination therapy was associated with the most favourable cost-effectiveness estimates among active treatments — the incremental cost per QALY gained was $60,800 relative to metformin and sulfonylurea combination therapy alone. Other active treatments added to metformin and sulfonylurea combination therapy were more costly and less effective in terms of QALYs gained compared with insulin NPH, although the differences were small (Range: 8.2190 QALYs with TZDs to 8.3251 QALYs with basal insulin).

Cost-effectiveness results were sensitive to variation in model inputs and assumptions (see Sensitivity analyses). Under the following scenarios, DPP-4 inhibitors became the most cost-effective option: a high disutility was assumed with insulin use, a higher risk of hypoglycemia among insulin users was modelled, and the costs of long-acting insulin analogues were applied to the basal insulin option rather than the cost of insulin NPH. However, even under these optimistic scenarios for DPP-4 inhibitors, the incremental cost per QALY gained exceeded $85,000 per QALY relative to metformin and sulfonylurea combination therapy alone. It should also be noted that the quality of evidence informing the variations in model inputs is limited or of low quality (see Study Limitations section below); hence, results from sensitivity analyses should be interpreted with caution.

The results of the cost-effectiveness analysis were also found to be sensitive to the daily doses assumed for insulin products. When doses from the included randomized controlled trials (RCTs) were used in the analyses rather than data from a patient sample in British Columbia, the costs of insulins were lower and their corresponding cost-effectiveness estimates were more favourable (see page 11, table 7).

Study Limitations

The key limitation of this study was the lack of clinical data from long-term, high-quality studies that evaluated the comparative efficacy of third-line agents in terms of clinically relevant end points. Because of the limited data, surrogate end points (e.g., A1C) were used to forecast the occurrence of long-term diabetes-related complications based on data from the UKPDS study. The validity of A1C in forecasting cardiovascular end points in patients with type 2 diabetes has been debated.[7,8] Moreover, the UKPDS Outcomes Model is based on data from patients who used older classes of drugs (e.g., metformin, sulfonylureas, and insulin). It is unclear whether or not the use of risk equations derived from patients using older classes of drugs for newer classes (e.g., TZDs and DPP-4 inhibitors) introduces significant bias in the projected incidence rates of diabetes complications.

Another key limitation of this study is related to the complexities involved in modelling changes in treatments over time. Diabetes is a progressive disease requiring the use of multiple treatment regimens over the life of the patient. There is uncertainty over the treatments patients will add on or switch to after inadequate control on third-line therapy. Moreover, there are difficulties in assessing whether benefits conferred are attributable to the treatment of interest or subsequent treatments. Because of these considerations, the primary economic analysis assumed that patients remained on their respective third-line therapy during their expected lifetime, without adding or switching to subsequent agents. Although this approach is not reflective of clinical practice given the progressive nature of diabetes, sensitivity analyses to examine the effect of this assumption revealed that it likely had minimal impact on cost-effectiveness results.

There was uncertainty regarding the disutility associated with insulin use,[9-11] weight gain,[12,13] and hypoglycemia.[6] In the absence of good quality data for these inputs, conservative estimates were used for the base-case analysis. Nevertheless, we performed sensitivity analyses to examine the impact of these assumptions on cost-effectiveness results (see Sensitivity Analyses for additional details). Further research is needed that explores the impact of insulin use, weight gain, and hypoglycemia on quality of life.

Finally, the primary economic analysis assumes no safety risks in using newer agents such as DPP-4 inhibitors. These drugs have not been on the market as long as other agents and safety data is still emerging. Hence, the cost-effectiveness estimates for newer agents reported here may prove to be optimistic if important safety risks are uncovered in the future.

Conclusions

This is the first Canadian cost-effectiveness analysis of treatments for type 2 diabetes that has compared third-line therapies, including the newer DPP-4 inhibitors, after inadequate control with metformin and sulfonylurea combination therapy. The findings suggest that the addition of insulin NPH to metformin and sulfonylurea combination therapy is the most cost-effective third-line therapy. However, under certain assumptions, the addition of DPP-4 inhibitors (sitagliptin) may be the most cost-effective option. 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 impact of insulin use and hypoglycemia on quality of life, the incidence of hypoglycemia across various treatments, and the clinical efficacy of DPP-4 inhibitors as third-line therapy. Well-designed studies are needed in these areas in order to more precisely define the cost-effectiveness of newer, more expensive, and less established antidiabetes medicines.

ECONOMIC EVALUATION

1 INTRODUCTION

Type 2 diabetes mellitus is a chronic, metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[14] When inadequately managed, diabetes is likely to result in poor glycemic control.[15] Impaired glycemic control, if prolonged, may result in diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, and lower limb amputation).[16,17] The global prevalence of diabetes is estimated to be 177 million and is projected to increase to 300 million by 2025.[18] It is estimated that 1.9 million Canadian men and women had been diagnosed with diabetes in 2005-2006, representing 6.2% of all men and 5.5% of all women. In addition, it is believed that a large number of Canadians have diabetes but have not been diagnosed.[19]

Treatment of patients with type 2 diabetes mellitus usually begins with lifestyle modifications and oral antidiabetes drugs. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes mellitus when glycemic control cannot be achieved by lifestyle interventions alone.[20-24] Recent utilization data indicate that the majority of patients with type 2 diabetes mellitus initiating pharmacotherapy in Canada are started on metformin.[25] As type 2 diabetes mellitus is a progressive disease, glycemic levels are likely to worsen over time. Most patients eventually require two or more oral antidiabetes drugs, or the addition of insulin, to achieve or maintain target blood glucose levels.[26,27] Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone. Following a detailed review of the clinical and cost-effectiveness of second-line agents for diabetes,[28] the Canadian Agency for Drugs and Technologies in Health (CADTH) recently issued an optimal therapy recommendation stating that sulfonylureas should be used as second-line therapy for most patients inadequately controlled on metformin alone.[29]

Eight classes of antidiabetes drugs are available as third-line therapy for patients with type 2 diabetes inadequately controlled on combination therapy with metformin and sulfonylureas: meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, basal insulins, bolus insulins, and biphasic insulins. A majority of guidelines[30-33] recommend that insulin should be started as a third-line agent for most patients; however, other guidelines recommend either insulin or an additional oral antidiabetes agent.[20,34]

Given the increasing prevalence of type 2 diabetes, there is a need to evaluate the evidence related to the clinical and cost-effectiveness of third-line drugs in order to facilitate their optimal use. As part of a larger initiative to determine the optimal use of third-line antidiabetes drugs, we sought to determine the cost-effectiveness of third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea combination therapy, based on our systematic review of the available clinical evidence.[1]

2 METHODS

2.1 Type of Economic Evaluation

A cost-utility analysis was conducted in which the results are reported as incremental cost per quality-adjusted life-year (QALY) gained.

2.2 Target Population

Patients with established type 2 diabetes that is inadequately controlled on metformin and a sulfonylurea were considered for this analysis. In the reference case analysis, patient characteristics (when available)

were obtained from a CADTH systematic review of 33 randomized controlled trials (RCTs) that investigated the use of third-line antidiabetes agents in patients with type 2 diabetes inadequately controlled on combination therapy with metformin and sulfonylureas.[1] Otherwise, patient characteristics were obtained from large RCTs or published Canadian observational studies (Table 1).[35]

Table 1: Characteristics of Hypothetical Patient Group

Parameter	Estimate	Reference
Risk Factors		
Age (years)	57.7 (9.7)	CADTH systematic review[1]
Duration of diabetes (years)	9.5 (6.3)	CADTH systematic review[1]
Weight (kg)	89 (18)	CADTH systematic review[1]
Height (m)	1.69 (0.15)	4-T Study[36]
BMI	31.2 (5.8)	CADTH systematic review[1]
Sex	57% male	CADTH systematic review[1]
Ethnicity	94% Caucasian 3% Afro-Caribbean 5% Asian-Indian	4-T Study[36]
A1C (%)	8.61 (1.0)	CADTH systematic review[1]
Smoking	Current = 16% Past = 49% Never = 35%	4-T Study[36] DiGEM trial[37]
Cholesterol (mmol/l)	4.5 (0.98)	4-T Study[36]
LDL (mmol/l)	3.3 (0.9)	4-T Study[36]
HDL (mmol/l)	1.2 (0.3)	4-T Study[36]
Systolic blood pressure (mmHg)	139 (16)	4-T Study[36]
History of diabetes related complications*		
History of ischemic heart disease	11%	DICE Study[35]
History of CHF	7%	DICE Study[35]
History of amputation	1%	DICE Study[35]
History of blindness	1%	Ontario[38] and Alberta Diabetes atlases[39]
History of renal failure	1%	Ontario[38] and Alberta Diabetes atlases[39]
History of stroke	5%	DICE Study[35]
History of MI	9%	DICE Study[35]
History of atrial fibrillation	4%	DICE Study[35]
History of PVD	3%	Östgren 2004,[40] Go 2001[41]

A1C = glycosylated hemoglobin; BMI = body mass index; CADTH = Canadian Agency for Drugs and Technologies in Health; CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PVD = peripheral vascular disease.
*Time since pre-existing event estimated based on data from Ontario Diabetes Economic Model.[42]

2.3 Treatments

Four different treatments were compared with placebo, all in combination with metformin and sulfonylureas: basal insulin, biphasic insulin, TZDs, and DPP-4 inhibitors. The price of the lowest cost alternative was applied for each drug class.

Alpha-glucosidase inhibitors and meglitinides, two additional classes indicated in Canada for the treatment of type 2 diabetes, were not included in the reference case because they are not widely used in Canadian clinical practice and do not yield significant improvements in glycemic control when added to

metformin and a sulfonylurea as third-line therapy.[1] A third class, GLP-1 analogues, was also excluded from the analysis as no agent within this class had been approved by Health Canada at the time of the analysis.

The majority of treatment strategies studied in the RCTs included in the CADTH systematic review of third-line therapies were classified as add-on (i.e., patients added their third-line treatment to metformin and sulfonylurea combination therapy) and a minority were classified as switch (i.e., discontinuation of both metformin and a sulfonylurea on initiation of the third-line therapy) or partial switch (i.e., discontinuation of either metformin or a sulfonylurea on initiation of third-line therapy). We therefore assumed that patients added third-line therapies to their existing treatment regimen of metformin and a sulfonylurea. However, because the use of TZDs is not indicated with metformin and sulfonylurea combination therapy in Canada, we conducted a sensitivity analysis for this class in which only metformin was continued after initiation of a TZD. It should be noted that because of the lack of clinical data, this sensitivity analysis assumes the same clinical effects as the combination of metformin, sulfonylurea, and a TZD. Further research is needed that compares the clinical effectiveness of adding a third-line agent to an existing regimen of metformin and a sulfonylurea versus partial switch strategies.

2.4 Perspective

This analysis was conducted from the perspective of a provincial health ministry.

2.5 Efficacy and Adverse Events

Treatment effects for the analysis were derived from a CADTH systematic review that included evidence from 33 RCTs investigating the use of third-line antidiabetes agents in patients with the disease that was inadequately controlled on combination therapy with metformin and a sulfonylurea.[1] In this review, estimates of treatment differences in terms of hemoglobin A1C and body weight were obtained from mixed treatment comparison (MTC) meta-analysis (Table 2). Results for hypoglycemia were not pooled using MTC meta-analysis because of a high degree of variability across studies in hypoglycemia definitions and control group event rates; rather, only pairwise meta-analysis was performed. For the purposes of the economic analysis, hypoglycemia event rates for each treatment strategy were estimated by multiplying relative risk estimates from pairwise meta-analyses by the baseline event rates for overall hypoglycemia (2.3 events per patient-year) reported in the 4-T trial.[36] The 4-T trial[36] was chosen as the source of baseline event rates because it is a large, well-conducted RCT of long duration. In the primary analysis, it was assumed that the addition of DPP-4 inhibitors (sitagliptin) to metformin plus a sulfonylurea had a similar effect to adding TZDs, despite the higher hypoglycemia rates observed in one DPP-4 inhibitor trial (relative risk [RR] 18.51 (2.52, 135.96)).[43] This assumption was made because of the imprecision (i.e., wide confidence interval [CI]) of the risk estimate and because it did not align with other studies of DPP-4 inhibitors.[44]

Table 2: Estimates of Treatment Differences from CADTH Systematic Review	
Treatment versus Placebo plus Metformin plus a Sulfonylurea	**Effect Estimates (95% CrI)**
a) Change from baseline A1C (%)	
Basal insulin + Met + SU	–1.17 (–1.57 to –0.81)
Biphasic insulin + Met + SU	–1.10 (–1.59 to –0.67)
TZD + Met + SU	–0.96 (–1.35 to –0.59)
DPP-4 (sitagliptin) + Met + SU	–0.89 (–1.51 to –0.26)
b) Change from baseline body weight (kg)	
Basal insulin + Met + SU	1.85 (0.54 to 3.09)
Biphasic insulin + Met + SU	3.35 (1.65 to 5.03)
TZD + Met + SU	3.10 (1.73 to 4.43)
DPP-4(sitagliptin) + Met + SU	1.11 (–1.36 to 3.57)
c) Overall hypoglycemia	
Basal insulin + Met + SU versus Met + SU + placebo	RR 1.73 (1.10 to 2.74)
TZD + Met + SU versus Basal Insulin + Met + SU	RR 0.65 (0.48 to 0.88)
Biphasic + Met + SU versus Basal Insulin + Met + SU	RR 1.24 (1.14 to 1.35)
DPP-4 inhibitor + Met + SU versus Met + SU + placebo*	RR 18.51 (2.52 to 135.96)

Source: Taken in part from *CADTH Clinical Report,*[1] Tables 12,14,17
CADTH = Canadian Agency for Drugs and Technologies in Health; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; Met = metformin; RR = relative risk; SU = sulfonylurea; TZD = thiazolidinedione.
*Because of the imprecision of this estimate and the lack of alignment with other studies indicating no increased risk of hypoglycemia, it was assumed in the economic analysis that addition of DPP-4 inhibitors (sitagliptin) to metformin plus a sulfonylurea had a similar effect on hypoglycemia rates as the addition of TZDs.

Most RCTs included in the meta-analysis were inadequately powered to detect differences between treatments in the rates of infrequent adverse events that may be of economic importance. These events include severe hypoglycemia in patients using insulin secretagogues or insulin and congestive heart failure in patients using TZDs. Event rates and treatment effects for such outcomes were therefore derived from large observational studies and RCTs. The baseline rates of severe hypoglycemia among patients using metformin (60 per 100,000 patients-years) as well as odds ratios (ORs) for patients using metformin plus a sulfonylurea (OR 4.04 (95% CI 3.27 to 4.98) or metformin plus a sulfonylurea plus insulin (OR 8.86 (95% CI 4.47 to 17.6), were derived from a population-based study by Bodmer et al.[45] Sensitivity analyses for this parameter were conducted using the higher rates of severe hypoglycemia reported in a study by Leese et al.[46]

An increased risk of congestive heart failure (CHF) was assumed in the reference case for patients using TZDs [hazard ratio [HR] 2.10 (95% CI 1.35 to 3.27).[47] One of the TZDs, rosiglitazone, has been reported to increase the risk of ischemic heart disease,[48] although data from the recently published RECORD trial[47] indicated no increase in risk. Because of the conflicting evidence,[47] TZDs were not assumed to incur an additional risk of ischemic heart disease in the reference case analysis.

The long-term safety profile of newer agents is largely unknown due to limited clinical experience in their use, and the evidence is often contradictory. Although data from longer-term clinical studies is required for more definitive assessment, the available data indicate that DPP-4 inhibitors are not associated with increased cardiovascular risk.[49] The Food and Drug Administration has reported cases of acute pancreatitis among patients using DPP-4 inhibitors,[50] although a large, recently published cohort study[51] reported no difference in risk of acute pancreatitis for initiators of sitagliptin (RR 1.0, 0.5 to 2.0) compared with those using metformin or glyburide. We therefore assumed no increases in cardiovascular risk (e.g., myocardial infarction, CHF) or pancreatitis among patients using DPP-4 inhibitors.

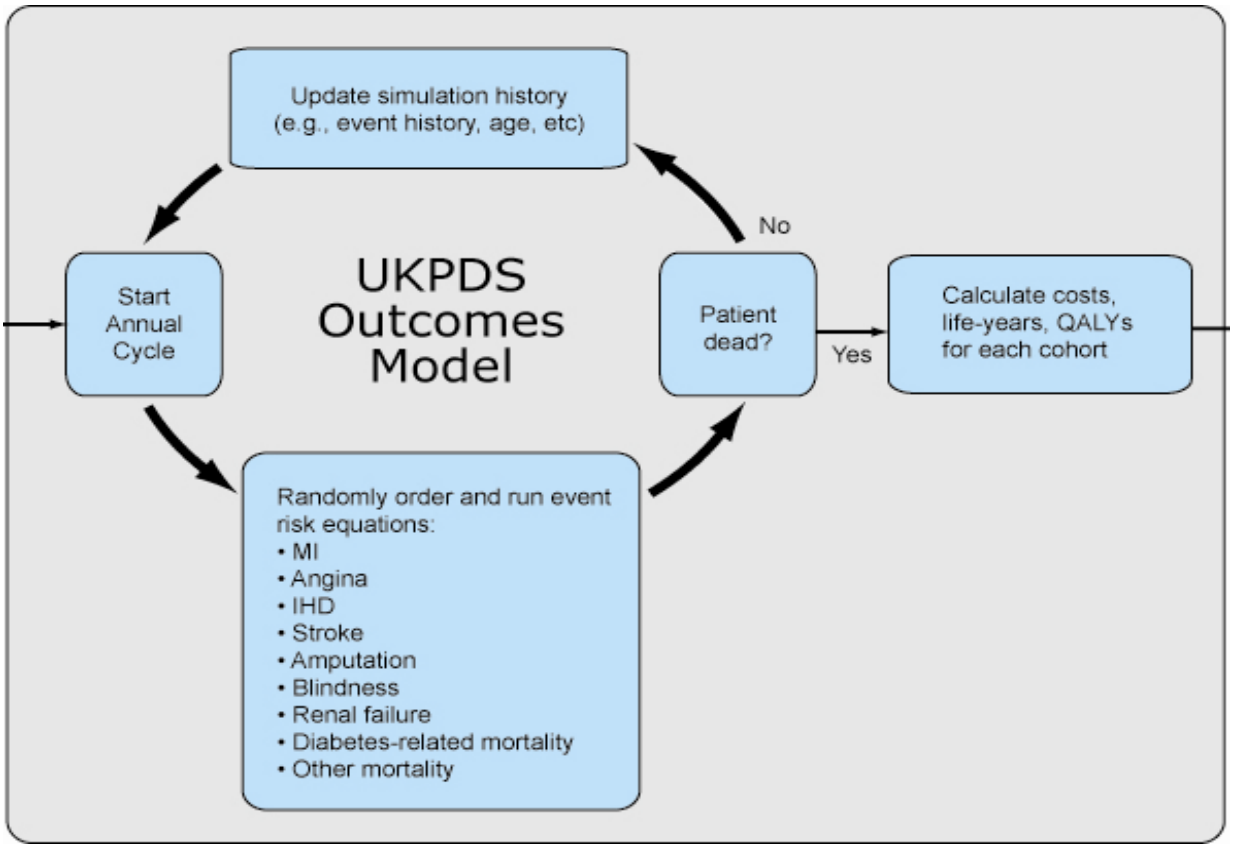
2.6 Time horizon

A 40-year time horizon was used for the reference case analysis.

2.7 Modelling

The incidence of diabetes-related complications over the expected remaining lifetime of a hypothetical patient cohort was forecasted using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (Figure 1).[2] The UKPDS Outcomes Model[2] is a computer simulation model that is used to forecast long-term health outcomes and cost consequences in patients with type 2 diabetes. The risk of developing seven diabetes-related complications (i.e., fatal or non-fatal myocardial infarction, other ischemic heart disease, stroke, heart failure, amputation, renal failure, and blindness) is estimated based on data from 3,642 patients with type 2 diabetes mellitus who were enrolled in the UKPDS. Each equation[2] estimates the absolute risk of developing a complication, based on patient characteristics (e.g., age and sex, A1C, systolic blood pressure, cholesterol, body mass index (BMI), smoking history, and history of diabetes-related complications). Simulations are based on a probabilistic discrete-time illness model with annual cycles.[2] Model projections have been validated against published clinical and epidemiological studies.[52]

Figure 1: Schematic of UKPDS Model and Its Application in this Economic Analysis



*Adapted and simplified from the original schematic by Clarke et al.[2]
IHD = ischemic heart disease; MI = myocardial infarction; QALY = quality-adjusted life-year; UKPDS = United Kingdom Prospective Diabetes Study.

Patients are initially assigned to one of the five treatment regimens; the effect estimates for risk factors (A1C, BMI, body weight) were based on data from the CADTH systematic review of third-line therapies.[1] Based on patient attributes and control of risk factors, patients were propagated through the model, and the cumulative incidence of diabetes-related complications was forecasted for each treatment during the 40-year time horizon.

Three other adverse events were also considered (overall hypoglycemia, severe hypoglycemia, and congestive heart failure [only for TZDs]). Patients using insulin have an increased risk of overall and severe hypoglycemia relative to those using other oral antidiabetes drugs. However, the UKPDS Outcomes Model[2] does not directly incorporate the costs and consequences associated with hypoglycemia. Because hypoglycemia has an impact on health-related quality of life (HRQoL) and in some instances (e.g., severe hypoglycemia) may result in health care resource use, it was necessary to capture any benefits conferred by third-line drugs associated with a lower risk of hypoglycemia. To do so, two submodels were developed that incorporated the increased risk of overall and severe hypoglycemia among patients using insulin and sulfonylureas.

Modeling CHF risk in the UKPDS Outcomes Model is challenging since it is predicted by a number of surrogates (e.g., A1C, cholesterol), all of which influence multiple outcomes within the model. An increased risk of CHF in patients using TZDs [HR 2.10 (95% CI 1.35 to 3.27)[47] was therefore incorporated by artificially increasing body weight by 30 kg. CHF is the only submodel in the UKPDS Outcomes Model that is influenced by body weight; therefore, no other outcomes were affected by the artificial increase in body weight.[2]

Modelling changes in treatment sequences over time is challenging with any model, including the UKPDS Outcomes Model.[2] There is uncertainty about which treatment patients will add-on or switch to after inadequate control on third-line therapy. Furthermore, when patients use multiple treatments over time, it is difficult to assess whether benefits conferred are attributable to the treatment of interest or subsequent treatments. Due to these considerations, it was assumed in the reference case that patients remained on their respective third-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; however, it enabled valid attribution of costs and consequences to each third-line treatment modelled in the analysis. The effect of this assumption was tested through sensitivity analyses, whereby patients using third-line therapy were assumed to add-on neutral protamine Hagedorn (NPH) insulin as fourth-line therapy after predefined criteria were met (i.e., when a patient's A1C level reached or surpassed 9.0%). The addition of insulin to the treatment regimen of patients inadequately controlled with oral medications is recommended in clinical practice guidelines.[20,53]) However, to conduct these sensitivity analyses within the UKPDS model, the weight and hypoglycemia inputs had to be front-loaded (i.e., applied in year one) because unlike A1C, these parameters could not be modified over time. As such, some elements of the sensitivity analysis results could not be discounted appropriately. In future, if the UKPDS model is updated to enable more seamless integration of changes in treatment sequences over time, reanalysis may be warranted.

2.8 Valuing Outcomes

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 an EuroQol 5-dimension (EQ-5D) score of 0.753 based on a US catalogue of EQ-5D scores from Sullivan et al.[3,4] Quality weights for modelled long-term diabetes-related complications were also obtained from Sullivan et al. when available.[3,4] Otherwise, utility scores were obtained from a study by Clarke et al., who also used the EQ-5D instrument.[54] Estimates from Clarke et al.[54] are often used in cost-effectiveness studies related to diabetes interventions.[55] However, unlike Sullivan et al.,[3,4] Clarke et al.[54] did not control for non-diabetes related complications or other confounding variables such as income, education, ethnicity, and number of comorbidities, all of which impact HRQoL.

Multiple complications were assumed to have an additive effect on utility.[2] 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 3: Utility Decrements Associated with Modelled Diabetic Complication Health States [3,4,54]

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*	–0.28	–0.28
Blindness	–0.0498	–0.0498
Renal failure*	–0.2630	–0.2630

*Utility decrements were not available from the US catalogue;[3,4] therefore, they were obtained from a study by Clarke et al.[54]

There is limited evidence regarding the impact of hypoglycemia and fear of hypoglycemia on HRQoL.[56] Moreover, widely cited evidence[6] in this area is of low quality.[56] For the reference case analysis, patients experiencing mild-to-moderate hypoglycemia were assumed to have a transient reduction in HRQoL.[57] Patients were assumed to move to a health state characterized by moderate anxiety, with or without depression, and some limitations in performing usual activities; thus, resulting in a disutility of 0.167 during the hypoglycemic episode.[5] Each mild-to-moderate hypoglycemic episode was assumed to last for 15 minutes, which coincides with the "15/15 rule", i.e., 15 grams of carbohydrate followed by 15 minutes of waiting.[58] Thus, each episode was associated with an annual decrement of 0.000004767 QALYs.[5] In contrast, those having a severe hypoglycemic episode were assumed to experience a transient reduction in HRQoL, followed by a chronic decrement in HRQoL due to fear of future hypoglycemic episodes.[56] An annual decrement of 0.01 was applied for each severe hypoglycemic event; the same decrement was applied in a recently published report[56] by the National Institute for Health and Clinical Excellence (NICE). Currie et al.[6] suggest a utility decrement of 0.047 associated with severe hypoglycemic episodes, and state that this utility decrement should be applied over one year. The face validity of this value is questionable as it implies that each severe hypoglycemic episode is equivalent to spending 17 days in a state of death, and that the disutility due to severe hypoglycemia is greater than that for more clinically severe events, such as myocardial infarction.[3,4] Indeed, NICE found that the Currie study had significant methodological limitations, and considered the disutilities overstated.[56] Nevertheless, we conducted a sensitivity analysis using the disutility of Currie et al.[6]

We did not apply a utility decrement for weight gain in the primary economic analysis. Most widely cited studies[12,13] derive such estimates from much larger weight differences (i.e., 13 kg to 30 kg)[12,13] and it is unclear whether these can be applied to the smaller weight differences between agents observed in the MTC meta-analysis of third-line therapies. It is also uncertain whether these utility decrements are sustained over time. Nevertheless, we performed a sensitivity analysis based on data presented in the NICE obesity guidelines, in which we assumed a utility decrement of 0.001950135 per unit increase in BMI.[12,13] This utility decrement was applied to each year of the simulation based on the estimated BMI for each treatment.

We did not apply a utility decrement for insulin use in the primary economic analysis. Because some studies have reported that insulin use is associated with a reduction in quality of life,[9-11] we conducted a sensitivity analysis where we assumed a one-time utility decrement of – 0.06 in year one based on trial data reported by Maddigan et al. showing that insulin use was associated with a difference in overall health utilities index-3 scores (– 0.06 [95% CI, – 0.03 to – 0.09]).[10] A decrement was only applied in year one based on clinical expert opinion indicating that patients would adapt to using insulin after one year. It should be noted that the estimated utility decrement reported by Maddigan et al. has limited face validity

as it exceeds the disutilities associated with certain serious clinical events (e.g., myocardial infarction). We therefore ran a subsequent analysis using the upper limit of the CI (– 0.03) reported by Maddigan.

2.9 Resource Use and Costs

2.9.1 Cost of Drugs

Unit costs for drugs were obtained from the Ontario Public Drug Program when available. (Appendix 1, Tables A1 and A2).[59] Otherwise, prices were obtained from other public drug programs in Canada.[60-63] For the base-case analysis, the price of the lowest cost alternative was applied for each drug class (i.e., price of generic glyburide for sulfonylureas, generic pioglitazone for TZDs, insulin NPH for basal insulin, biphasic human insulin for biphasic insulin) plus a 10% mark-up and $7.00 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[64] for each treatment. 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 obtained from a convenience sample of patients with type 2 diabetes in British Columbia.[1] These doses differed from those in some of the RCTs included in the MTC meta-analysis.[36,65-67] We therefore ran sensitivity analyses where the dose of insulin was varied based on data from the RCTs.[36,65-67]

2.9.2 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 (Table 4).[42] 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.[42] Costs were inflated to 2009 Canadian dollars using the Health Component of the Canadian Consumer Price Index. The average annual cost for patients without diabetes-related complications who were using metformin plus a sulfonylurea was $1,689,[42] while those using third-line therapy had an annual cost of $1,689[42] plus the additional cost of third-line therapy and blood glucose test strips.

Table 4: Management Costs of Long-Term Diabetes-Related Complications*[42]

Complications	Fatal ($)	Non-Fatal ($)	In Subsequent Years ($)
Ischemic heart disease	0	5,623	3,246
Myocardial infarction	9,422	17,964	2,809
Heart failure	0	16,434	4,607
Stroke	8,865	24,469	3,395
Amputation	0	37,957	5,199
Blindness	0	3,006	2,142
Renal failure	0	24,355	11,054

*Costs inflated to 2010 Canadian dollars (C$) using the health component of the Consumer Price Index.

2.9.3 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.[56] Resource utilization associated with managing a severe hypoglycemic episode was based on a study by Leese et al.[46] (Table 5) and NICE.[56] Management costs were based on data from the Alberta Case Costing Database (Table 5).[68] Because resource use was derived from the United Kingdom, we presented this information to diabetes expert members of the Canadian Optimal Medication Prescribing and Utilization Service Expert Review Committee for verification. In general, they felt the 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, biasing results against pharmacotherapies that are associated with an increased risk of hypoglycemia (e.g., insulin).

Table 5: Resource Use and Costs Related to a Severe Hypoglycemic Episode[46,56,68]

Resource Use	Unit Cost ($)	Receiving*	Weighted ($)
Glucagon	93.69	90%	84.32
Consultation with ambulance services only	600	34%	204.07
Consultation with primary or emergency care only	208	7%	14.59
Consultation with primary or emergency care and ambulance service†	809	52%	420.49
Direct or indirect hospital admission†	4,302	28%	1,204.67
Average cost per severe hypoglycemic episode			**1,928.14**

*Data from the United Kingdom.[56]
†Unit cost from Alberta.[68]

2.9.4 Costs Related to Self-Monitoring of Blood Glucose

Patients using certain antidiabetes 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 recent utilization study in Ontario (Table 6).[69] A cost of $0.72 per test strip plus a pharmacy fee of $7.00 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 sensitivity analysis was conducted where the additional cost of test strips was not considered.

Table 6: Mean Daily Utilization of Blood Glucose Test Strips in 2008 by Seniors in the OPDP, by Type of Pharmacotherapy[69]

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

OPDP = Ontario Public Drug Program.

2.9.5 Discount rate

All costs and outcomes were discounted on a 5% per year basis, as recommended by the CADTH guidelines.[70]

2.9.6 Handling of Uncertainty

Univariate Sensitivity Analyses

Univariate sensitivity analyses were conducted to explore the impact of variation in model inputs and assumptions. Parameters varied in sensitivity analyses were selected based on findings from our cost-effectiveness analysis of second-line therapy, in which we employed a similar methodology.[1] The second-line therapy sensitivity analysis results indicated that the results of the present study were most likely to be sensitive to the following changes:

- Use of the most expensive agent within drug class rather than the lowest cost alternative (e.g., insulin glargine rather than insulin NPH).
- Assumption that patients using oral medications as third-line therapy add-on insulin NPH when A1C ≥ 9% (rather than remain on third-line therapy only over a lifetime).
- Alpha-glucosidase inhibitors included as a comparator in the analysis.
- Use of direct estimates of effect rather than estimates from MTC meta-analysis.
- Use of insulin doses from RCTs rather than convenience sample from British Columbia.[71]

- Assumption of a higher incidence of severe hypoglycemia in patients using insulin (from Leese et al.[46] as opposed to Bodmer et al.[45])
- Assumption that weight gain is associated with a disutility.[12,13]
- Removal of test strip costs from the analysis.
- Assumption that insulin use is associated with a disutility in year one.[10]
- Reduced time horizon (10 years rather than 40 years).

Cost-effectiveness Acceptability Curves

A non-parametric bootstrapping method,[72,73] consisting of 999 bootstrap iterations of 100 patients each, 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 999 bootstrap iterations, were plotted as cost-effectiveness acceptability curves 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[74] across a range of willingness-to-pay thresholds, according to the following formula:

Net monetary benefit = $\lambda * E - C$

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

3 RESULTS

3.1 Cost of Treatments

In the reference case, insulin NPH had the lowest treatment cost; however, when the additional cost of test strips was included, the cost of insulin NPH was similar to that of generic pioglitazone and the lowest cost DPP-4 inhibitor. Generic pioglitazone, DPP-4 inhibitors, and insulin NPH were less expensive than rosiglitazone, long-acting insulin analogues, biphasic human insulin, or biphasic insulin analogues (Table 7). However, when we applied insulin doses from RCTs rather than the convenience sample from British Columbia, insulin NPH had the lowest treatment cost even after the additional cost of test strips.

Table 7: Average Daily Costs of Treatments with and without the Additional Costs of Blood Glucose Test Strips, Stratified by Source of Insulin Dose				
Treatment	**Insulin Dose from British Columbia Convenience Sample***		**Insulin Dose from Included RCTs†**	
	Daily treatment cost without test strips‡ ($)	**Daily treatment cost with test strips§ ($)**	**Daily treatment cost without test strips ($)**	**Daily treatment cost with test strips ($)**
Insulin NPH	1.95	3.60	1.08	2.72
Pioglitazone¶	2.50	3.41	2.50	3.41
Rosiglitazone	5.00	5.92	5.00	5.92
Biphasic human insulin	3.81	5.45	1.88	3.52
DPP-4 inhibitors	2.88	3.80	2.88	3.80
Long-acting insulin analogues	3.04	4.69	2.04	3.68
Biphasic insulin analogues	4.34	5.98	1.88	3.51

DPP = dipeptidyl peptidase; NPH = neutral protamine Hagedorn; RCT= randomized controlled trial.
*Insulin doses obtained from a patient sample in British Columbia: 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.
†Insulin doses obtained from RCTs[36,65,67] included in the systematic review: 0.35 U/kg,[67] 0.42 U/kg,[67] 0.53U/kg,[36] and 0.76U/kg[65] U/kg for long-acting insulin analogues, insulin NPH, biphasic insulin analogues, and biphasic human insulin respectively.
‡The cost of the lowest cost alternative was applied for each drug class plus a 10% mark-up and $7.00 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.
§Patients using insulin were assumed to use 2.1 test strips per day while those using oral drugs in combination with sulfonylureas used 1.16 test strips per day, based on data from Ontario Drug Benefit.
¶Based on the cost of 30 mg generic pioglitazone in Saskatchewan, Alberta, and Non-Insured Health Benefits (NIHB) program; in Ontario, generic pioglitazone costs less ($1.57) under the Ministry's Exceptional Access program.

3.2 Reference Case Analysis

With the exception of CHF in patients using TZDs, differences in 40-year cumulative incidence rates of long-term diabetes complications between active comparators were small (absolute ≤ 1%) (Table 8). However, absolute risks for active treatments were lower compared with metformin plus a sulfonylurea alone, particularly for myocardial infarction, stroke, amputation, and blindness.

Table 8: Cumulative Incidence of Long-Term Diabetes Related Complications During a 40-Year Period: Primary Economic Analysis					
Complications	**Met + SU**	**Met + SU + Basl**	**Met + SU + Bipl**	**Met + SU + TZD***	**Met + SU DPP-4 (sitagliptin)**
IHD	8.9%	8.4%	8.5%	8.3%	8.5%
MI	25.5%	24.4%	24.5%	26.7%	24.5%
CHF	11.3%	11.1%	11.6%	20.7%*	11.0%
Stroke	11.4%	10.8%	10.9%	12.2%	11.1%
Amputation	5.8%	4.6%	4.7%	4.7%	5.0%
Blindness	5.7%	5.2%	5.1%	5.0%	5.3%
Renal Failure	3.4%	3.3%	3.3%	3.1%	3.3%

Basl = basal insulin; Bipl = biphasic insulin; CHF = congestive heart failure; DPP = dipeptidyl peptidase; IHD = ischemic heart disease; Met = metformin; MI = myocardial infarction; SU = sulfonylurea; TZDs = thiazolidinediones,
*The reference case assumes that TZDs are associated with an increased risk of CHF based on evidence from the RECORD trial.[47]

Total lifetime costs and QALYs, as well as incremental cost-effectiveness results from the primary economic analysis, are presented in Table 9. Among the active treatments, basal insulin was associated with the lowest total lifetime costs ($44,206), while use of biphasic insulin incurred the highest lifetime costs ($48,317). With the exception of TZDs, there were very small differences in QALYs gained between active treatments (Range of 8.3059 with DPP-4 inhibitor to 8.3251 with basal insulin). Among active treatments, basal insulin was associated with the most favourable cost-effectiveness estimate, with an incremental cost of $60,049 per QALY gained. Other active treatments were more expensive and less effective than basal insulin.

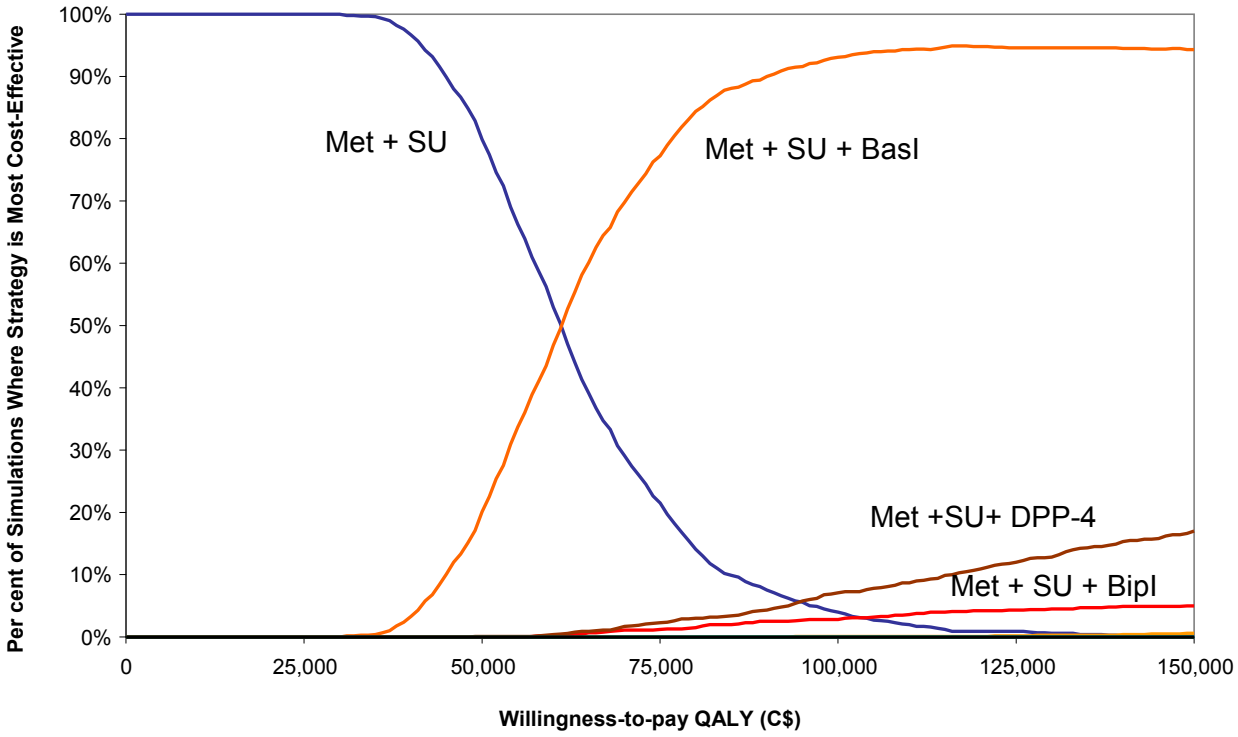
Table 9: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results from the Reference Case Analysis

Treatment	Average Costs Incurred during Lifetime ($)	Average QALYs Gained during Lifetime	Incremental Cost-Effectiveness Results
Met + SU	39,128	8.2405	NA
Met + SU + Basl	44,206	8.3251	$60,049 per QALY gained (relative to Met + SU)
Met + SU + DPP-4 (sitagliptin)	44,717	8.3059	Dominated by Met + SU + Basl
Met + SU + TZD*	45,936	8.2191	Dominated by Met + SU + Basl
Met + SU + Bipl	48,317	8.3198	Dominated by Met + SU + Basl

Basl = basal insulin ; DPP = dipeptidyl peptidase; Met = metformin; NA = not applicable; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione.
*The reference case assumes that TZDs are associated with an increased risk of CHF based on evidence from the RECORD trial.[47]

The cost-effectiveness acceptability curve (Figure 2) shows that basal insulin had the highest probability of being most cost-effective beyond willingness-to-pay thresholds of about $62,000 per QALY.

Figure 2: Cost-Effectiveness Acceptability Curve for the Reference Case Economic Analysis



BasI = basal insulin; BipI = biphasic insulin; DPP = dipeptidyl peptidase; SU = sulfonylurea; Met = metformin.

3.3 Sensitivity Analyses

Cost-effectiveness results were sensitive to variation in model inputs and assumptions. This finding is attributable to the similar treatment costs between generic pioglitazone, insulin NPH, biphasic human insulin, and DPP-4 inhibitors (sitagliptin). In particular, cost-effectiveness results varied depending on the assumed impact of hypoglycemia, weight gain, and insulin injections on HRQoL; dose and choice of insulin products; and rates of severe hypoglycemia (Table 10).

Impact of Mild-to-Moderate Hypoglycemia on Health-Related Quality of Life

In the reference case analysis, patients experiencing mild-to-moderate hypoglycemia were assumed to have a transient reduction in HRQoL.[57] Each mild-to-moderate hypoglycemic episode was assumed to last for 15 minutes, with an annual decrement of 0.000004767 QALYs.[5] Levy et al.[75] reported that each mild-to-moderate hypoglycemic episode was associated with a chronic disutility of 0.0033 QALYs over one year, implying that each mild-to-moderate episode is equivalent to spending 1.2 days in a state of death (i.e., utility equals zero). When we applied this disutility in a sensitivity analysis, DPP-4-inhibitors (sitagliptin) emerged as the most cost-effective option, with an incremental cost-utility ratio (ICUR) of $90,007 per QALY (relative to metformin and a sulfonylurea alone). Other treatments were either dominated or extendedly dominated.*

Impact of Severe Hypoglycemia on Health-Related Quality of Life

In the reference case analysis, those having a severe hypoglycemic episode were assumed to have a transient reduction in HRQoL, followed by a chronic decrement of 0.01 (based on data from NICE[56]) due to a fear of future hypoglycemic episodes. The disutility estimate for severe hypoglycemia used by NICE[56]

* Extended dominance refers to a treatment that is dominated by a mix of alternative therapies. A mix of therapies would result in higher QALYS gained at an equivalent cost as providing all patients a particular treatment.

is smaller than that reported elsewhere. Currie et al.[6] suggest that a utility decrement of 0.047 should be applied over one year after an episode of severe hypoglycemia. This estimate is of questionable face validity as it is equivalent to spending 17 days in a state of death, implying that severe hypoglycemia is a more dire consequence in terms of quality of life than even myocardial infarction (which has a utility decrement of 0.041).[3,4] Nevertheless, we ran a sensitivity analysis using the estimate by Currie et al., and found a negligible impact on cost-effectiveness results. Basal human insulin remained the most favourable option among active comparisons, with an ICUR of $69,892 per QALY gained.

Impact of Weight Gain on Health-Related Quality of Life

We did not apply a utility decrement for weight gain in the reference case analysis. However, we performed a sensitivity analysis assuming a utility decrement of 0.001950135 per unit increase in BMI, based on data presented in the NICE obesity guidelines†.[12,13] In this scenario, basal insulin remained the most cost-effective option; however, the cost-effectiveness estimates for insulin NPH became less favourable — the ICUR increased from $60,049 to $75,537 per QALY gained relative to metformin and a sulfonylurea.

Impact of Insulin Injections on Health-Related Quality of Life

We did not apply a utility decrement for insulin use in the reference case analysis. Some studies have reported that insulin use is associated with a reduction in quality of life;[9-11] therefore, we ran a sensitivity analysis where we assumed a one time decrement of –0.06 based on data from a trial by Maddigan et al.[10] Because this estimate exceeded the disutilities for even some serious complications (e.g., myocardial infarction),[3,4] we ran a subsequent analysis using the lower limit of the CI (–0.03). This decrement was only applied in year one based on clinical expert opinion. When these disutilities for insulin were applied in a sensitivity analysis, results for insulin NPH became less favourable. In fact, DPP-4 inhibitors became the most cost-effective option for third-line therapy (with an ICUR of $85,561 relative to metformin and a sulfonylurea alone) when the larger decrement was applied.

Doses of Insulin Products

The doses of insulin NPH (0.75 U/kg) and biphasic human insulin (1.5 U/kg) assumed in the model were based on a dataset from patients with type 2 diabetes in British Columbia. The doses reported in this British Columbia dataset were higher than those in some of the RCTs included in the MTC meta-analysis.[36,65-67] We therefore ran sensitivity analyses where the dose of insulin was varied, based on data from the RCTs.[36,65-67] For this sensitivity analysis, we assumed an insulin NPH dose of 0.42 U/kg and a biphasic insulin dose of 0.76 U/kg.[36,65-67] In this scenario, cost-effectiveness estimates for basal insulin became more favorable — the ICUR decreased from $60,049 to $37,607 per QALY gained relative to metformin and a sulfonylurea.

Choice of Insulin Product within Class

The primary economic analysis applied the lowest cost comparator within each class and assumed treatment effects at the class level. For example, we applied pooled treatment effects from all basal insulin products (e.g., insulin glargine, insulin NPH, and insulin detemir) and assumed the treatment cost of insulin NPH. However, we ran additional analyses where we used the treatment costs of different drugs within each class. When we applied the treatment cost for insulin glargine, rather than insulin NPH, cost-effectiveness results for basal insulin deteriorated significantly, such that DPP-4 inhibitors became the most cost-effective strategy with an ICUR of $85,561 per QALY gained relative to metformin and a sulfonylurea. Insulin glargine was associated with an ICUR of $175,037 per QALY gained relative to DPP-4 inhibitors. Similarly, when we used the price of rosiglitazone rather than generic pioglitazone, the lifetime costs of TZDs increased and became even less favourable than in the reference case analysis.

† Decrement calculated from NICE obesity guidelines (0.56*-0.001762115+0.46*-0.002094241)[12,13]

Rates of Severe Hypoglycemia

The baseline rates of severe hypoglycemia among patients using metformin, metformin plus a sulfonylurea, or metformin plus a sulfonylurea plus insulin were derived from a population-based study by Bodmer et al.,[45] who reported 0.0006, 0.002, and 0.005 severe events per patient-year for metformin, metformin plus sulfonylureas, and metformin plus sulfonylureas plus insulin respectively. When we ran a sensitivity analysis based on the higher estimates reported by Leese et al.[46] (i.e., 0.0005, 0.009, and 0.118 events per patient-year), DPP-4 inhibitors became the most cost-effective strategy with an ICUR of $85,561 per QALY gained relative to metformin plus a sulfonylurea. Basal insulin was associated with an ICUR of $95,973 per QALY gained relative to DPP-4 inhibitors.

Lower Cost of Pioglitazone

Pioglitazone is not listed as a benefit in the Ontario Drug Benefit Formulary, although it is a listed benefit in the Saskatchewan Public Drug Plan. The unit cost of generic pioglitazone 30 mg in Saskatchewan ($2.20) was used in the reference case analysis. However, generic pioglitazone 30 mg, authorized in Ontario through the Ministry's Exceptional Access Program, is reimbursed at a unit cost of $1.57. When we re-ran the cost-effectiveness analysis using the Ontario cost, the cost-effectiveness estimates did not change significantly. Basal human insulin remained the most cost-effective option with an incremental cost of $60,049 per QALY. Other treatments were more expensive and less effective than basal human insulin. However, the ICUR for DPP-4 inhibitors relative to generic pioglitazone went from being less expensive and more effective (dominant) to $26,262 per QALY.

Other Sensitivity Analyses

Cost-effectiveness results were generally robust in other sensitivity analyses: adding insulin NPH when A1C ≥9%; using direct estimates of effect; higher disutility associated with severe hypoglycemia; and inclusion of alpha-glucosidase inhibitors as a comparator. Basal insulin continued to be the most cost-effective third-line treatment, with incremental cost per QALY values ranging from $59,951 to $63,245. Results, however, were sensitive to inclusion of the cost of test strips in the analysis, as well as the time horizon. When the cost of test strips was excluded, cost-effectiveness estimates for basal insulin became more favourable — the ICUR decreased from $60,049 to $41,414 per QALY gained relative to metformin and a sulfonylurea. When time horizons of five or 10 years were used rather than 40 years, the ICUR for insulin NPH increased from $60,049 to $182,885 and $104,568 per QALY gained relative to metformin and a sulfonylurea respectively.

Table 10: Summary of Results from Sensitivity Analyses				
Analysis	**Met + SU + Basl**	**Met + SU + Bipl**	**Met + SU + TZD***	**Met + SU DPP-4**
Primary economic analysis	**$60,049 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Price of rosiglitazone used rather than generic pioglitazone.	**$60,049 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Price of long-acting insulin analogue used rather than insulin NPH.	**$175,037 (relative to Met + SU + DPP-4)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	**$85,561 (relative to Met + SU)**
Cost of pioglitazone from Ontario Ministry's Exceptional Access Program rather than cost in Saskatchewan.	**$60,049 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Use estimates of effect from direct pairwise meta-analyses.	**$59,951 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Model assumes that patients use Met + TZD rather than Met + SU + TZD (since Met + SU + TZD is not indicated for use in Canada).	**$60,049 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Patients add-on insulin NPH when A1C ≥ 9% (rather than static third-line therapy over lifetime).	**$63,245 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Patients using insulin NPH in combination with metformin and SU drop SU and switch to biphasic human insulin when A1C ≥ 9% (rather than static third-line therapy over lifetime).	**$70,771 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
alpha-glucosidase inhibitors included as a comparator (Δ A1C, –0.46 [–0.96 to 0.03]; Δ weight –0.43 (–2.20 to 1.44)].	**$60,049, (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by a blend of Met + SU and Met + SU + Basl	dominated by Met + SU + Basl
Insulin dose for basal human insulin and biphasic human insulin from RCTs[36,65-67] (rather than doses from BC dataset).[36]	**$37,797 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Pioglitazone not associated with any adverse events.	**$60,049, (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by a blend of Met + SU and Met + SU + Basl	dominated by Met + SU oral antidiabetes drug + Basl
Higher rate of severe hypoglycemia (from Leese et al.[46]	**$96,973 (relative to Met + SU + Basl)**	dominated by Met + SU + DPP-4	dominated by Met + SU + DPP-4	**$85,561 (relative to Met + SU)**

Table 10: Summary of Results from Sensitivity Analyses				
Analysis	**Met + SU + Basl**	**Met + SU + Bipl**	**Met + SU + TZD***	**Met + SU DPP-4**
as opposed Bodmer et al.[45])				
Higher disutility associated with severe hypoglycemia (from Currie et al. rather than NICE).	**$69,892 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Higher disutility associated with mild-to-moderate hypoglycemia (from Levy et al.[75] rather than the CADTH insulin analogues report[57]).	dominated by a blend of Met + SU and Met + SU + DPP-4	dominated by Met + SU + DPP-4	dominated by Met + SU + DPP-4	**$90,007 (relative to Met + SU)**
Model incorporates reduced quality of life associated with increased weight gain.[12,13]	**$75,537 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by a blend of Met + SU and Met + SU + Basl	dominated by Met + SU + Basl
Price of test strips not included in cost-effectiveness analysis (as opposed to included, as per published utilization data).	**$41,414 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by Met + SU + Basl
Cost of DPP-4 inhibitors is $2.30 rather than $2.55.	**$60,049 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by Met + SU + Basl	dominated by a blend of Met + SU and Met + SU + Basl
Disutility of 0.030 associated with insulin use in year one (rather than no disutility).	**$78,661 (relative to Met + SU)**	dominated by Met + SU + DPP-4	dominated by Met + SU + DPP-4	**$664,044 (relative to Met + SU + Basl)**
Disutility of 0.060 associated with insulin use in year one (rather than no disutility).	dominated by a blend of Met + SU and Met + SU + DPP-4	dominated by Met + SU + DPP-4	dominated by Met + SU + DPP-4	**$85,561 (relative to Met + SU)**
Time horizon of 10 years (rather than 40 years).	**$104,568 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by a blend of Met + SU and Met + SU + Basl	dominated by Met + SU + Basl
Time horizon of five years (rather than 40 years).	**$182,885 (relative to Met + SU)**	dominated by Met + SU + Basl	dominated by a blend of Met + SU and Met + SU + Basl	dominated by Met + SU + Basl

Basl = basal insulin; Bipl = biphasic insulin; CADTH = Canadian Agency for Drugs and Technologies in Health; DPP = dipeptidyl peptidase; Met = metformin; NICE = National Institute for Health and Clinical Excellence; SU = sulfonylurea; TZDs = thiazolidinediones.

4 DISCUSSION

4.1 Summary of Main Findings

This is the first Canadian cost-effectiveness analysis of treatments for type 2 diabetes that has compared third-line therapies, including the newer DPP-4 inhibitors, after inadequate control with metformin and sulfonylurea combination therapy. We found that the addition of insulin NPH to metformin and sulfonylurea combination therapy was associated with the most favourable cost-effectiveness estimates among active treatments — the incremental cost per QALY gained in the reference case analysis was $60,800 relative to metformin and sulfonylurea combination therapy alone. Other active treatments added to metformin and sulfonylurea combination therapy were more costly and less effective in terms of QALYs gained compared with insulin NPH, although the absolute differences in both costs and consequences were small. Cost-effectiveness results were, however, sensitive to variation in model inputs and assumptions. Under the following scenarios, DPP-4 inhibitors became the most cost-effective option: a high disutility was assumed with insulin use, a higher risk of hypoglycemia among insulin users was modelled, and the costs of long-acting insulin analogues were applied to the basal insulin option rather than the cost of insulin NPH.

4.2 Strengths and Limitations

There are a number of strengths of this study. First, this is the first economic analysis to simultaneously assess the relative cost-effectiveness of newer and older treatments available for third-line antidiabetes therapy in Canada. Second, clinical inputs, when available, were derived from a recent systematic review and MTC meta-analysis, which used both direct and indirect evidence, specifically in patients with type 2 diabetes that is inadequately controlled with metformin and sulfonylurea combination therapy. Third, our analysis followed a transparent and accepted methodology and adheres to the Guidelines for the Economic Evaluation of Health Technologies in Canada.[70] Fourth, the Therapeutic Review Panel (TRP), which is comprised of endocrinologists, family physicians, pharmacists, and health economists, provided advice throughout the analysis. Fifth, this economic evaluation uses the well-validated UKPDS Outcomes Model.[2] The ability of the UKPDS Outcome Model[2] to forecast long-term diabetes-related complications in patients with type 2 diabetes mellitus has been validated against published clinical and epidemiological studies.[76] Sixth, as recommended by economic guidelines,[3,4] disutility estimates used in the current economic analyses were obtained from a community-based US EQ-5D catalogue.[3,4] Finally, detailed sensitivity and variability analyses were performed to examine the robustness of results to variation in model parameters and assumptions.

Despite its strengths, this analysis has certain limitations that warrant discussion. First, there were considerable weaknesses in the available clinical evidence. A majority of RCTs included in CADTH's systematic review of third-line therapies were assessed as being of poor methodological quality, were less than one year in duration, and had inadequate power to detect differences in clinically relevant end points. As well, there were possible limitations to the external validity of the available clinical evidence, as described in detail in the systematic review report.[1] Because of the lack of sufficient data on clinically relevant outcomes, surrogate end points (e.g., A1C) were used to forecast the occurrence of long-term diabetes-related complications. The validity of surrogate outcomes, particularly A1C, in forecasting cardiovascular end points in patients with type 2 diabetes has been debated.[7,8] Moreover, the UKPDS Outcomes Model is based on data from patients who used older classes of drugs (e.g., metformin, sulfonylureas, insulin). It is unclear whether equations derived from patients using older classes of drugs can be applied to newer agents (e.g., TZDs and DPP-4 inhibitors).

It is also noteworthy that the available clinical evidence for some classes of drugs in the MTC meta-analysis was more substantive than others. For example, evidence from the DPP-4 inhibitor class was limited to a single RCT comparing sitagliptin with placebo, both added to metformin and sulfonylureas; there were no trials involving saxagliptin or vildagliptin (which were not approved by Health Canada at the

time of this therapeutic review). In contrast, there were 13 RCTs for basal insulins (insulin NPH or long-acting insulin analogues) added to metformin and sulfonylureas.

With respect to safety, we were unable to include the potential risks of newer agents, such as DPP-4 inhibitors, as there is relatively limited clinical experience in their use. Consequently, the analysis may be biased somewhat against older agents, such as insulin or TZDs, as their adverse effect profile is better characterized. If safety data emerges over time suggesting that DPP-4 inhibitors are associated with harm, then cost-effectiveness estimates for DPP-4 inhibitors would be less favourable than reported here.

Apart from issues related to the clinical evidence, certain aspects of the modelling approach may also have introduced a degree of bias in the results. The UKPDS model does not explicitly incorporate a number of morbidities (e.g., peripheral neuropathy and ulceration) related to diabetes.[2] Furthermore, some complications are represented as a single end point (e.g., blindness and end-stage renal disease) in the model rather than intermediate states (e.g., retinopathy and nephropathy) that may themselves be associated with reduced HRQoL. Since a reduced incidence of these outcomes and the resulting benefits in terms of HRQoL and reduced treatment costs are not captured, use of the UKPDS model may result in slight overestimation of incremental cost-effectiveness ratios. However, the impact of this factor on cost-effectiveness estimates is likely minimal since the CADTH meta-analysis reported only modest differences between active comparators in terms of glycemic control.

Modelling changes in treatment sequences over time is challenging with any model, including the UKPDS Outcomes Model.[2] There is uncertainty about which treatment patients will add-on or switch to after inadequate control on third-line therapy. Furthermore, when patients use multiple treatments over time, it is difficult to assess whether benefits conferred are attributable to the treatment of interest or subsequent treatments. Because of these considerations, it was assumed in the primary economic analysis that patients remained on their respective third-line therapy over their expected lifetime, without adding or switching to subsequent agents. Since this approach is not reflective of clinical practice given the progressive nature of diabetes, a sensitivity analysis was conducted whereby patients were assumed to add insulin as fourth-line therapy once A1C had reached 9.0% on third-line therapy. However, to conduct these sensitivity analyses within the UKPDS model, the weight and hypoglycemia inputs had to be front-loaded (i.e., applied in year one) because unlike A1C, these parameters could not be modified over time. As such, results from these sensitivity analyses should be interpreted with caution as some elements are not discounted appropriately. In future, if the UKPDS model is updated to enable more seamless integration of changes in treatment sequences over time, reanalysis of these sensitivity analyses may be warranted.

Modelling the increased risk of CHF associated with TZD use in the UKPDS model was challenging as there is no risk multiplier for this event. As such, the risk of CHF was artificially increased among patients using TZDs by increasing body weight by 30 kg among this patient population. CHF is the only submodel in the UKPDS Outcomes Model that is directly influenced by BMI.[2] However, this approach would have had a minor impact on the incidence of other cardiovascular outcomes that are influenced by CHF.

With respect to the inputs used in the analysis, there was considerable uncertainty regarding the disutility associated with insulin use,[9-11] weight gain,[12,13] and hypoglycemia,[6] as well as event rates for severe hypoglycemia. In the absence of good data for these inputs, conservative estimates were used for the reference case analysis. Because of the similar daily cost of insulin NPH, generic pioglitazone, and DPP-4 inhibitors, cost-effectiveness results were sensitive to variation in these disutilities. For example, when a large disutility was applied for insulin use, DPP-4 inhibitors became the most cost-effective option. Hence, a more precise understanding of the relative cost-effectiveness of third-line agents requires further research to estimate the incidence of severe hypoglycemia in insulin users, as well as the impact of insulin use, weight gain, and hypoglycemia on quality of life.

4.3 Results in Relation to Previous Studies

NICE recently conducted a cost-effectiveness analysis of third-line therapies in the management of type 2 diabetes.[77] NICE compared six treatments in the management of diabetes: human insulin, pioglitazone, glargine, biphasic insulin analogue, rosiglitazone, and exenatide. NICE also used the UKPDS Outcomes Model to forecast long-term diabetes-related complications and cost consequences across the various treatments, and reported that human insulin was the most cost-effective option.[77] Unlike our analysis, NICE cost-effectiveness estimates were robust to variation in model inputs and assumptions. This difference may be due to the fact that DPP-4 inhibitors were not considered by NICE. In our analysis, DPP-4 inhibitors were more cost-effective than insulin NPH in a number of sensitivity analyses because of their similar clinical efficacy and cost.

4.4 Policy Considerations

This report provides policy-makers with evidence to make informed decisions regarding the prescribing and use of third-line diabetes pharmacotherapies in their jurisdictions. Findings, however, are specific to patients who have inadequate glycemic control with metformin and sulfonylurea combination therapy, which represents the most commonly used approach to second-line therapy.[78]

In some instances, patients may be unwilling or unable to use insulin as their third-line therapy and may wish to use an oral diabetes agent instead. While insulin NPH was the most cost-effective option in most cases, a DPP-4 inhibitor was most cost-effective in the most pessimistic scenarios with respect to the tolerability and acceptability of insulin. Other oral agents available for third-line treatment were less cost-effective than DPP-4 inhibitors. Apart from considerations of cost-effectiveness, it is worth noting that many patients who choose a DPP-4 inhibitor as third-line therapy will eventually require insulin as fourth-line therapy due to the progressive nature of diabetes. Although combined use of a DPP-4 inhibitor with insulin is not currently approved in Canada, DPP-4 inhibitors are indicated with insulin in Europe, and this indication is under review by the Food and Drug Administration in the US. Hence, there is a risk that DPP-4 inhibitors initiated as third-line therapy may be continued with insulin, especially if combined use with insulin is eventually approved in Canada. Such treatment regimens would be associated with significant costs and uncertain clinical and economic benefits.

4.5 Generalizability

This analysis was conducted for Canadian provincial ministries of health using Canadian cost data (such as that of blood glucose test strips), clinical characteristics of patients with diabetes in Canada, and validation of inputs by Canadian diabetes experts. Within the limitations of the available clinical data, and modelling of long-term outcomes using surrogate indicators, the results of this cost-effectiveness analysis should be generalizable to all Canadian settings, but application of these results to other settings may be inappropriate.

5 CONCLUSIONS

This is the first Canadian cost-effectiveness analysis that has compared third-line therapies for the management of type 2 diabetes, including the newer DPP-4 inhibitors. The findings suggest that for most patients, the use of insulin NPH is the most cost-effective third-line therapy. This result was driven primarily by price and efficacy — insulin NPH is either lower or similar in price (depending on the dose used) than other treatment options and it is associated with the largest improvements in QALYs gained. Sensitivity analyses demonstrated that DPP-4 inhibitors (sitagliptin) may be the most cost-effective option under scenarios that were more pessimistic regarding insulin than the reference case, although these results should be interpreted with caution because of the low quality of the underlying clinical data. Furthermore, the long-term safety profile of newer agents, such as DPP-4 inhibitors, is largely unknown because of limited clinical experience; hence, the analysis may be biased to a degree against older

agents such as insulin. In order to define the relative cost-effectiveness of newer third-line agents versus older agents with greater certainty, longer-term studies that provide more robust data on clinically important outcomes, safety, quality of life, and patient preferences are required.

6 REFERENCES

1. Canadian Agency for Drugs and Technologies in Health. Therapeutic review report: Clinical review. Third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylureas [DRAFT]. Ottawa: The Agency; 2010 Mar 31.
2. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004 Oct;47(10):1747-59.
3. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Med Care. 2005 Jul;43(7):736-49.
4. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006 Jul;26(4):410-20.
5. Agency for Healthcare Research and Quality [Internet]. Rockville (MD): Agency for Healthcare Research and Quality. Calculating the U.S. population-based EQ-5D index score; 2005 [cited 2007 Oct 10]. Available from: http://www.ahrq.gov/rice/EQ5Dscore.htm
6. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006 Aug;22(8):1523-34.
7. Lassere MN, Johnson KR, Boers M, Tugwell P, Brooks P, Simon L, et al. Definitions and validation criteria for biomarkers and surrogate endpoints: development and testing of a quantitative hierarchical levels of evidence schema. J Rheumatol. 2007 Mar;34(3):607-15.
8. Rosen CJ. The rosiglitazone story--lessons from an FDA Advisory Committee meeting. N Engl J Med. 2007 Aug 30;357(9):844-6.
9. Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JM, et al. Utilities and disutilities for type 2 diabetes treatment-related attributes. Qual Life Res. 2007 Sep;16(7):1251-65.
10. Maddigan SL, Feeny DH, Majumdar SR, Farris KB, Johnson JA. Health Utilities Index mark 3 demonstrated construct validity in a population-based sample with type 2 diabetes. J Clin Epidemiol. 2006 May;59(5):472-7.
11. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections: preferences of Canadians with type 2 diabetes. Diabetes Care. 2005 Sep;28(9):2243-5.
12. National Collaborating Centre for Primary Care. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children [Internet]. London: National Institute for Health and Clinical Excellence (NICE); 2006. (NICE clinical guideline 43). [cited 2009 Dec 1]. Available from: http://guidance.nice.org.uk/CG43
13. Macran S. The relationship between body mass index and health-related quality of life [Internet]. York (UK): Outcomes Research Group, Centre for Health Economics; 2004. (Discussion paper 190). [cited 2010 Jan 22]. Available from: http://www.york.ac.uk/inst/che/pdf/DP190.pdf
14. Diabetes in Canada [Internet]. 2nd edition. Ottawa: Health Canada; 2002. [cited 2007 Aug 1]. Available from: http://www.phac-aspc.gc.ca/publicat/dic-dac2/pdf/dic-dac2_en.pdf
15. Diabetes in Canada: facts & figures [Internet]. Ottawa: Public Health Agency of Canada; 2008. [cited 2009 Mar 20]. Available from: http://www.phac-aspc.gc.ca/publicat/2008/ndfs-fnrd-08/ndfs_ff-fnrd_fc-eng.php
16. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet. 1998;352(9131):837-53.

17. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.

18. The prevalence and costs of diabetes [Internet]. Toronto: Canadian Diabetes Association; 2007. Pub no. 114007 06-295 06/06 Q-50M. [cited 2009 Aug 24]. Available from: http://www.diabetes.ca/Files/prevalence-and-costs.pdf

19. Report from the national diabetes surveillance system: diabetes in Canada, 2008 [Internet]. Ottawa: Public Health Agency of Canada; 2008. [cited 2009 Jan 23]. (Cat. HP32-2/2006). Available from: http://www.phac-aspc.gc.ca/publicat/2008/ndssdic-snsddac-08/index-eng.php

20. Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes [Internet]. 2008 [cited 2010 Jan 27];32(suppl 1):i-S201. Available from: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf

21. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009 Jan;32(1):193-203.

22. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: National clinical guideline for management in primary and secondary care (update) [Internet]. London (UK): Royal College of Physicians; 2008. [cited 2008 Dec 19]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG66diabetesfullguideline.pdf

23. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2008 Feb;79(2):196-203.

24. Genuth S. The UKPDS and its global impact. Diabet Med. 2008 Aug;25 Suppl 2:57-62.

25. Utilization of oral antiglycemics in Canada. [unpublished dataset]. Ottawa (ON): Brogan, Inc.; 2008.

26. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998 Sep 12;352(9131):854-65.

27. Turner RC, Cull CA, Frighi V, Holman RR, UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA. 1999 Jun 2;281(21):2005-12.

28. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with type 2 diabetes inadequately controlled on metformin: a systematic review and cost-effectiveness analysis [DRAFT]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 2).

29. Canadian Agency for Drugs and Technologies in Health. Optimal therapy recommendations for the prescribing and use of second-line therapy for patients with type 2 diabetes inadequately controlled on metformin [Internet]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 5). [cited 2010 Aug 6]. Available from: http://www.cadth.ca/media/pdf/C1110_OT_Reccommendations_final_e.pdf

30. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: the management of type 2 diabetes [Internet]. London: National Institute for Health and Clinical Excellence; 2009. (NICE clinical guideline 87). [cited 2010 Jan 21]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf

31. Managing type 2 diabetes in south Australia [Internet]. Adelaide: Government of South Australia, Department of Health; 2008. [cited 2009 Jan 19]. Available from: http://www.publications.health.sa.gov.au/cgi/viewcontent.cgi?article=1001&context=dis

32. American Diabetes Association. Standards of medical care in diabetes - 2010. Diabetes Care [Internet]. 2010 Jan [cited 2010 Jan 21];33(Supp 1):S11-S61. Available from: http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html

33. Management of type 2 diabetes [Internet]. Wellington: New Zealand Guidelines Group (NZGG); 2003. [cited 2009 Jan 19]. Available from: http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineCatID=30&guidelineID=36

34. IDF clinical guidelines task force. Global guideline for type 2 diabetes [Internet]. Brussels: International Diabetes Federation; 2005. [cited 2009 Jan 19]. Available from: http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf

35. Harris SB, Ekoe JM, Zdanowicz Y, Webster-Bogaert S. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). Diabetes Res Clin Pract. 2005 Oct;70(1):90-7.

36. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med [Internet]. 2007 Oct 25 [cited 2009 Dec 3];357(17):1716-30. Available from: http://content.nejm.org/cgi/reprint/357/17/1716.pdf

37. Farmer AJ, Wade AW, French DP, Simon J, Yudkin P, Gray A, et al. Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial [Internet].2009. [cited 2010 Aug 6]. Available from: http://www.hta.ac.uk/project/1330.asp

38. Hux JE, Booth GL, Slaughter PM, Laupacis A, Eds. Diabetes in Ontario: an ICES practice atlas [Internet]. Toronto: Institute for Clinical Evaluative Sciences; 2003. [cited 2008 Jan 23]. Available from: http://www.ices.on.ca/webpage.cfm?site_id=1&org_id=31&morg_id=0&gsec_id=0&item_id=1312

39. Alberta Diabetes Atlas 2007 [Internet]. Edmonton: Institute of Health Economics; 2007. [cited 2008 Jan 23]. Available from: http://www.achord.ca/documents/AlbertaDiabetesAtlas2007_002.pdf

40. Ostgren CJ, Merlo J, Rastam L, Lindblad U. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. Diabetes Obes Metab. 2004 Sep;6(5):367-74.

41. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001 May 9;285(18):2370-5.

42. O'Reilly D, Hopkins R, Blackhouse G, Clarke P, Hux J, Guan J, et al. Development of an Ontario Diabetes Economic Model (ODEM) and application to a multidisciplinary primary care diabetes management program [Internet]. Hamilton (ON): Program for Assessment of Technology in Health (PATH); 2006. 120 p. [cited 2010 Aug 6]. Available from: http://www.path-hta.ca/Libraries/Reports/Development_of_an_Ontario_Diabetes_Economic_Model_ODEM_and_Application_to_a_Multidisciplinary_Primary_Care_Diabetes_Management_Program.sflb.ashx

43. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007 Sep;9(5):733-45.

44. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with diabetes inadequately controlled on metformin: A systematic review and cost-effectiveness analysis [Internet]. Ottawa: The Agency; 2010 Jan. [cited 2010 May 14]. (Optimal therapy report; vol. 4 no. 2). Available from: http://www.cadth.ca/media/pdf/C1110_SR_Report_final_e.pdf

45. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care. 2008 Nov;31(11):2086-91.

46. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care [Internet]. 2003 Apr [cited 2009 Feb 26];26(4):1176-80. Available from: http://care.diabetesjournals.org/cgi/reprint/26/4/1176

47. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 5;373:2125-35.

48. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71.

49. Wolf R, Frederich R, Fiedorek F, Donovan M, Xu Z, Harris S, et al. Evaluation of CV Risk in the Saxagliptin Clinical Trials. Poster presented at: 2009 June 5-9. Princeton, NJ, Wilminngton, DE.

50. MedWatch the FDA safety information and adverse event reporting program: safety information [Internet]. Silver Spring (MD): US Food and Drug Administration. Sitagliptin (marketed as Januvia and Janumet); 2009 Sep [cited 2010 Feb 26]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm183800.htm

51. Dore DD, Seeger JD, Chan KA. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin. 2009;25(4):1019-27.

52. Mount Hood 4 Modeling Group. Computer modeling of diabetes and its complications: a report on the fourth Mount Hood Challenge Meeting. Diabetes Care [Internet]. 2007 [cited 2008 Dec 19];30(6):1638-46. Available from: http://care.diabetesjournals.org/cgi/reprint/30/6/1638

53. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2006 Aug;29(8):1963-72.

54. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making. 2002;22(4):340-9.

55. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ [Internet]. 2008 Apr 17 [cited 2009 Apr 1];336(7654):1177-80. Available from: http://www.bmj.com/cgi/reprint/336/7654/1177

56. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: the management of type 2 diabetes [Internet]. London: National Institute for Health and Clinical Excellence (NICE); 2008. [cited 2009 Apr 9]. (Clinical guideline 66). Available from: http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf

57. Canadian Agency for Drugs and Technologies in Health. An economic evaluation of insulin analogues for the treatment of patients with type 1 and type 2 diabetes mellitus in Canada [Internet]. Ottawa: The Agency; 2008. (Optimal therapy report; vol. 2 no. 4). [cited 2008 Apr 11]. Available from: http://cadth.ca/media/compus/reports/compus_Economic_IA_Report.pdf

58. Ahern J, Tamborlane WV. Steps to reduce the risks of severe hypoglycemia. Diabetes Spectr [Internet]. 1997 [cited 2008 Jan 18];10(1):39-41. Available from: http://journal.diabetes.org/diabetesspectrum/97v10n01/pg39.htm

59. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary / comparative drug index [database on the Internet]. Toronto: The Ministry; 2009 [cited 2009 Oct 10]. Available from: http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html

60. Alberta Health & Wellness. Interactive Drug Benefit List [database on the Internet]. Edmonton: Government of Alberta; 2009 [cited 2009 Oct 19]. Available from: http://idbl.ab.bluecross.ca/idblprod/load.do

61. Manitoba Health. Manitoba drug interchangeability formulary: schedule [Internet]. 61st ed. Winnipeg: Manitoba Health; 2009 Aug 17. [cited 2007 Feb 13]. Available from: http://www.gov.mb.ca/health/mdbif/schedule.pdf

62. Régie de l'assurance maladie du Québec. List of medications [Internet]. Amended edition. Québec (QC): Gouvernement du Québec; 2009 Aug 19. [cited 2009 Oct 19]. Available from: https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_mod2_2009_08_19_en.pdf Including amendment no.2, correction no.3.

63. Saskatchewan Health. Online formulary [database on the Internet]. Regina: Government of Saskatchewan; 2000 -; 2009 [cited 2009 Oct 19]. Available from: http://formulary.drugplan.health.gov.sk.ca/

64. ATC/DDD Index 2010 [Internet]. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health; 2009. [cited 2010 May 17]. Available from: http://www.whocc.no/atc_ddd_index/

65. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care. 2005 Feb;28(2):254-9.

66. Goudswaard AN, Stolk RP, Zuithoff P, de Valk HW, Rutten GE. Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. J Fam Pract [Internet]. 2004 May [cited 2009 Dec 4];53(5):393-9. Available from: http://www.jfponline.com/Pages.asp?AID=1703

67. De Mattia G, Laurenti O, Moretti A. Comparison of glycaemic control in patients with Type 2 diabetes on basal insulin and fixed combination oral antidiabetic treatment: results of a pilot study. Acta Diabetol. 2009 Mar;46(1):67-73.

68. Health costing in Alberta: 2006 annual report [Internet]. Edmonton: Alberta Health and Wellness; 2006 Jul. 323 p. [cited 2007 Feb 14]. Available from: http://www.health.alberta.ca/documents/Case-Cost-Hospital-04-05.pdf

69. Gomes T, Juurlink DN, Shah BR, Paterson JM, Mamdani M. Blood glucose test strip use: patterns, costs, and potential savings associated with reduced testing. ICES Investigative Report [Internet]. Toronto: Institute for Clinical Evaluative Sciences; 2009. [cited 2010 May 14]. Available from: http://www.ices.on.ca/file/Blood%20Glucose%20Test%20Strip_Dec2009.pdf

70. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3rd. ed. Ottawa: The Agency; 2006. [cited 2007 Feb 9]. Available from: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

71. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ. 2009 Feb 17;180(4):400-7.

72. Berger ML, Bingefors K, Hedblom EC, Pashos CL, Torrance GW, editors. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville (NJ): International Society for Pharmacoeconomics and Outcomes Research; 2003.

73. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ. 1997 Jul;6(4):327-40.

74. Dahlof C, Dimenas E, Olofsson B. Documentation of an instrument for assessment of subjective CNS-related symptoms during cardiovascular pharmacotherapy. Cardiovascular Drugs & Therapy. 1989;3(6):919-27.

75. Levy AR, Christensen TL, Johnson JA. Utility values for symptomatic non-severe hypoglycaemia elicited from persons with and without diabetes in Canada and the United Kingdom. Health Qual Life Outcomes [Internet]. 2008 [cited 2010 Mar 17];6:73. Available from: http://www.hqlo.com/content/pdf/1477-7525-6-73.pdf

76. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin. 2004 Aug;20 Suppl 1:S27-S40.

77. Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes [Internet]. NICE short clinical guideline 87. London: National Institute for Health and Clinical Excellence; 2009. [cited 2009 Jul 9]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG87ShortGuideline.pdf

78. Canadian Agency for Drugs and Technologies in Health. Current utilization of second-line therapy by patients with type 2 diabetes inadequately controlled on metformin [DRAFT]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 3).

79. PPS pharma publication buyers guide. Ontario ed. Moncton (NB): Total Pricing Systems Inc.; 2009.

APPENDIX 1: COST COMPARISON TABLES

Costs are manufacturer list prices, unless otherwise specified.

Table A1: Cost of Oral Antidiabetes Drugs Available in Canada

Drug / Comparator	Strength	Dosage Form	Price ($)	Mean Recommended Doses	Average Daily Drug Cost ($)
DPP-4 inhibitors					
Sitagliptin (Januvia)*	100 mg	Tablet	2.55	100 mg daily	2.55
Saxagliptin (Onglyza)*	5 mg	Tablet	2.55	5 mg daily	2.55
TZDs					
Pioglitazone (generics)†	15 mg 30 mg 45 mg	Tablet	1.57 2.20 3.31	15 mg to 45 mg daily	1.57 to 3.31
Rosiglitazone (Avandia)‡	2 mg 4 mg 8 mg	Tablet	1.49 2.34 3.35	4 mg to 8 mg daily	2.34 to 3.35
Insulin Secretagogues, Meglitinides					
Nateglinide (Starlix)‡	60 mg 120 mg	Tablet	0.58 0.58	60 mg to 180 mg daily	0.58
Repaglinide (Gluconorm)‡	0.5 mg 1.0 mg 2.0 mg	Tablet	0.32 0.345 0.35	0.5 mg to 4 mg daily	0.32 to 0.70
Alpha-glucosidase inhibitors					
Acarbose (Glucobay)	50 mg 100 mg	Tablet	0.26 0.36	50 mg to 100 mg, 3 times daily	0.78 to 1.08

Sources: Ontario Drug Benefit[59] (Feb 2010) prices unless stated otherwise.
DPP = dipeptidyl peptidase; TZD = thiazolidinedione.
*Quebec[62] (January 2010).
†Manitoba[61] (Feb 2010).
‡Saskatchewan[63] (Feb 2010).

Table A2: Cost of Insulin Products Available in Canada				
Drug / Comparator	**Strength**	**Dosage Form**	**Price ($)**	**Cost per mL ($)**
Rapid acting insulin analogues				
Insulin aspart (NovoRapid)	100 U/mL	5 x 3 mL cartridge 10 mL vial	55.47 27.71	3.70 2.77
Insulin glulisine (Apidra)	100 U/mL	5 x 3 mL prefilled pen 10 mL vial	47.47 23.74	3.16 2.37
Insulin lispro (Humalog)	100 U/mL	5 x 3 mL prefilled pen 5 x 3 mL cartridge 10 mL vial	66.99* 53.75 26.85	4.47 3.58 2.69
Short-acting human insulin				
Humulin-R	100 U/mL	5 x 3 mL cartridge 10 mL vial	39.26 20.00	2.62 2.00
Novolin ge Toronto	100 U/mL	5 x 3 mL cartridge 10 mL vial	40.03 20.40	2.67 2.04
Intermediate-acting human insulin				
Humulin-N	100 U/mL	5 x 3 mL cartridge 10 mL vial	39.26 20.00	2.62 2.00
Novolin ge NPH	100 U/mL	5 x 3 mL cartridge 10 mL vial	39.88 20.40	2.66 2.04
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 x 3 mL cartridge 10 mL vial	86.87 57.91	5.79 5.79
Insulin detemir (Levemir)	100 U/ml	5 x 3 mL cartridge	98.48	6.57
Pre-mixed				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/ml	5 x 3 mL cartridge	51.87	3.46
Humalog Mix 25 Lispro/lispro protamine	100 U/mL (25% and 75%)	5 x 3 mL cartridge	53.75	3.58
Humalog Mix 50 Lispro/lispro protamine	100 U/mL (50% and 50%)	5 x 3 mL cartridge	53.75	3.58
Novolin ge 30/70	100 U/mL	5 x 3 mL cartridge 10 mL vial	39.84 20.40	2.66 2.04
Humulin 30/70	100 U/mL	5 x 3 mL cartridge 10 mL vial	39.26 20.00	2.62 2.00
Novolin ge 40/60	100 U/mL	5 x 3 mL cartridge	40.80	2.72
Novolin ge 50/50	100 U/mL	5 x 3 mL cartridge	40.80	2.72

Source: Ontario Drug Benefit[59] (Feb 2010) prices unless stated otherwise.
NPH = neutral protamine Hagedorn.
*Pharmaceutical Pricing System Buyer's Guide[79] (January 2009).