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OPTIMAL THERAPY REPORT

COMPUS

March 2008

An Economic Evaluation of Insulin Analogues
for the Treatment of Patients with Type 1 and
Type 2 Diabetes Mellitus in Canada



Supporting Informed Decisions

À l'appui des décisions éclairées

This report was prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH). This report, which was prepared with the advice and assistance of economic and clinical experts, is a comprehensive review of the public literature available to CADTH. The authors have also considered input from other stakeholders. The information in this report should not be used as a substitute for the application of professional judgement in any decision making process. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this Report.

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ABBREVIATIONS

A1c	glycosylated hemoglobin
BMI	body mass index
C	Canadian
CADTH	Canadian Agency for Drugs and Technologies in Health
CARDS	Collaborative AtoRvastatin Diabetes Study
CCC	clinical classification category
CDM	CORE Center for Outcomes Research diabetes model
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHF	congestive heart failure
CI	confidence interval
CIHI	Canadian Institute for Health Information
CMG	case mix groups
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CORE	Center for Outcomes Research
CPI	consumer price index
CUA	cost-utility analysis
CV	cardiovascular
DCCT	Diabetes Control and Complications Trial
DIN	drug identification number
DM	diabetes mellitus
EQ-5D	EuroQol (quality of life) measure
ESRD	end-stage renal disease
F/P/T	Federal/Provincial/Territorial
HDL	high-density lipoprotein
HI	human insulin (conventional)
HRQoL	health-related quality of life
IA	insulin analogue
IAsp	insulin aspart
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IDet	insulin detemir
IGlar	insulin glargine
IHD	ischemic heart disease
ILis	insulin lispro
kg	kilogram
LDL	low-density lipoprotein
LE	life expectancy
LOS	length of stay
MDI	multiple daily injection

MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
mL	millilitre
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
NIHB	non-insured health benefits
NNT	number needed to treat
NPH	neutral protamine Hagedorn
NPHS	National Population Health Survey
NPL	neutral protamine lispro
NR	not reported
OAD	oral antidiabetic agent
OCCP	Ontario Case Costing Project
ODBF	Ontario Drug Benefit Formulary
ODD	Ontario Diabetes Database
ODEM	Ontario Diabetes Economic Model
OLS	ordinary least squares
PBAC	the Pharmaceutical Benefits Advisory Committee
PCEHM	Panel on Cost-Effectiveness in Health and Medicine
PHARMAC	the Pharmaceutical Management Agency of New Zealand
PVD	Peripheral vascular disease
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life-years
QoL	quality of life
QPC	quality priority conditions
QWB-SA	quality of well-being, self-administered version
RCT	randomized controlled trial
RIW	resource intensity weight
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SG	standard gamble
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TC:HDL-C	total cholesterol to high-density lipoprotein (HDL) cholesterol ratio
TTO	time trade-off
UKPDS	United Kingdom Prospective Diabetes Study
WBQ	well-being questionnaire
WMD	weighted mean difference
WTP	willingness-to-pay

1 INTRODUCTION

1.1 COMPUS

In March 2004, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) was launched by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — as a service to federal, provincial, and territorial jurisdictions, and other stakeholders. COMPUS is a nationally coordinated program, funded by Health Canada.

The goal of COMPUS is to optimize drug-related health outcomes and the cost-effective use of drugs by identifying and promoting optimal drug prescribing and use. Where possible, COMPUS builds on existing applicable Canadian and international initiatives and research. COMPUS achieves its goal through three main approaches:

- identifying evidence-based optimal therapy in prescribing and use of specific drugs
- identifying gaps in clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to COMPUS through various channels, including stakeholder input and expert advice, including the following:

COMPUS Advisory Committee (CAC): the CAC is comprised of representatives from the Federal/Provincial/Territorial health ministries and related health organizations.

COMPUS Expert Review Committee (CERC): CERC is an expert advisory body of health and other professionals with expertise in drug therapy and evaluation of evidence.

COMPUS was asked to identify and promote optimal therapy related to proton pump inhibitors (PPIs) and diabetes management. The work in this document addresses the use of insulin analogues (i.e., insulin aspart, insulin lispro, insulin glargine, insulin detemir) for the management of diabetes mellitus.

1.2 Project Overview

The Conference of Federal, Provincial, and Territorial Deputy Ministers of Health directed COMPUS to focus on diabetes mellitus (DM) as a priority area for improving drug prescribing and use. Management of DM was identified as a priority area based on criteria including:

- large deviations from optimal utilization (over- or under-use)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- to the extent that evidence is available, potential to effect change in prescribing and use.

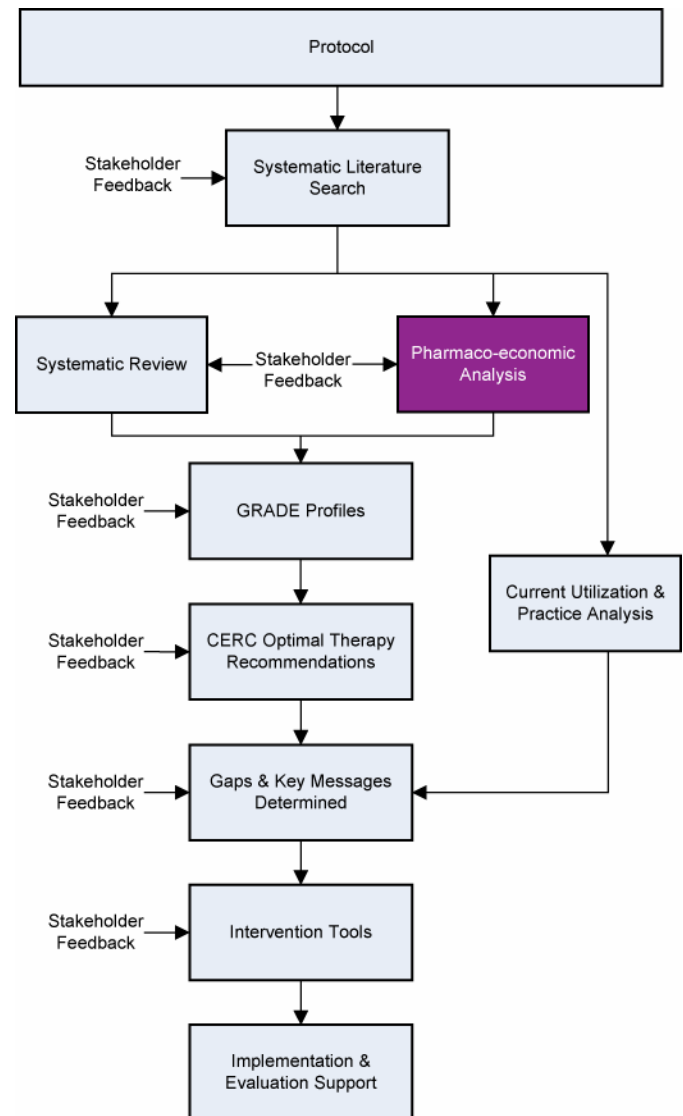
This report presents results of an economic evaluation of insulin analogues, compared with human insulin, in the treatment of patients with DM.

1.3 Goal

Once a topic is selected, COMPUS undertakes activities related to key areas in the COMPUS procedure. The CAC provide advice and guidance throughout the process, from topic identification, through to feedback and approval of recommendations and supporting interventions. CERC provides expert advice and recommendations on the topic area relating to the identification, evaluation and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at various stages in the COMPUS process.

To identify and promote the implementation of evidence-based and cost-effective optimal therapy in the prescribing and use of long- and rapid-acting insulin analogues, COMPUS follows the process outlined in the flow chart to the right.

This report represents the results of an economic evaluation of insulin analogues, compared with human insulin, in the treatment of patients with DM (purple box). Stakeholder feedback was collated for consideration by CERC in the creation of the final document.



1.3 Background

Diabetes mellitus (DM) is a chronic disease characterized by the body's inability to produce sufficient insulin or properly use insulin.¹ Type 1 diabetes mellitus (T1DM) occurs in approximately 5% to 10% of patients with DM, and results when little or no insulin is made by the body.² Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused by some form of insulin resistance; the body makes insulin, but is unable to use it properly.² There are many clinical manifestations that result from DM, including microvascular (e.g., retinopathy, neuropathy and nephropathy) and macrovascular (e.g., coronary artery disease, peripheral artery disease, and cerebrovascular disease) complications.

The prevalence of diabetes worldwide is estimated to be 177 million and is projected to increase to 300 million by 2025.³ Data from the Health Canada National Diabetes Surveillance System suggest that over 1 million (4.8%) Canadians aged 20 years and older were diagnosed with diabetes in 1998/99.² However, as an estimated 2.7% of the adult population have undiagnosed T2DM,⁴ true prevalence of this disorder may be closer to 1.9 million.⁵

Duration and quality of life may be significantly diminished in individuals who have DM. Life expectancy for patients with T1DM and T2DM may be decreased by as much as 15 years and 5 to 10 years, respectively.² In 1999, an estimated 6,137 deaths in Canada were directly attributable to DM.² This number is projected to increase to almost 17,500 deaths annually by 2050.² Furthermore, DM contributes to 41,500 deaths in Canada each year.³ Results from the 1998/99 Canadian National Population Health Survey indicate that 64.5% of people with DM, compared with 90.8% of individuals without DM, report their health to be good or better ($p < 0.05$).

Evidence from the Diabetes Control and Complications Trial (DCCT),⁶ which involved 1,441 patients with T1DM enrolled in 29 medical centres across Canada and the United States, and the United Kingdom Prospective Diabetes Study (UKPDS)⁷ demonstrated the value of maintaining tight glycemic control [i.e., glycosylated hemoglobin (A1c) values of $< 7.0\%$] in preventing or delaying the onset of diabetes-related complications. In combination with lifestyle measures (i.e., weight control, proper nutrition, and adequate exercise), medications play an important role in managing glycemic control in patients with DM.⁸ For patients with T1DM, insulin injections are required daily.⁴ For patients with T2DM, insulin therapy is recommended if adequate glycemic control is not achieved by other measures [exercise, diet, and/or other antidiabetic agents (OADs)].⁴

1.4 Technology Description

Two main types of insulin agents are available in Canada: human insulin (HI) and insulin analogues (IAs).⁴ HI, a biosynthetic insulin prepared using recombinant DNA technology, is available in short-acting and intermediate-acting formulations. When used in combination, short-acting and intermediate-acting HI span the prandial and basal components of insulin replacement. Table 1 provides a summary of the insulin formulations that were included in this economic evaluation.

Table 1: Insulin formulations available in Canada examined in the economic evaluation

Insulin Type	Trade Names	Action
Rapid-acting IA	Humalog® (insulin lispro) NovoRapid® (insulin aspart)	Onset: 10-15 minutes Peak: 60-90 minutes Duration: 4-5 hours
Short-acting HI (Regular HI)	Humulin®-R Novolin®ge Toronto	Onset: 0.5-1hour Peak: 2-4 hours Duration: 5-8 hours
Intermediate-acting HI (Insulin NPH)	Humulin®-N Novolin®ge NPH	Onset: 1-4 hours Peak: 5-8 hours Duration: up to 18 hours
Long-acting IA	Lantus® (insulin glargine) Levemir® (insulin detemir)	Onset: 90 minutes Peak: no peak Duration: 24 hours

HI=human insulin; IA=insulin analogue; NPH=neutral protamine Hagedorn

The pharmacokinetic and pharmacodynamic profile of HI, however, is such that it does not always does not replicate basal and meal-time endogenous insulin secretion and, subsequently, may not provide optimal glycemic control.⁹

The IAs have been developed in response to the limitations of HI. These agents target the basal-bolus components separately.⁹ Rapid-acting IAs closely mimic the short action of endogenous meal-time insulin secretion.⁹ Long-acting IAs do not mimic basal endogenous insulin secretion; rather, they promote a prolonged, non-fluctuating basal level of insulin activity.⁹

1.5 Statement of the Issue

Insulin agents are one of the fastest growing therapeutic class of drugs in Canada.¹⁰ More than C\$181 million was spent on the purchase of insulin agents in Canadian retail pharmacies in 2005 – an increase of 17.5% from 2004.¹⁰ It has been suggested that the recent growth in expenditures has been driven largely by “conversion” of patients from HIs to IAs.¹¹

HIs are listed for reimbursement on all provincial and territorial public drug plan formularies. Acquisition costs of IAs are greater than those of HIs, and reimbursement for IAs differs by jurisdiction.^{12,13} Long-acting IAs are not listed for reimbursement on any of the public drug plans (except for insulin glargine – IGLar – in British Columbia and Quebec, under Special Authority coverage), while coverage for rapid-acting IAs differs by jurisdiction. Nevertheless, public drug plans are receiving an increasing number of requests for initiation therapy with the IAs over HIs.^{10,11} To assist policy makers and health care providers in making informed decisions regarding the reimbursement and prescribing of IAs, both clinical and economic evidence is needed. However, a comprehensive search of the literature did not identify any recent Canadian economic evaluations that addressed this topic. Thus, a need existed to provide evidence-based information surrounding the optimal use of IAs for the management of DM in Canada.

2 OBJECTIVE

The objective of this economic assessment was to determine the cost-effectiveness of using IAs in the management of T1DM and T2DM, compared to HIs, in Canada. The results of this analysis may assist those who are responsible for making informed judgments on the reimbursement and prescribing of IAs for the management of DM.

3 RESEARCH QUESTIONS

The following research questions were developed to address the stated objective:

- Is the use of insulin aspart (IAsp) cost-effective compared with the use of regular HI (Humulin-R, Novolin Toronto) in the treatment of patients with:
 - DM type 1?
 - DM type 2?
- Is the use of insulin lispro (ILis) cost-effective compared with the use of regular HI (Humulin-R, Novolin Toronto) in the treatment of patients with:
 - DM type 1?
 - DM type 2?
- Is the use of insulin glargine (IGlar) cost-effective compared with the use of insulin neutral protamine Hagedorn (NPH) in the treatment of patients with:
 - DM type 1?
 - DM type 2?
- Is the use of insulin detemir (IDet) cost-effective compared with the use of insulin NPH in the treatment of patients with:
 - DM type 1?
 - DM type 2?

4 STUDY DESIGN AND METHODS

The Center for Outcomes Research (CORE) diabetes model (CDM) was used to conduct the economic evaluation.¹⁴ The CDM was selected because of:

- its ability to simulate 14 diabetes-related complications¹⁵ and their associated cost consequences in patients with *either* type 1 or type 2 DM
- the availability of extensive validation studies comparing model predictions of diabetes-related complications to epidemiological and clinical studies¹⁵⁻¹⁷
- its transparency.¹⁸

4.1 Model Structure

The CDM employs a Markov structure consisting of 15 sub-models that simulate diabetes-related complications.¹⁴ Each sub-model uses time-, state-, and diabetes-type dependant probabilities obtained from peer-reviewed published literature.¹⁴ To overcome the “memoryless” properties of Markov models, each sub-model is interconnected using tracker variables to allow one complication to influence the development of another complication. Sub-models also run in parallel to account for the development of concomitant complications reflective of a real-world clinical setting. Patient characteristics, risk factors, and complication history are taken into account using mathematical algorithms performed by a data processor programmed in C++ (Microsoft® Visual Studio 6.0, Enterprise Edition).¹⁹

Each sub-model was programmed separately using TreeAge (TreeAge Software Inc., Williamstown, Massachusetts)²⁰ and C++ (Microsoft Visual Studio 6.0, Enterprise Edition).¹⁹ Inconsistencies between software were identified and programming errors were corrected. A total of 66 second- and third-order validation analyses were performed across the gamut of complications simulated in the CDM.¹⁵ Data from the 66 different validation analyses demonstrate that the CDM provides a reasonably accurate simulation of outcomes observed in a real-world setting. Correlation of second-order validation analyses (performed against published epidemiological studies from which data was used to construct the model) produced an R^{2a} value of 0.9574.¹⁵ An R^2 value of 0.9023 was observed for third-order validation analyses (performed against published epidemiological studies from which data was not used to construct the model).¹⁵

4.2 Type of Economic Evaluation

Three types of economic evaluation were conducted: A cost-effectiveness analysis, a cost-utility analysis, and a cost-consequence analysis.

4.3 Target Population

The target populations examined in the model were adult patients with T1DM; and adult patients with T2DM who had not reached treatment goals with a regimen of diet, physical activity, or OADs and required insulin therapy.⁴

Demographic characteristics for patients with T1DM were obtained from the Diabetes Control and Complications Trial (DCCT)⁷ (Table 2). Ethnicity of the simulated cohort was modified to reflect a Canadian setting using data obtained from the 2001 Canadian Census.²¹

Demographic characteristics for patients with T2DM (Table 3) were obtained from the National Health and Nutrition Examination Survey (NHANES) in the USA²² (limited to data collected from patients with T2DM) and cross referenced with data on 404 patients in Ontario identified as having DM.²³ Ethnicity of the simulated cohort of patients with T2DM was modified to reflect a Canadian setting, using data obtained from the 2001 Canadian Census.²¹ Furthermore, demographic characteristics of the cohort were validated by clinical experts from the COMPUS Expert Review Committee (CERC) to ensure that they were reflective of the Canadian clinical context.

^a An R^2 value, or correlation coefficient, measures the strength of association. Values range from 0 to 1, with 0 representing no statistical correlation, and 1 representing a perfect fit between the data and line drawn between them. (Get Epidemiology & Biostatistics Reference)

Table 2: Baseline characteristics of a simulated cohort of adult patients with type 1 DM

Characteristic	Baseline Value
Patient Demographics	
Mean Age (Years) ^{24,25}	27 years
Duration of Diabetes (Years) ^{24,25}	9 years
Proportion Male ^{24,25}	53.50%
Risk Factors	
A1c (%) ⁷	8.9%
Systolic Blood Pressure (mm Hg) ^{24,25}	115 mm Hg
Body Mass Index (kg/m ²) ^{24,25}	23.75 kg/m ²
Total Cholesterol (mmol/L) ^{24,25}	4.88 mmol/L
High Density Lipoprotein Cholesterol (mmol/L) ^{24,25}	1.26 mmol/L
Low Density Lipoprotein Cholesterol (mmol/L) ^{24,25}	2.87 mmol/L
Mass (kg) ^{24,26}	68.83 kg
Triglycerides (mmol/L) ^{24,25}	0.98 mmol/L
Ethnic Group	
Caucasian ²¹	88%
African-American ²¹	3%
Asian ²¹	7%
Hispanic ²¹	1%
Other ²¹	2%
Cardiovascular Disease	
Angina Pectoris ^{24,25}	1.90%
Atrial Fibrillation ^{24,25}	3.00%
Left Ventricular Hypertrophy Detected by ECG ^{24,25}	3.00%
Renal Disease	
Microalbuminuria ^{24,25}	10.00%
Retinopathy	
Background Diabetic Retinopathy ^{24,25}	100%

A1c=glycosylated hemoglobin; DM=diabetes mellitus; ECG=electrocardiogram; kg=kilogram; L=Liter; m=metre; mm Hg=millimeters of mercury; mmol=millimole

Table 3: Baseline characteristics of a simulated cohort of adult patients with type 2 DM

Characteristic	Baseline Value
Patient Demographics	
Mean Age (Years) ^{23,27}	60 years
Duration of Diabetes (Years) ^{23,27}	11 years
Proportion Male ^{23,27}	49%
Risk Factors	
A1c (%) ²³	8.14
Systolic Blood Pressure (mm Hg) ^{23,27}	137 mm Hg
Body Mass Index (kg/m ²) ²⁷	32 kg/m ²
Total Cholesterol (mmol/L) ²⁷	5.74 mmol/L
High Density Lipoprotein Cholesterol (mmol/L) ²⁷	1.13 mmol/L
Low Density Lipoprotein Cholesterol (mmol/L) ²⁷	3.13 mmol/L
Mass (kg) ^{26,27}	91.3 kg
Triglycerides (mmol/L) ²⁷	2.66 mmol/L
Ethnic Group	
Caucasian ²¹	87%
African-American ²¹	3%
Hispanic ²¹	1%
Asian ²¹	7%
Other ²¹	2%
Cardiovascular Disease	
Stroke ^{23,27}	8.10 %
Angina Pectoris ²⁸	11.20%
Myocardial Infarction ^{23,27}	11%
Congestive Heart Failure ^{23,27}	9.20%
Peripheral Vascular Disease ²³	8.7%
Renal Disease	
Microalbuminuria ²⁹	28.20%
Gross Proteinuria ²⁹	7.60%
End-Stage Renal Disease ²⁹	0.40%
Retinopathy	
Background Diabetic Retinopathy ²⁸	39.00%
Proliferative Diabetic Retinopathy ²⁸	3.00%
Other Complications	
Peripheral Neuropathy ³⁰	30.00%
Foot Ulcer ³¹	10.50%
Amputation ^{23,31}	1.0%
Cataract ²⁸	14.00%
Macular Edema ²⁸	4.00%
Blindness ²³	1.3%

A1c=glycated hemoglobin; DM=diabetes mellitus; ECG=electrocardiogram; kg=kilogram; L=Liter; m=metre; mm Hg=millimeters of mercury; mmol=millimole

4.4 Treatment Comparators

Treatment comparisons in this economic analysis were reflective of Canadian clinical practice;⁴ rapid-acting IAs (ILis and IAsp) were compared with regular HI. Long-acting IAs (IGlar and IDet) were compared with insulin NPH (Table 4).

Treatment*†	Control*
ILis (Humalog)	Regular HI (either Humulin-R or Novolin ge Toronto)
IAsp (NovoRapid)	Regular HI (either Humulin-R or Novolin ge Toronto)
IGlar (Lantus)	Insulin NPH (either Humulin N or Novolin ge NPH)
IDet(Levemir)	Insulin NPH (either Humulin N or Novolin ge NPH)

DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NPH=neutral protamine Hagedorn

* Model assumes a 65 to 35 ratio of cartridges to vials

† Model assumes that treatment strategies use human insulin as the basal/bolus treatment

4.5 Efficacy of Treatment Comparators

Meta-analyses were conducted to estimate clinical (e.g., A1c, overall hypoglycemia, severe hypoglycemia) and patient-relevant outcomes associated with the use of IAs, compared with HI, in patients with T1DM and T2DM.^{32,33} Detailed results from the meta-analyses are presented in the COMPUS Optimal Therapy Reports.^{32,33}

4.5.1 A1c

Table 5 provides the weighted mean difference (WMD) between mean A1c(%) values at endpoint across treatment strategies for patients with T1DM and T2DM^{32,33}

Treatment	Control	Type 1 DM		Type 2 DM	
		WMD% (95% CI)	I ²	WMD% (95% CI)	I ²
ILis	HI	-0.01 (-0.11, 0.08)	20.20%	-0.03 (-0.12, 0.06)	0%
IAsp	HI	-0.12 (-0.19, -0.06)	0%	-0.09 (-0.21, 0.04)	47.10%
IGlar	NPH	-0.11 (-0.21, -0.02)	38.8%	-0.05 (-0.13, 0.04)†	13.40%
IDet	NPH	-0.05 (-0.13, 0.03)	0%	0.14 (-0.01, 0.28) †	38.2%

CI=Confidence Interval; DM=diabetes mellitus; HI=human insulin; I²=heterogeneity among included studies;

IAs=insulin analogues; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NA = not applicable; NPH=neutral protamine Hagedorn; WMD= weighted mean difference

*Taken from the COMPUS Optimal Therapy Reports^{32,33}

†Used analogue + oral antidiabetic (OAD) agent versus NPH + OAD in type 2 patients to generate input parameter

4.5.2 Overall hypoglycemia

Meta-analytic estimates of the rate ratio^{32,33} – an outcome measure that captures recurrent events – for overall hypoglycemic events between treatment strategies are presented in Table 6. The rate of mild to moderate hypoglycemic events per patient-year for patients in the HI treatment arm was assumed to be

24.36 for patients with T1DM³⁴ and 10.20 for patients with T2DM.³⁵ To estimate the rate of mild to moderate hypoglycemic events in the IA treatment groups, the rate for the HI treatment group was multiplied by the rate ratio.

Table 6: Meta-analytic estimates* of the rate ratio of overall hypoglycemic events for IAs versus HI in the treatment of patients with type 1 and type 2 DM							
Treatment	Control	Patients with Type 1 DM			Patients with Type 2 DM		
		Rate Ratio	95% CI		Rate Ratio	95% CI	
ILis	HI	1.02	0.95	1.09	0.97	0.91	1.03
IAsp	HI	0.97	0.88	1.08	0.72	0.64	0.8
IGlar	NPH	0.82	0.52	1.28	0.82	0.64	1.06
IDet	NPH	0.84	0.74	0.97	0.54	0.5	0.58

CI=Confidence Interval; DM=diabetes mellitus; HI=human insulin; IAs=insulin analogues; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NA = not applicable; NPH= neutral protamine Hagedorn

*Taken from the COMPUS Optimal Therapy Reports^{32,33}

4.5.3 Severe hypoglycemia

The rate of severe hypoglycemia (i.e., requiring third-party assistance) for patients with T1DM and T2DM in the HI treatment groups was obtained from single high-quality studies.^{34,36} Patients with T1DM were assumed to have a rate of 0.96 severe hypoglycemic events per patient-year,³⁴ and patients with T2DM were assumed to experience 0.28 severe hypoglycemic events per patient-year.³⁶

The relative risk (RR) of severe hypoglycemia across treatment strategies in patients with T1DM and T2DM was estimated by meta-analysis^{32,33} (Table 7). To estimate the rate of severe hypoglycemia in the IA groups, the meta-analytic estimates of RR for each IA treatment group were multiplied by the rate of severe hypoglycemia in the HI treatment groups.

Table 7: Meta-analytic results* for the relative risk of severe hypoglycemic events for IAs versus HI in the treatment of patients with type 1 and type 2 DM							
Treatment	Control	Patients with Type 1 DM			Patients with Type 2 DM		
		RR	95% CI		RR	95% CI	
ILis	HI	0.83	0.64	1.07	0.43	0.08	2.37
IAsp	HI	0.83	0.66	1.05	0.39	0.11	1.36
IGla	NPH	0.82	0.52	1.29	0.66	0.29	1.48
IDet	NPH	0.74	0.58	0.96	0.75	0.03	20.01

CI=Confidence Interval; DM=diabetes mellitus; HI=human insulin; IAs=insulin analogues; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NPH= neutral protamine Hagedorn; RR=relative risk

*Taken from the COMPUS Optimal Therapy Reports^{32,33}

4.6 Audience and Perspective

The target audience for this economic evaluation was decision-makers in public drug benefit programs, health professionals, and patients with DM. The economic evaluation took the perspective of a third-party provincial payer as recommended in guidelines issued by the Canadian Agency for Drugs and Technologies in Health (CADTH).³⁷ Therefore, only direct costs to the publicly funded health care system were considered.

4.7 Time Horizon

The time horizon simulated in the model was 60 years for patients with T1DM and 35 years for patients with T2DM. This life-time time horizon is consistent with guidelines for computer modeling of diabetes and adheres to *Guidelines for the Economic Evaluation of Technologies: Canada* by the Canadian Agency for Drugs and Technologies in Health.³⁷

4.8 Modelling

The CDM model uses surrogate outcomes (e.g., A1c, systolic blood pressure, total cholesterol to high-density lipoprotein ratio) to forecast the occurrence of diabetes-related complications (e.g., myocardial infarction, stroke, angina, congestive heart failure, peripheral vascular disease, neuropathy, foot ulcer, retinopathy, macular edema, cataract, nephropathy, hypoglycemia, ketoacidosis, lactic acidosis, and non-specific mortality).¹⁴

In the present analysis, progression to long-term complications was based solely upon A1c differences between treatment groups. The analysis assumed that, for each treatment strategy, A1c values estimated by meta-analysis^{32,33} were sustained for a duration of one year. For each subsequent year, A1c values were assumed to increase or “drift” by 0.045%⁶ and 0.15%³⁸ per annum for patients with T1DM and T2DM, respectively. Due to an absence of data, the model assumed the A1c drift for HI and IAs to be identical. Life expectancy of patients for the analysis was derived from Statistics Canada Life Tables.³⁹

The cycle length for each Markov sub-model was one year, with the exception of the foot ulcer sub-model (cycle=1 month), severe hypoglycemic episode requiring assistance sub-model (cycle=3 months), and the mild to moderate hypoglycemic episode sub-model (cycle =1 day).^{14,15}

4.9 Valuing Outcomes

Where available, health-related quality of life (HRQoL) scores were obtained using the EuroQol (quality of life) measure (EQ-5D). The EQ-5D⁴⁰ is a widely used multi-attribute health status classification system.⁴¹ CADTH and the National Institute for Health and Clinical Excellence (NICE) have issued guidance that supports the use of indirect measurement instruments like the EQ-5D that use preferences obtained from the “informed” general public.³⁷ However, in some instances, EQ-5D scores were not available for health states in the model. The instrument utilized and disutility associated with those health states are provided in Table 8.

4.9.1 Disutilities of chronic health states

Where available, HRQoL scores (utilities) for chronic health states were obtained from the US EQ-5D catalogue^{42,43}. The US EQ-5D catalogue^{42,43} was generated using community-based, nationally representative data from the Medical Expenditure Panel Survey (MEPS). The US catalogue^{42,43} provides mean EQ-5D scores while controlling for chronic conditions and determinants of health (e.g., age, gender, income, education, race, number of co-morbid conditions, etc).⁴⁴ Although generated from a US population, the preference scores should be generalizable to Canada,⁴⁵ as instrument scores travel well and are applicable in other countries.⁴⁵

T2DM was assumed to have a median EQ-5D score of 0.800;^{42,43} and T1DM, a median EQ-5D score of 0.783 (i.e., a disutility of 0.017 over the utility of 0.800 for T2DM⁴⁶).

Disutilities for chronic health states experienced within the first year (applied over one year) were based upon the International Classification of Diseases (ICD-9)⁴² or clinical classification category (CCC)⁴³ EQ-5D

Index scores.^{42,43} Preference scores in subsequent years were based on quality priority conditions (QPC) estimates where individuals were asked if they had *ever been diagnosed with the condition in the past* (i.e., Did you ever have a stroke before?).^{42,43} In instances where QPC estimates were unavailable, we assumed that the disutility based on ICD-9 or CCC scores (sustained condition within the year) for the chronic condition remained constant over time (Table 8).

4.9.2 Disutility of hypoglycemic episodes

Estimates of the impact of hypoglycemic episodes on HRQoL have varied considerably.⁴⁷⁻⁴⁹ In the current analysis, the disutility of a severe hypoglycemic episode was determined assuming that the effect of such an episode would result in a downward movement in the US EQ-5D score⁵⁰ for the dimensions of usual activities, and for anxiety and depression.⁴⁷ That is, patients experiencing severe hypoglycemic episodes were assumed to move to a state characterized by extreme anxiety, with or without depression, and the inability to perform usual activities. Thus, a severe hypoglycemic episode would be associated with a disutility of 0.5485 during the period of the event.⁵⁰ Applying this disutility over a 24-hour period^b translates into a decrement of 0.001503 QALYs per severe hypoglycemic episode⁵⁰ (Table 8).

Similarly, patients experiencing mild hypoglycemic episodes were assumed to move from a health state of having no problems to a state characterized by moderate anxiety, with or without depression, and having some problems with performing usual activities, thus resulting in a disutility of 0.167 during the episode.⁵⁰ Each mild to moderate hypoglycemic episode was assumed to last for 15 minutes, which coincides with the 15/15 rule: 15 grams of carbohydrate followed by 15 minutes of waiting.⁵² Furthermore, glucagon takes approximately 10-15 minutes to react as it relies on endogenous stores of insulin.⁵³ Thus, each episode was associated with a decrement of 0.00004767 QALYs⁵⁰ (Table 8).

^b The 24-hour period was based on an estimate that 20% of patients who experience a severe hypoglycemic episode are managed as in-patients,⁴⁹ and 80% as out-patients in the ER (~6-hour wait time in ER).⁵¹ This assumption should bias in favour of insulin analogues, as many patients that experience severe hypoglycemic episodes do not visit the ER or hospital. (i.e., 0.20*96 hours + 0.80*6 hours= 24 hours)

Table 8: Disutilities for health states in the economic evaluation of IAs in patients with type 1 and type 2 DM

Health State	Disutility of Health State	95% CI	Disutilities Derived From...	Technique
MI, year of event ⁴²	-0.0409222	(-0.0412357, -0.0406087)	US survey – 38,678 adults	EQ-5D
MI, subsequent years ⁴³	-0.012	0.0002	US survey – 38,678 adults	EQ-5D
Angina, year of event ⁴²	-0.0411989	(-0.0415174, -0.0408804)	US survey – 38,678 adults	EQ-5D
Angina, subsequent years ⁴²	-0.024	0.0002	US survey – 38,678 adults	EQ-5D
CHF, year of event ⁴³	-0.0546	0.0010	US survey – 38,678 adults	EQ-5D
CHF, subsequent years ⁴³	-0.018	0.0002	US survey – 38,678 adults	EQ-5D
Stroke, year of event ⁴²	-0.0523513	(-0.052622, -0.0520806)	US survey – 38,678 adults	EQ-5D
Stroke, subsequent years ⁴²	-0.040	0.0002	US survey – 38,678 adults	EQ-5D
Peripheral vascular disease ⁵⁴	-0.021	p-value=.745	293 type 1 DM patients – The Netherlands	EQ-5D
Microalbuminuria ⁵⁵	-0.012	p-value=0.6349	1,348 type 2 DM patients – The Netherlands	EQ-5D
Gross proteinuria ⁴⁶	-0.017	0.10	784 type 1 DM patients – US	QWB-SA
Dialysis ⁵⁶⁻⁵⁸	-0.16	NA	192 dialysis patients – Canada	EQ-5D
Functioning kidney transplant ⁵⁶⁻⁵⁸	-0.03	NA	16 type 1 DM patients with ESRD	SG
Diabetic retinopathy ⁴²	-0.0155836	(-0.0158968, -0.0152703)	US survey – 38,678 adults	EQ-5D
Blindness and low vision ⁴²	-0.0497859	(-0.0501705, -0.0494014)	US survey – 38,678 adults	EQ-5D
Cataract ⁴²	-0.0170832	(-0.0172664, -0.0169)	US survey – 38,678 adults	EQ-5D
Macular edema ^{*42}	-0.0170832	(-0.0172664, -0.0169)	US survey – 38,678 adults	EQ-5D
Neuropathy ⁴²	-0.0243702 -0.0378704	(-0.0246054, -0.024135) (-0.0381297, -0.0376111)	US survey – 38,678 adults	EQ-5D
Active uninfected diabetic ulcer ⁵⁹	-0.09	NA	107 members of the general public (aged 17-70) in Rotterdam	TTO
Active uninfected diabetic ulcer ⁵⁹	-0.14	NA	107 members of the general public (aged 17-70) in Rotterdam	TTO
Amputation ⁶⁰	-0.266	(-0.476, -0.055)	3192 type 2 diabetic patients – UK	EQ-5D
Severe hypoglycemic episode requiring assistance ⁵⁰	-0.5485†	NA	US national survey – 4,048 adults ⁵⁰	EQ-5D
Mild to moderate hypoglycemic episode ⁵⁰	-0.167‡	NA	US national survey – 4,048 adults ⁵⁰	EQ-5D

CHF= congestive heart failure; CI=confidence interval; DM=diabetes mellitus; IAs=insulin analogues; NA=not available; EQ-5D=EuroQol; MI=myocardial infarction; SG= standard gamble;TTO=time trade-off; QWB-SA=Quality of well-being, self-administered version; UK=United Kingdom; US=United States; 11313= EQ-5D five-digit descriptor of state by extreme anxiety/depression and the inability to perform usual activities; 11212= EQ-5D five-digit descriptor of state characterized by moderate anxiety/depression and having some problems with performing usual activities

*Assumed same disutility as cataract¹⁴

†assumed that a severe hypoglycemic episode would be reflected in movement from a health state having no problems with usual activities and no anxiety/depression, to a state characterized by extreme anxiety/depression and the inability to perform usual activities(11313); disutility applied over one day^{49,51}

‡ assumed that a mild/moderate hypoglycemic episode would be reflected in movement from a health state having no problems with usual activities and no anxiety/depression, to a state characterized by moderate anxiety/depression and some problems with performing usual activities (11212); disutility applied over 15 minutes^{52,53}

4.9.3 Disutility of fear of hypoglycemia

Anxiety or fear of future hypoglycaemic episodes may have a detrimental impact on health related-quality of life (HRQoL).^{61,62} However, estimates of the impact of fear on HRQoL have varied considerably.⁶³⁻⁶⁷ To examine the effect of fear of hypoglycemia on results, sensitivity analyses were conducted using a disutility of -0.0052, a disutility that has been used by the National Institute of Clinical Excellence (NICE)⁶⁸ and the Pharmaceutical Management Agency of New Zealand (PHARMAC) in their evaluations.⁶⁹

The CDM accommodates fear of hypoglycemia by applying a chronic utility decrement (i.e., 0.0052) in the regular HI and insulin NPH arms only. That is, no utility decrement is applied in the IA arm.

4.10 Resource Use and Costs

4.10.1 Prescription drug costs

Where available, unit costs for prescription drugs were obtained from the Ontario Drug Benefit Formulary (ODBF)/Comparative Drug Index (June 6, 2007).¹² When unit costs were not available in the ODBF, costs were obtained from the PPS[®] Pharma Buyers Guide Ontario Edition July 2007¹³ or by contacting the manufacturer. Unit costs for HI and IAs are presented in Table 9.

4.10.2 Prescription drug utilization

Estimates of the mean daily dose for each treatment, for patients with T1DM and T2DM, were obtained from physician and pharmacist members of CERC. The large cost differential between vials and cartridges necessitated an estimation of the proportion of patients using cartridges. In the 2005/2006 fiscal year, approximately 65% of insulin agents dispensed were in the form of cartridges or penfills (Ontario Ministry of Health and Long-Term Care utilization data –COMPUS Advisory Committee: Personal Communication, 2007). However, as IDet is available only as a cartridge in Canada, the cartridge cost was used in the model. Tables 10 and 11 present the mean daily cost for each treatment strategy for patients with T1DM and T2DM, respectively.

4.10.3 Management costs of diabetes complications

When available, resource utilization and costs of diabetes-related complications were obtained from the Ontario Diabetes Economic Model (ODEM).²³ Estimates for the cost of managing diabetes-related complications (provided in Table 12) include inpatient and outpatient costs, cost of emergency room visits, subsequent prescription drug claims, and long-term and home care services costs.²³ Event costs in Table 12 accrue within the year in which a complication occurs, whereas state costs reflect ongoing costs in subsequent years for ongoing management of the complication. When cost and resource use for a health state was not available from the ODEM, data were obtained from published costing studies^{14,71-73} or recent CADTH publications.^{56,57} All costs for the analysis were inflated to 2007 Canadian dollars (Table 12) using the health component of the Consumer Price Index.⁷⁴

Table 9: Unit costs for insulin and insulin IA agents examined in economic analysis

Product	Generic Name	DIN*	Package Size	Price per Package (C\$)
Rapid-acting IAs:				
NovoRapid vial 10 mL, 100 units/mL	Insulin aspart	2245397	1 x 10 mL	25.34 [†]
NovoRapid cartridge 3 mL, 100 units/mL	Insulin aspart	2244353	5 x 3 mL	50.71 [†]
Humalog vial 10 mL, 100 units/mL	Insulin lispro	2229704	1 x 10 mL	25.79 [†]
Humalog cartridge 3 mL, 100 units/mL	Insulin lispro	2229705	5 x 3 mL	51.59 [†]
Regular HI:				
Humulin R vial 10mL, 100 units/mL	Insulin regular	586714	1 x 10 mL	17.20 [†]
Humulin R cartridge 3mL, 100 units/mL	Insulin regular	1959220	5 x 3 mL	35.68 [†]
Novolin ge Toronto vial 10 mL, 100 units/mL	Insulin regular	2024233	1 x 10 mL	18.33 [†]
Novolin ge Toronto Penfill (cartridge) 3 mL, 100 units/mL	Insulin regular	2024284	5 x 3 mL	35.97 [†]
Long-acting IAs:				
Levemir cartridge 3 mL, 100 units/mL	Insulin detemir	2271842	5 x 3 mL	109.86 [‡]
Lantus cartridge 3 mL, 100 units/mL	Insulin glargine	2251930	5 x 3 mL	109.87 [§]
Lantus vial 10 mL, 100 units/mL	Insulin glargine	2245689	1 x 10 mL	55.07 [§]
Insulin NPH:				
Humulin N vial 10 mL, 100 units/mL	Insulin NPH	587737	1 x 10 mL	17.20 [†]
Humulin N cartridge 3 mL, 100 units/mL	Insulin NPH	1959239	5 x 3 mL	35.68 [†]
Novolin ge NPH vial 10 mL, 100 units/mL	Insulin NPH	2024225	1 x 10 mL	18.33 [†]
Novolin ge NPH penfill (cartridge) 10 mL, 100 units/mL	Insulin NPH	2024268	5 x 3 mL	35.97 [†]

C\$=Canadian \$; DIN=drug identification number; HI=human insulin; IA=insulin analogue

* Drug Identification Number (DIN) obtained from Health Canada Drug Products Database, July 2007^o

[†]Ontario Drug Benefits Formulary/Comparative Drug Index- July 1, 2007¹²

[‡] Danielle Groleau, NovoNordisk Canada, Mississauga, ON: personal communication, July 4, 2007

[§] PPS® Pharma Buyers Guide, Ontario Edition, July 2007¹³

Table 10: Average daily dose* (units per kg per day) and average cost (C\$) for insulin treatment strategies among patients with type 1 DM in the economic model			
Treatment	Products Available in Canada	Average Daily Dose (Units per kg –Day)*	Average Cost (C\$) per Day
Rapid-acting IAs	NovoRapid vial 10 mL, 100 units/mL	0.52	\$1.10
	NovoRapid cartridge 5 x 3 mL, 100 units/mL		
	Humalog vial 10 mL, 100 units/mL		\$1.12
	Humalog cartridge 5 x 3 mL, 100 units/mL		
Regular HI	Humulin-R vial 10 mL, 100 units/mL	0.68	\$1.02
	Humulin-R cartridge 5 x 3mL, 100 units/mL		
	Novolin ge Toronto vial 10 mL, 100 units/mL		
	Novolin ge Toronto Penfill (cartridge) 5 x 3 mL, 100 units/mL		
Long-acting IAs	Levemir cartridge 5 x 3 mL, 100 units/mL	0.28	\$1.41†
	Lantus cartridge 5 x 3 mL, 100 units/mL		\$1.29
	Lantus vial 10 mL, 100 units/mL		
Intermediate-acting HI	Humulin-N vial 10 mL, 100 units/mL	0.34	\$0.51
	Humulin-N cartridge 5 x 3 mL, 100 units/mL		
	Novolin ge NPH vial 10 mL, 100 units/mL		
	Novolin ge NPH penfill (cartridge) 5 x 3mL, 100 units/mL		

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; IAs=insulin analogues

*Model assumes that the average adult patient with type 1 DM weighs 69 kg.²⁴⁻²⁶ Patients use an average cartridge: vial ratio of 65:35; estimates of mean daily dose for each treatment, for patients with type 1 and type 2 DM, from physicians and pharmacists on the COMPUS expert review committee

† IDet is only available as a cartridge in Canada. Thus, acquisition costs for IDet were assumed to be higher relative to IGlar. This may bias results against IDet

4.11 Discount Rate

Both costs and outcomes (QALYs) were discounted at a rate of 5%, as recommended by CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada*.³⁷ Discount rates of 0% and 3% were examined in sensitivity analyses.³⁷

4.12 Handling Uncertainty

Deriving confidence intervals (CIs) for ICERs are complex to construct and interpret; therefore, cost-effectiveness acceptability curves (CEAC) were constructed to summarize uncertainty.⁷⁵ A non-parametric bootstrapping method,^{41,76} using second order Monte Carlo simulation^{77,78c} in which 1,000 patients were simulated through the model 1,000 times, was used to estimate the mean and standard deviation of life expectancy, quality-adjusted life expectancy, and costs for each treatment regimen. Incremental costs and incremental effectiveness derived from the 1,000 iterations were plotted on the cost-effectiveness plane (scatter plot). A CEAC was generated, based on the proportion of sample means falling below a range of willingness-to-pay (WTP) thresholds on the scatter plot.

^c Second-order simulation is argued to be the appropriate method for probabilistic sensitivity analysis,⁷⁷ as policy decisions are concerned with treatment effects across the population level.⁷⁷

Deterministic sensitivity analyses⁷⁷ were performed to examine the impact of varying A1c values and the discount rate. To address uncertainty surrounding hypoglycemic episodes, univariate sensitivity analyses, varying the disutility of episodes (severe and mild) and the cost of managing a severe hypoglycemic event, were performed.

Table 11: Average daily dose* (units per kg per day) and average cost (C\$) for insulin treatment strategies among patients with type 2 DM in the economic model			
Treatment	Products Available in Canada	Average Daily Dose (Units per kg –Day)	Average Cost (C\$) per Day
Rapid-acting IAs	NovoRapid vial 10 mL, 100 units/mL	0.98	\$2.76
	NovoRapid cartridge 5 x 3 mL, 100 units/mL		
	Humalog vial 10 mL, 100 units/mL		\$2.81
	Humalog cartridge 5x 3 mL, 100 units/mL		
Regular HI	Humulin-R vial 10 mL, 100 units/mL	1.2	\$2.38
	Humulin-R cartridge 5x 3 mL, 100 units/mL		
	Novolin ge Toronto vial 10mL, 100 units/mL		
	Novolin ge Toronto Penfill (cartridge) 5x 3 mL, 100 units/mL		
Long-acting IAs	Levemir cartridge 5x 3 mL, 100 units/mL	0.53	\$3.54†
	Lantus cartridge 5 x 3 mL, 100 units/mL		\$3.24
	Lantus vial 10mL, 100 units/mL		
Intermediate-acting HI	Humulin-N vial 10 mL, 100 units/mL	0.75	\$1.49
	Humulin-N cartridge 5x 3 mL, 100 units/mL		
	Novolin ge NPH vial 10 mL, 100 units/mL		
	Novolin ge NPH penfill (cartridge) 5 x 3 mL, 100 units/mL		
	Novolin ge 30/70 penfill (cartridge), 5 x 3 mL, 100 units/mL		
	Humulin 30/70 vial 10 mL, 100 units/mL		
	Humulin 30/70 cartridge 5x 3mL, 100 units/mL		

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; IAs=insulin analogues

*Model assumes that the average patient with type 2 DM weighs 91 kg.^{26,27} Patients use an average cartridge: vial ratio of 65:35; estimates of mean daily dose for each treatment, for patients with type 1 and type 2 DM, from physicians and pharmacists on the COMPUS expert review committee

†Insulin detemir is only available as a cartridge in Canada. Thus, acquisition costs for insulin detemir were assumed to be higher, relative to insulin glargine

Table 12: Management costs of health states, in 2007 Canadian dollars

Description of Event or State	Adjusted Diabetes Complications Cost (C\$ 2007)*
AMI model	
Myocardial infarction, year of event, fatal ²³	9,177
Myocardial infarction, year of event, non-fatal ²³	17,498
Myocardial infarction, each subsequent year ²³	2,736
Angina model	
Angina, year of onset ²³	5,477
Angina, each subsequent year ²³	3,162
Congestive heart failure model	
Congestive heart failure, year of onset ²³	16,007
Congestive heart failure, each subsequent year ²³	4,488
Stroke model	
Stroke, year of event, fatal ²³	8,636
Stroke, year of event, non-fatal ²³	23,834
Stroke, each subsequent year ²³	3,307
Peripheral vascular disease model	
Peripheral vascular disease, year of onset ^{72,73}	1,508
Nephropathy submodel	
Dialysis, ongoing therapy ^{56,57}	75,772
Transplant costs, year 1 ^{56,57}	86,816
Transplant cost, each subsequent year ^{56,57}	36,506
Retinopathy	
Severe vision loss/blindness, year of onset ²³	2,928
Severe vision loss/blindness, each subsequent year ²³	2,086
Cataract model	
Cataract extraction, year of event ²³	3,871
Cataract extraction, each subsequent year ²³	2,437
Neuropathy model	
Symptomatic neuropathy, onset ^{71,79}	165
Foot ulcer model	
Uninfected ulcer ^{71,79}	1216
Infected ulcer ^{71,79}	2,431
Gangrene ⁷⁹	8,687
Amputation, year of event ²³	36,973
Amputation, each subsequent year ²³	5,064
Ketoacidosis/lactic acidosis models	
Ketoacidosis/lactic acid event ^{71,79}	3,895
Hypoglycemia model	
Severe hypoglycemic event requiring assistance ⁷¹	129

AMI=acute myocardial infarction; C\$=Canadian \$

* Inflated to 2007 Canadian dollars using the health component of the Consumer Price Index (CPI)

5 RESULTS

5.1 IAsp Versus Regular HI

5.1.1 Type 1 DM

a) *Base-case analysis*

Life expectancy and quality-adjusted life expectancy

Treatment of T1DM with IAsp was estimated to increase life expectancy by 0.066 years, relative to treatment with regular HI. Patients using IAsp were estimated to have a quality-adjusted life expectancy (QALE) of 11.016 years, compared to a QALE of 10.961 years for patients using regular HI. Results from the base-case analysis are presented in Table 13.

Table 13: Summary of results from base-case analysis comparing IAsp and regular HI among patients with type 1 DM			
	IAsp	Regular HI	Difference Between IAsp and Regular HI
Life expectancy [years]*	14.496	14.43	0.066
Undiscounted life expectancy [years]	30.317	30.054	0.263
Quality-adjusted life expectancy (QALE) [years]*	11.016	10.961	0.055
Undiscounted QALE [years]	22.622	22.411	0.211
Total Direct Costs [C\$]*	71,551	72,171	-620
ICER [• costs* / • LE*]			Cost saving†
ICUR [• costs* / • QALE (or QALYs gained)*]			Cost saving‡

C\$=Canadian \$; HI=human insulin; IAsp=insulin aspart; ICER=incremental cost-effectiveness ratio; ICUR=incremental cost-utility ratio; LE= life expectancy; QALE=quality-adjusted life expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained; cost saving refers to a treatment strategy that is more effective and less costly

‡ Cost in C\$ per incremental quality adjusted life-year gained; cost saving refers to a treatment strategy that is more effective and less costly

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for a patient with T1DM using IAsp were estimated to be C\$620 less than the total lifetime costs for a patient using regular HI. Management of renal complications comprised the largest cost differential (C\$715) between treatment strategies. Mean discounted lifetime direct costs for each treatment strategy in patients with T1DM are provided in Table 14.

Table 14: Summary of estimated direct costs* comparing IAsp and regular HI in the treatment of patients with type 1 DM

Costing Component	IAsp	Regular HI	Cost Differential(C\$)
Treatment costs	5,947	5,458	489
Management costs†	15,632	15,548	84
Management of cardiovascular complications	7,588	7,636	-48
Management of renal complications	18,413	19,128	-715
Management of neuropathy/ulcer/amputation	11,609	11,784	-175
Management of eye disease	9,122	9,124	-2
Management of hypoglycemia	2,100	2,356	-256
Management of keto/lactic acidosis	1,140	1,137	3
Total direct costs [over lifetime]	71,551	72,171	-620

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart

*Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetic complications over lifetime

Table 15 presents data on the predicted time-to-event, in years, for each diabetes-related complication by treatment, and the difference in time-to-event (days) between treatments strategies. Model simulations project that patients using IAsp will experience diabetes-related complications later in life (88-117 days) than those using regular HI.

Table 15: Time free of diabetes-related complications in years, by treatment strategy

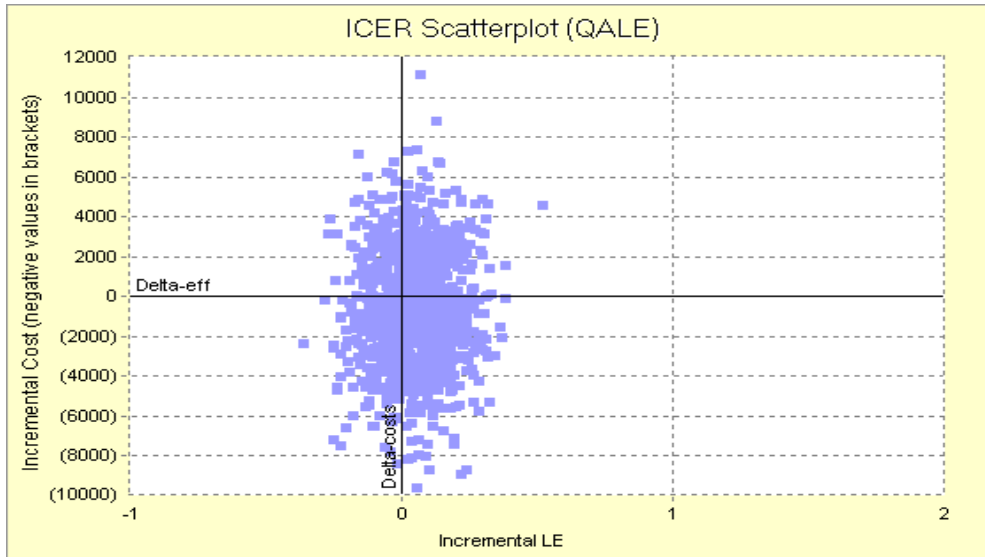
Diabetes Complication	Time to Event (Years) IAsp		Difference(Days)
		Short acting- HI	
Severe vision loss/blindness	24.18	23.94	88
End-stage renal disease	29.52	29.24	102
Ulcer, first	24.76	24.47	106
Amputation, ulcer	28.67	28.39	102
Neuropathy	8.78	8.46	117
Peripheral vascular disease, onset	29.08	28.81	99
Congestive heart failure, first event	28.63	28.37	95
Angina	28.7	28.46	88
Myocardial infarction, event	28.98	28.7	102
Stroke, event	29.74	29.49	91

HI=human insulin; IAsp=insulin aspart

b) Sensitivity analyses

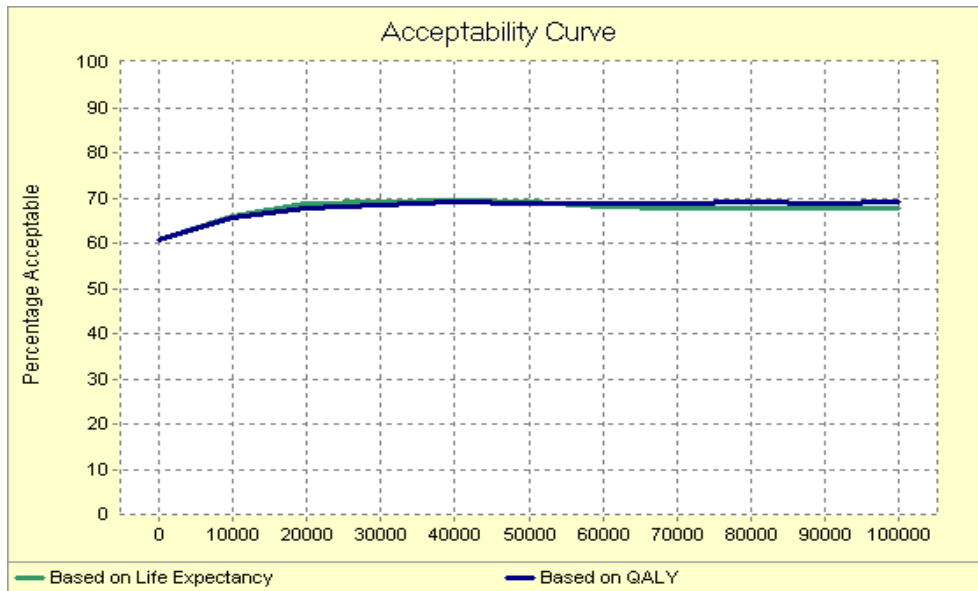
The ICER scatterplot (Figure 1) and CEAC (Figure 2) suggest that, relative to regular HI, and at WTP thresholds of \$50,000 and C\$100,000 per QALY gained, IAsp has a 68.8% and 69.4% chance of being cost-effective, relative to regular HI. The CEAC plateaus at a probability of 70% indicate that there is reasonable probability that IAsp is not cost-effective at thresholds less than \$100,000 per QALY gained.

Figure 1: Incremental cost-utility scatter plot of IAsp, relative to regular HI, in the treatment of patients with type 1 DM



DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Figure 2: CEAC of IAsp, relative to regular HI, in the treatment of patients with type 1 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; QALY=quality-adjusted life-year

Results from the univariate sensitivity analyses show that the model was sensitive to changes in A1c (Table 16).

Table 16: Results from univariate sensitivity analyses comparing IAsp, relative to regular HI, in the treatment of patients with type 1 DM	
	ICUR (C\$ per QALY gained)
Base-Case Analysis*	Cost Saving†
Variation in change in A1c	
No A1c difference between treatments	\$104,598
Variation in discount rates	
0% costs, 0% QALYs	Cost Saving†
3% costs, 3% QALYs	Cost Saving†
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	Cost Saving†
0.0000285 (15 minutes in a state with utility=0)	Cost Saving†
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	Cost Saving†
0.00274 (1 day in a state with utility=0)	Cost Saving†
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	Cost Saving†
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	Cost Saving†

A1c=glycosylated hemoglobin; C\$=Canadian\$; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ICUR=incremental cost-utility ratio; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.12 (-0.19, -0.06)^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycemic episode,⁵⁰ 0.000004767 QALYs lost for a mild to moderate hypoglycemic episode,⁵⁰ and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹

† Cost-saving refers to a strategy that is less costly and more effective

5.1.2 Type 2 DM

a) *Base-case analysis*

Life expectancy and quality-adjusted life expectancy

Treatment of T2DM with IAsp was estimated to increase life expectancy by 0.017 years, relative to treatment with regular HI. Patients using IAsp are projected to have a quality-adjusted life expectancy (QALE) of 5.899 years compared to 5.884 years for patients using regular HI. Results from the base-case analysis are presented in Table 17.

Table 17: Summary of results from base-case analysis comparing IAsp and regular HI among patients with type 2 DM

	IAsp	Regular HI	Difference Between IAsp and regular HI
Life expectancy [years]*	7.888	7.871	0.017
Undiscounted life expectancy [years]	11.679	11.633	0.046
Quality-adjusted life expectancy (QALE) [years]*	5.899	5.884	0.015
Undiscounted QALE [years]	8.673	8.635	0.038
Total direct costs [C\$]*	63,792	63,459	333
ICER [• costs* / • LE*]			19,055†
ICUR [• costs* / • QALE (or QALYs gained)*]			22,488‡

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; LE=life expectancy; QALE=Quality adjusted life-expectancy; ICER= incremental cost-effectiveness ratio; ICUR=incremental cost-utility ratio

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained

‡ Cost in C\$ per incremental quality-adjusted life-year gained

Lifetime costs and cost-effectiveness

The expected lifetime cost for a patient with T2DM using regular HI is C\$335 less than the corresponding cost for a patient using IAsp. This yields an incremental cost of C\$22,488 per QALY gained for IAsp, relative to regular HI in patients with T2DM. Treatment costs comprise the largest cost differential (C\$1,181) of direct costs. Table 18 presents the mean discounted lifetime direct costs for each treatment strategy in patients with T2DM.

Table 18: Summary of projected direct costs* (C\$) comparing IAsp and regular HI in the treatment of patients with type 2 DM

Costing Component	IAsp	Regular HI	Cost Differential (C\$)
Treatment costs	8,526	7,345	1,181
Management costs†	9,977	9,959	18
Management of cardiovascular complications	23,409	23,458	-49
Management of renal complications	6,552	6,864	-312
Management of neuropathy/ulcer/amputation	10,018	10,083	-65
Management of eye disease	5,004	5,026	-22
Management of hypoglycemia	306	724	-418
Management of keto/lactic acidosis	0	0	0
Total direct costs (over lifetime)	63,792	63,459	333

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart

*Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetic complications over lifetime

Table 19 presents the predicted time-to-event in years for each diabetes-related complication by treatment, and the difference (in days) in time-to-event for each comparator. Patients taking IAsp are expected to experience diabetes-related complications slightly later (11-29 days) in life than patients using regular HI.

Table 19: Time free of diabetes complications in years for each strategy

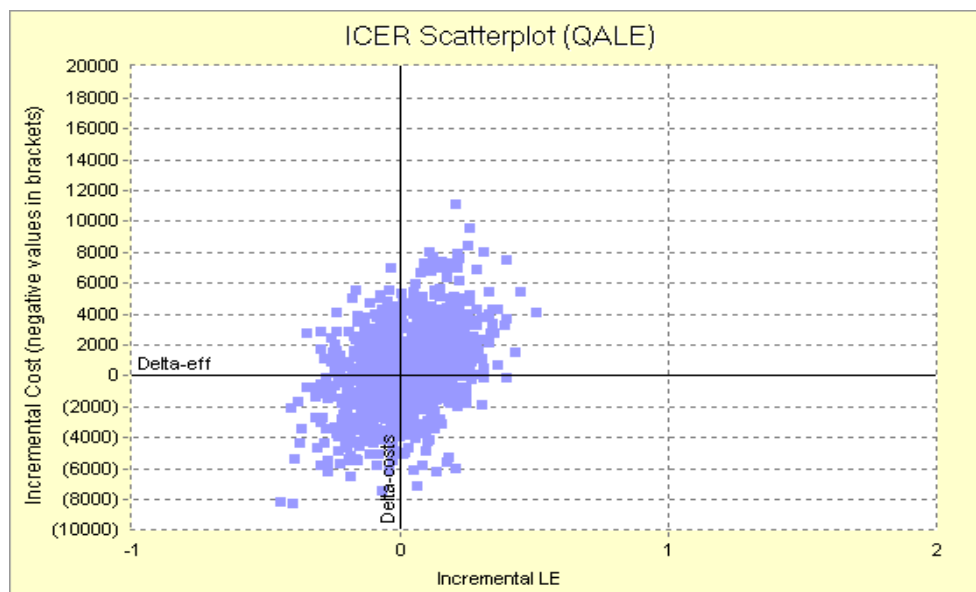
Diabetes Complication	Time to Event (Years)		Difference (Days)
	IAsp	Regular HI	
Severe vision loss/blindness	10.92	10.86	22
End-stage renal disease	11.55	11.5	18
Ulcer, first	9.52	9.46	22
Amputation, ulcer	11.12	11.07	18
Neuropathy	5.61	5.53	29
Peripheral vascular disease, onset	9.78	9.71	26
Congestive heart failure, first event	9.56	9.51	18
Angina	9.56	9.53	11
Myocardial infarction, event	9.92	9.87	18
Stroke, event	10.34	10.31	11

HI=human insulin; IAsp=insulin aspart

b) Sensitivity analyses

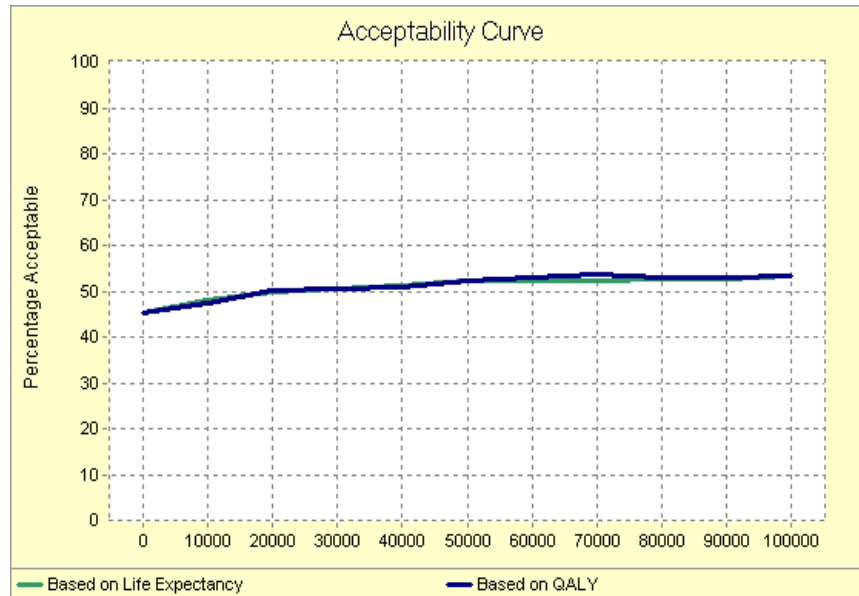
The ICER scatterplot (Figure 3) and CEAC (Figure 4) suggest that, relative to regular HI, IAsp has a 52.3% chance of being cost-effective, at a WTP threshold of C\$50,000 per QALY gained. The CEAC plateaus at a probability of 53% indicating that there is reasonable probability that IAsp is not cost-effective at thresholds less than \$100,000 per QALY gained.

Figure 3: Incremental cost-utility scatter plot of IAsp, relative to regular HI, in the treatment of patients with type 2 DM



DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Figure 4: CEAC of IAsp, relative to regular HI, in the treatment of patients with type 2 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; QALY=quality-adjusted life-year

Results from univariate sensitivity analyses show that the model was sensitive to changes in A1c, costs associated with management of severe hypoglycemic episodes, and incorporation of a disutility associated with fear of hypoglycemia (Table 20).

Table 20: Results from univariate sensitivity analyses comparing IAsp, relative to regular HI, in the treatment of patients with type 2 DM	
	ICUR(\$C per QALY gained)
Base-Case Analysis*	\$22,488
Variation in change in A1c	
No A1c difference between treatments	\$543,584
Variation in discount rates	
0% costs, 0% QALYs	\$13,601
3% costs, 3% QALYs	\$17,843
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	\$22,494
0.0000285 (15 minutes in a state with utility=0)	\$22,401
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	\$22,487
0.00274 (1 day in a state with utility=0)	\$19,055
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	Cost saving†
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$4,429

A1c=glycosylated hemoglobin; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ICUR= incremental cost-utility ratio; C=Canadian; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.09 (-0.21, -0.04)^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycemic episode,⁵⁰ 0.000004767 QALYs lost for a mild to Moderate hypoglycaemic episode⁵⁰, and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹

† Cost-saving refers to a strategy that is less costly and more effective

5.2 ILis Versus Regular HI

5.2.1 Type 1 DM

a) Base-case analysis

Life expectancy and quality-adjusted life expectancy

Treatment of T1DM with ILis was estimated to increase life expectancy by 0.007 years, relative to treatment with regular HI. Patients taking ILis were projected to have a QALE of 10.997 years compared to 10.991 years for patients taking regular HI. Base-case analysis results are presented in Table 21.

	ILis	Regular HI	Difference between ILis and regular HI
Life expectancy [years]*	14.472	14.465	0.007
Undiscounted life expectancy [years]	30.215	30.201	0.014
Quality-adjusted life expectancy (QALE) [years]*	10.997	10.991	0.006
Undiscounted QALE [years]	22.542	22.528	0.014
Total direct costs [C\$]*	71,976	71,794	182
ICER [• costs*/• LE*]			26,385†
ICUR [• costs*/• QALE*]			28,996‡

C=Canadian; DM=diabetes mellitus; HI=human insulin; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; ILis=insulin lispro; LE= life expectancy; QALE=quality-adjusted life-expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained

‡ Cost in C\$ per incremental quality-adjusted life-year gained

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for a patient with T1DM using ILis were estimated to be C\$182 more than that for a patient using regular HI. This yields incremental costs of C\$ 28,996 per QALY gained for patients prescribed ILis as opposed to regular HI. Treatment costs (C\$ 570) comprise the largest cost differential of direct costs between treatments. Mean discounted lifetime direct costs for each treatment strategy for patients with T1DM are provided in Table 22.

Costing Component	ILis	Regular HI	Cost Differential(C\$)
Treatment costs	6,041	5,471	570
Management costs†	15,589	15,606	-17
Management of cardiovascular complications	7,612	7,636	-24
Management of renal complications	18,739	18,754	-15
Management of neuropathy/ulcer/amputation	11,624	11,678	-54
Management of eye disease	9,129	9,150	-21
Management of hypoglycemia	2,100	2,358	-258
Management of keto/lactic acidosis	1,142	1,141	1
Total direct costs (over lifetime)	71,976	71,794	182

C=Canadian; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro

*Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetic complications over lifetime

Table 23 presents data on the predicted time-to-event, in years, for each diabetes-related complication by treatment, and the difference in time-to-event (days) across treatment strategies. For all complications other than peripheral vascular disease, patients using ILis are expected to experience diabetes-related complications slightly later in life than patients using regular HI. For instance, the model projects that a patient using ILis would develop end-stage renal disease four days later than a patient prescribed regular HI.

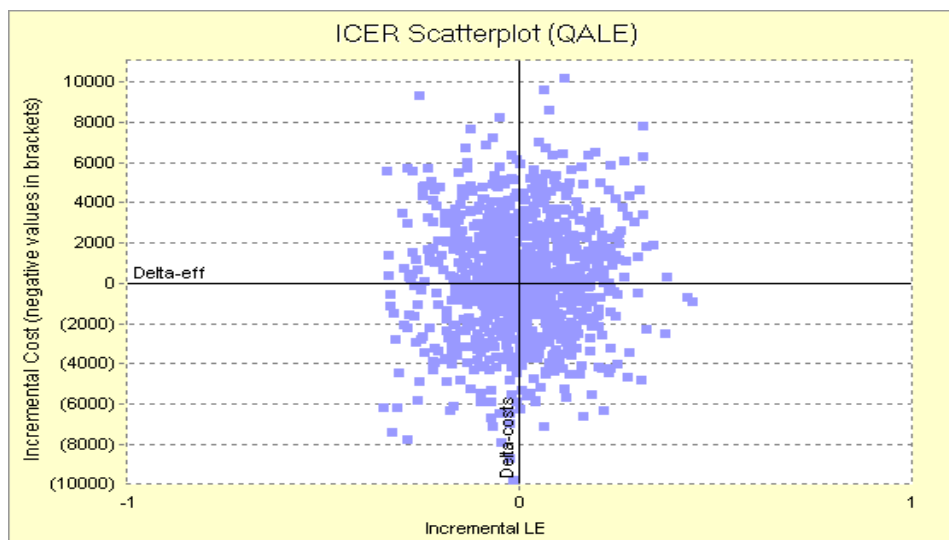
Table 23: Time free of diabetes-related complications, in years, for each strategy			
Diabetes Complication	Time to Event (Years)		Difference (Days)
	ILis	Regular HI	
Severe vision loss/blindness	24.08	24.05	11
End-stage renal disease	29.4	29.39	4
Ulcer, first	24.66	24.63	11
Amputation, ulcer	28.57	28.54	11
Neuropathy	8.65	8.62	11
Peripheral vascular disease, onset	28.96	28.96	0
Congestive heart failure, first event	28.52	28.51	4
Angina	28.61	28.59	7
Myocardial infarction, event	28.87	28.86	4
Stroke, event	29.65	29.63	7

HI=human insulin

b) Sensitivity analyses

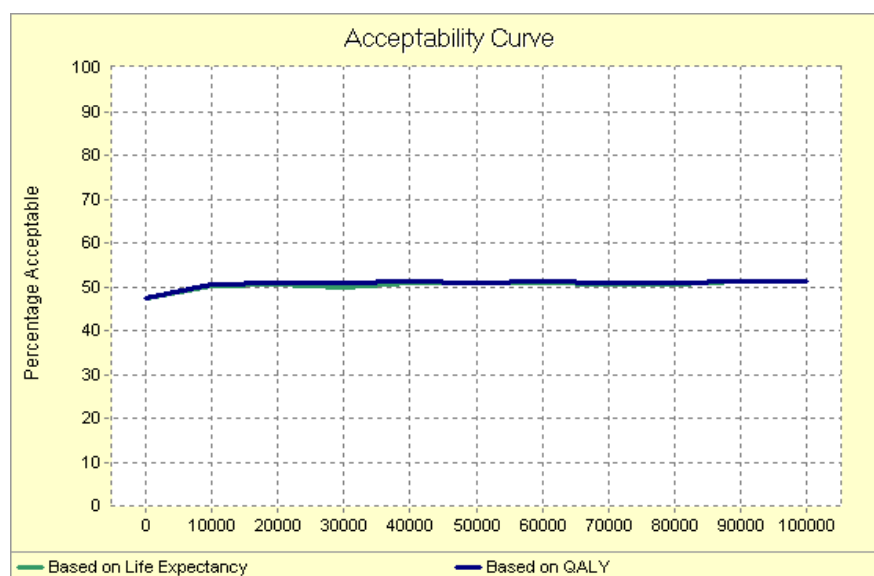
The ICER scatterplot (Figure 5) and CEAC (Figure 6) suggest that relative to regular HI, ILis has a 51.2% chance of being cost-effective at a WTP threshold of C\$50,000 per QALY gained. The CEAC plateaus at 50%, indicating that there is a 50% chance that ILis insulin analogues are not cost-effective at WTP thresholds <\$100,000 per QALY gained.

Figure 5: Incremental cost-utility scatter plot of ILis, relative to regular HI, in the treatment of patients with type 1 DM



DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Figure 6: CEAC of ILis, relative to regular HI, in the treatment of patients with type 1 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; QALY=quality-adjusted life-year

Results from univariate sensitivity analyses show that the model was sensitive to changes in A1c and costs associated with management of severe hypoglycemic episodes (Table 24).

Table 24: Results from univariate sensitivity analyses comparing ILis, relative to regular HI, in the treatment of patients with type 1 DM	
	ICUR (C\$ per QALY gained)
Base-Case Analysis*	\$28,996
Variation in change in A1c	
No A1c difference between treatments	\$673,041
Variation in discount rates	
0% costs, 0% QALYs	\$35,385†
3% costs, 3% QALYs	\$30,394‡
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	\$29,006
0.0000285 (15 minutes in a state with utility=0)	\$29,010‡
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	\$28,987
0.00274 (1 day in a state with utility=0)	\$28,983
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	Cost saving†
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$1,117

A1c=glycosylated hemoglobin; C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; ICUR= incremental cost-utility ratio; ILis=insulin lispro; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.01 (-0.19, 0.08)^{32,33}, discount rate of 5% for both costs and QALYs,³⁷ 0.001503 QALYs lost for a severe hypoglycemic episode,⁵⁰ 0.000004767 QALYs lost for a mild to moderate hypoglycemic episode,⁵⁰ and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹

† Cost-saving refers to a strategy that is less costly and more effective

‡ SA results derived from the mean values of 1,000 samples of 1,000 iterations; counterintuitive ICUR may be attributable to small A1c differences, in combination with inadequate number of samples

5.2.2 Type 2 DM

a) Base-case analysis

Life expectancy and quality-adjusted life expectancy

Treatment of T2DM with ILis was estimated to increase life expectancy by 0.007 years, relative to treatment with regular HI. Patients using ILis are projected to have a quality-adjusted life expectancy (QALE) of 5.773 years compared to 5.767 for patients using regular HI. Results from the base-case analysis are presented in Table 25.

	ILis	Regular HI	Difference Between ILis and Regular HI
Life expectancy [years]*	7.73	7.723	0.007
Undiscounted life expectancy [years]	11.322	11.308	0.014
Quality-adjusted life expectancy (QALE) [years]*	5.773	5.767	0.006
Undiscounted QALE [years]	8.392	8.382	0.01
Total direct costs [C\$]*	66,274	65,490	784
ICER [• costs* / • LE*]			107,062†
ICUR [• costs* / • QALE*]			130,865‡

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; QALE=quality-adjusted life expectancy; ICER= incremental cost-effectiveness ratio; ICUR=incremental cost-utility ratio; ILis=insulin lispro; LE= life expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained

‡ Cost in C\$ per incremental quality-adjusted life-year gained

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for patient with T2DM using ILis is estimated to be C\$784 more than that for a patient using regular HI. This yields an incremental cost of C\$130,865 per QALY gained for ILis relative to regular HI. Treatment costs comprise the largest cost differential (C\$1,298) between treatment strategies. Mean discounted lifetime direct costs for each treatment strategy for patients with T2DM are provided in Table 26.

Costing Component	ILis	Regular HI	Cost Differential (C\$)
Treatment costs	8,521	7,223	1,298
Management costs†	9,801	9,805	-4
Management of cardiovascular complications	23,851	23,938	-87
Management of renal complications	8,446	8,494	-48
Management of neuropathy/ulcer/amputation	10,198	10,184	14
Management of eye disease	5,124	5,130	-6
Management of hypoglycemia	333	716	-383
Management of keto/lactic acidosis	0	0	0
Total direct costs [over lifetime]	66,274	65,490	784

C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro

*Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetes complications over lifetime

Table 27 presents data on the predicted time-to-event, in years, for each diabetes complication by treatment, and the difference in time-to-event (days) between treatment strategies. Model simulations project that patients taking ILis will experience diabetes complications slightly later in life (four to 11 days) than those using regular HI.

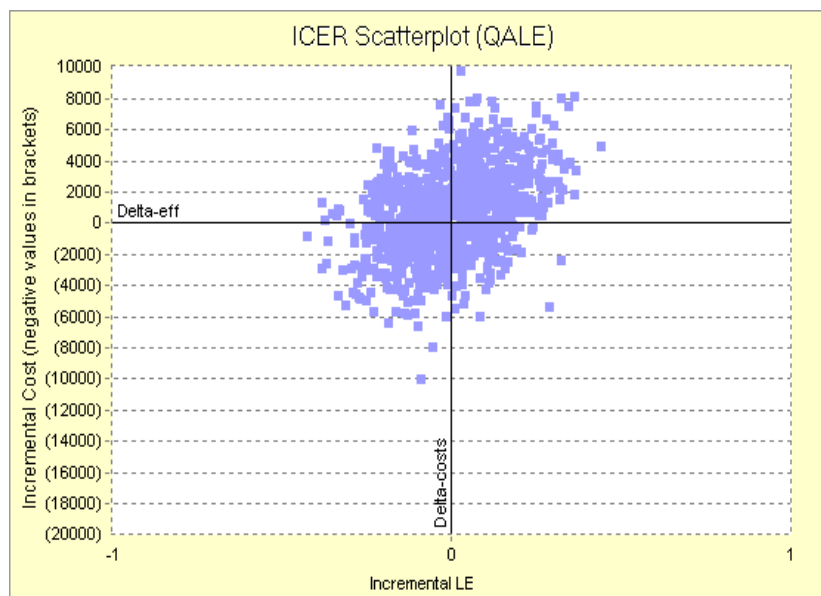
Table 27: Time free of diabetes complications in years for each strategy			
Diabetes Complication	Time to Event (years)		Difference (Days)
	ILis	Regular HI	
Severe vision Loss/blindness	10.51	10.5	4
End-stage renal disease	11.17	11.15	7
Ulcer, first	9.15	9.14	4
Amputation, ulcer	10.77	10.76	4
Neuropathy	5.07	5.05	7
Peripheral vascular disease, onset	9.3	9.28	7
Congestive heart failure, first event	9.16	9.14	7
Angina	9.26	9.23	11
Myocardial infarction, event	9.52	9.51	4
Stroke, event	10.07	10.04	11

HI=human insulin; ILis=insulin lispro

b) Sensitivity analyses

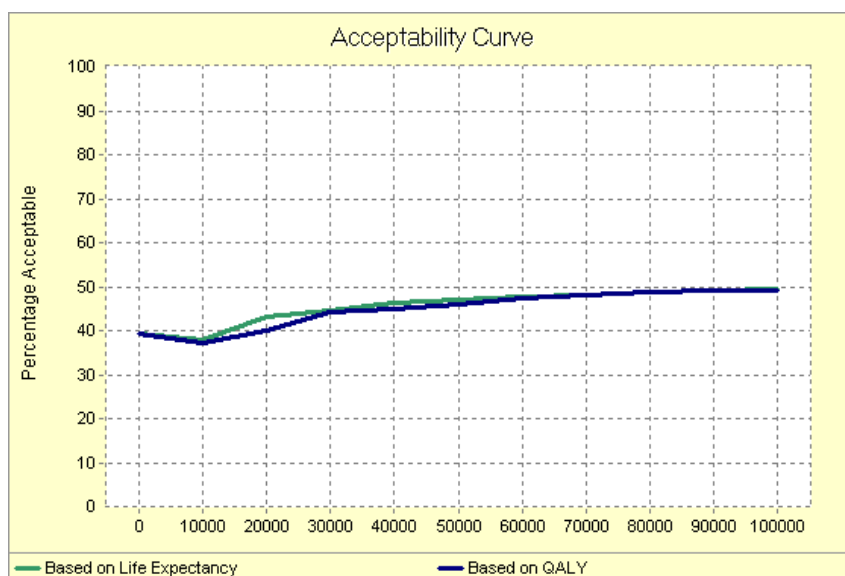
The ICER scatterplot (Figure 7) and CEAC (Figure 8) suggest that, relative to regular HI, and at WTP thresholds of C\$50,000 and C\$100,000 per QALY gained, ILis has a 46.3% and 49.4% chance of being cost-effective. The CEAC in Figure 8 appears to plateau at 50%, indicating that there is at least a 50% chance that insulin analogues are not cost-effective at WTP thresholds <\$100,000 per QALY gained.

Figure 7: Incremental cost-utility scatter plot of ILis, relative to regular HI, in the treatment of patients with type 2 DM



DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Figure 8: CEAC of ILis, relative to regular HI, in the treatment of patients with type 2 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; QALY=quality-adjusted life-year

Results from univariate sensitivity analyses show that the model was sensitive to changes in A1c, costs associated with management of severe hypoglycemic episodes, and incorporation of a disutility associated with fear of hypoglycemia (Table 28).

Table 28: Results from univariate sensitivity analyses comparing ILis, relative to regular HI, in the treatment of patients with type 2 DM	
	ICUR (C\$ Per QALY Gained)
Base-Case Analysis*	\$130,865
Variation in change in A1c	
No A1c difference between treatments	\$80,445‡
Variation in discount rates	
0% costs, 0% QALYs	\$103,296
3% costs, 3% QALYs	\$120,532
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	\$130,821‡
0.0000285 (15 minutes in a state with utility=0)	\$130,712
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	\$130,603
0.00274 (1 day in a state with utility=0)	\$120,617
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	Cost saving†
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$12,115

A1c=glycosylated hemoglobin; C\$=Canadian \$; DM=diabetes mellitus; HI=human insulin; ICUR= incremental cost-utility ratio; ILis=insulin lispro; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.01 (-0.19, 0.08)^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycemic episode⁵⁰, 0.00004767 QALYs lost for a mild to moderate hypoglycemic episode⁵⁰, and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹

† Cost-saving refers to a strategy that is less costly and more effective

‡ SA results derived from the mean values of 1,000 samples of 1,000 iterations; counterintuitive ICUR may be attributable to small A1c differences, in combination with an inadequate number of samples

5.3 IGlAr Versus Insulin NPH

5.3.1 Type 1 DM

a) Base-case analysis

Life expectancy and quality-adjusted life expectancy

Treatment of T1DM with IGlAr was estimated to increase life expectancy by 0.045 years, relative to treatment with insulin NPH. Patients using IGlAr were estimated to have a quality-adjusted life expectancy (QALE) of 11.136 years compared to a QALE of 11.097 years for patients taking insulin NPH. Results from the base case are presented in Table 29.

	IGlar	Insulin NPH	Difference Between IGlAr and Regular HI
Life expectancy [years]*	14.636	14.591	0.045
Undiscounted life expectancy [years]	30.970	30.762	0.208
Quality-adjusted life expectancy (QALE) [years]*	11.136	11.097	0.039
Undiscounted QALE [years]	23.141	22.973	0.168
Total direct costs [C\$]*	70,751	67,328	3,423
ICER [• costs* / • LE*]			76,293†
ICUR [• costs* / • QALE*]			87,932‡

C\$=Canadian \$; DM=diabetes mellitus; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; IGlAr=insulin glargine; LE= life expectancy; NPH=neutral protamine Hagedorn; QALE=quality adjusted life-expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained

‡ Cost in C\$ per incremental quality-adjusted life-year gained

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for a patient with T1DM using IGlAr were estimated to be C\$3423 greater than the corresponding cost for a patient using insulin NPH. This yields an incremental cost of C\$87,932 per QALY gained, for patients taking IGlAr, relative to insulin NPH. Treatment costs comprised the largest cost differential (C\$4248) of direct costs. Table 30 presents the mean discounted lifetime direct cost for each treatment strategy.

Costing Component	IGlar	Insulin NPH	Cost Differential (C\$)
Treatment costs	7,006	2,758	4,248
Management costs†	15,719	15,709	10
Management of cardiovascular complications	7,638	7,614	24
Management of renal complications	16,770	17,208	-438
Management of neuropathy/ulcer/amputation	11,211	11,374	-163
Management of eye disease	9,165	9,155	10
Management of hypoglycemia	2,090	2,365	-275
Management of keto/lactic acidosis	1,152	1,145	7
Total direct costs (over lifetime)	70,751	67,328	3,423

C=Canadian; DM=diabetes mellitus; IGlAr=insulin glargine; NPH=neutral protamine Hagedorn

*Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetic complications over lifetime

Table 31 presents data on the predicted time-to-event in years for each diabetes-related complication by treatment, and the difference (in days) in time-to-event between treatment strategies. Model simulations project that patients taking IGlargin will experience diabetes complications later in life (69-113 days) compared with insulin NPH.

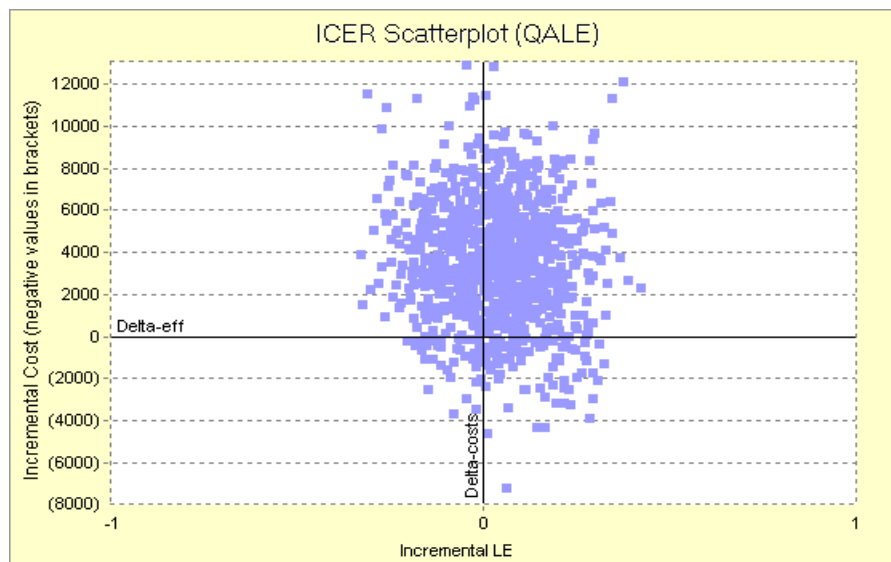
Table 31: Time free of diabetes complications in years for each strategy			
Diabetes Complication	Time to Event (Years)		Difference (Days)
	IGlargin	Insulin NPH	
Severe vision loss/blindness	24.75	24.56	69
End-stage renal disease	30.22	30	80
Ulcer, first	25.45	25.22	84
Amputation, ulcer	29.33	29.12	77
Neuropathy	9.70	9.39	113
Peripheral vascular disease, onset	29.80	29.57	84
Congestive heart failure, first event	29.23	29.03	73
Angina	29.27	29.1	62
Myocardial infarction, event	29.65	29.44	77
Stroke, event	30.37	30.17	73

IGlargin=insulin glargine; NPH=neutral protamine Hagedorn

b) Sensitivity Analyses

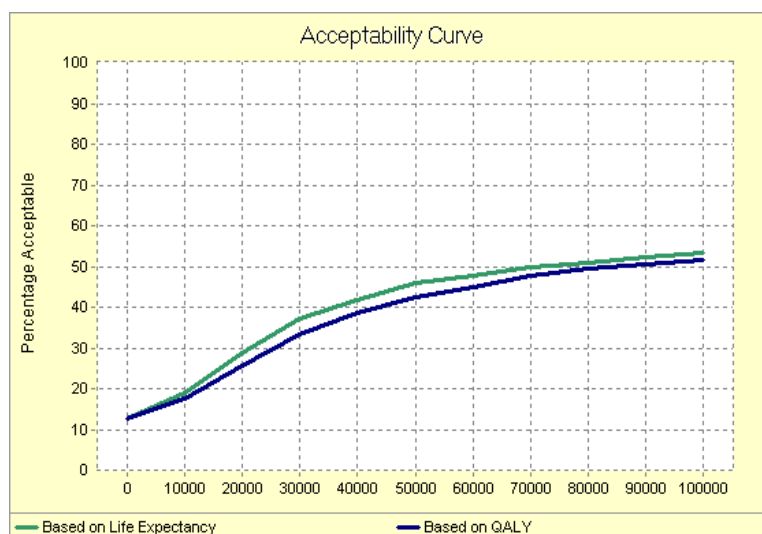
The ICER scatterplot (Figure 9) and CEAC (Figure 10) suggest that, relative to insulin NPH, and at WTP thresholds of C\$50,000 and C\$100,000 per QALY gained, IGlargin has a 42.5% and 51.7% chance of being cost-effective.

Figure 9: Incremental cost-utility scatter plot of IGlargin relative to insulin NPH in the treatment of patients with type 1 DM



DM=diabetes mellitus; ICER=incremental cost-effectiveness ratio; IGlargin=insulin glargine; LE=lifetime expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life expectancy

Figure 10: CEAC of IGlAr relative to insulin NPH in the treatment of patients with type 1 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; IGlAr=insulin glargine; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year

Table 32 presents results from the univariate sensitivity analyses. Results were extremely sensitive to changes in A1c, discount rate, cost of IGlAr, cost associated with management of severe hypoglycemic episodes, and disutility associated with fear of hypoglycemia.

Table 32: Results from univariate sensitivity analyses comparing IGlAr, relative to insulin NPH, in the treatment of patients with type 1 DM	
	ICUR (C\$ Per QALY Gained)
Base-case Analysis*	\$87,932
Variation in change in A1c	
No A1c difference between treatments	\$916,401
Variation in discount rates	
0% costs, 0% QALYs	\$45,645
3% costs, 3% QALYs	\$66,828
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	\$87,934
0.0000285 (15 minutes in a state with utility=0)	\$87,747
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	\$87,934
0.00274 (1 day in a state with utility=0)	\$87,968
Variation in cost of IGlAr	
15% decrease in cost	\$60,860
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	\$71,067
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$17,225

A1c=glycosylated hemoglobin; C\$=Canadian \$; DM=diabetes mellitus; ICUR= incremental cost-utility ratio; IGlAr=insulin glargine; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.11 (-0.21, -0.02)^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycemic episode⁵⁰, 0.00004767 QALYs lost for a mild to moderate hypoglycemic episode⁵⁰, and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹

† SA results derived from the mean values of 1,000 samples of 1,000 iterations; counterintuitive ICUR may be attributable to small A1c differences, in combination with inadequate number of samples

5.3.2 Type 2 DM

a) Base-case analysis

Life expectancy and quality-adjusted life expectancy

Treatment of T2DM with IGLar was estimated to increase life expectancy by 0.011 years, relative to treatment with insulin NPH. Patients using IGLar were estimated to have a quality-adjusted life expectancy (QALE) of 5.806 years compared to a QALE of 5.798 years for patients taking insulin NPH. Results from the base case are presented in Table 33.

	IGlar	Insulin NPH	Difference Between IGLar and Insulin NPH
Life expectancy [years]*	7.772	7.761	0.011
Undiscounted life expectancy [years]	11.411	11.391	0.02
Quality-adjusted life expectancy (QALE) [years]*	5.806	5.798	0.008
Undiscounted QALE [years]	8.462	8.448	0.014
Total direct costs [C\$]*	67,132	62,187	4,945
ICER [• costs* / • LE*]			448,876†
ICUR [• costs* / • QALE*]			642,994‡

C\$=Canadian \$; DM=diabetes mellitus; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; IGLar=insulin glargine; LE= life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life-expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained

‡ Cost in C\$ per incremental quality-adjusted life-year gained

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for a patient with T2DM using IGLar were estimated to be C\$4,945 greater than those for a patient using insulin NPH. This yields an incremental cost of C\$642,994 per QALY gained, for patients taking IGLar, relative to insulin NPH. Treatment costs comprised the largest cost differential (C\$ 5,335) of direct costs. Table 34 presents the mean discounted lifetime direct costs for each treatment strategy.

Costing Component	IGlar	Insulin NPH	Cost Differential(C\$)
Treatment costs	9,869	4,534	5,335
Management costs†	9,850	9,849	1
Management of cardiovascular complications	23,767	23,833	-66
Management of renal complications	7,936	8,016	-80
Management of neuropathy/ulcer/amputation	10,131	10,113	18
Management of eye disease	5,084	5,124	-40
Management of hypoglycemia	495	718	-223
Management of keto/lactic acidosis	0	0	0
Total direct costs [over lifetime)	67,132	62,187	4,945

C\$=Canadian \$; DM=diabetes mellitus; IGLar=insulin glargine; NPH=neutral protamine Hagedorn

* Discounted at 5%

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetic complications over lifetime

Table 35 presents data on the predicted time-to-event in years for each diabetes-related complication by treatment, and the difference (in days) between treatment strategies. Model simulations project that patients taking IGLar will experience diabetes complications slightly later in life (four to 11 days) compared with insulin NPH.

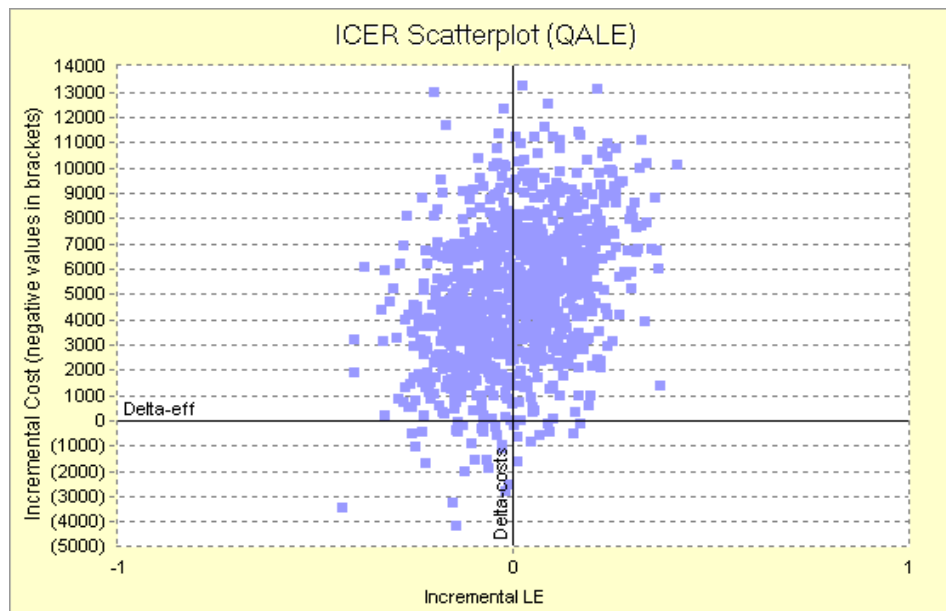
Table 35: Time free of diabetes complications in years for each strategy			
Diabetes Complication	Time to Event (Years)		Difference (Days)
	IGlar	Insulin NPH	
Severe vision loss/blindness	10.61	10.58	11
End-stage renal disease	11.26	11.24	7
Ulcer, first	9.25	9.23	7
Amputation, ulcer	10.86	10.85	4
Neuropathy	5.19	5.17	7
Peripheral vascular disease, onset	9.41	9.38	11
Congestive heart failure, first event	9.26	9.23	11
Angina	9.33	9.32	4
Myocardial infarction, event	9.62	9.59	11
Stroke, event	10.14	10.11	11

IGlar=insulin glargine; NPH=neutral protamine Hagedorn

b) Sensitivity analyses

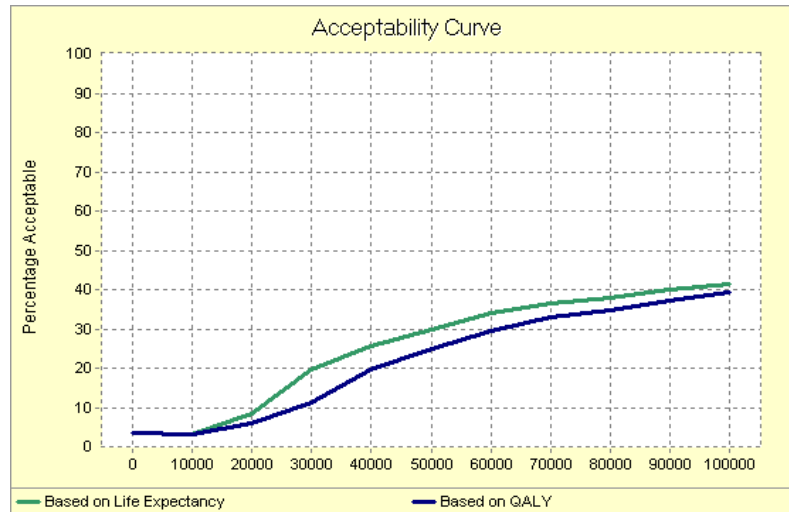
The ICER scatterplot (Figure 11) and CEAC (Figure 12) suggest that, relative to insulin NPH, and at WTP thresholds of C\$50,000 and C\$100,000 per QALY gained, IGLar has a 25.1% and 39.3% chance of being cost-effective in patients with T2DM.

Figure 11: Incremental cost-utility scatter plot of IGLar, relative to insulin NPH, in the treatment of patients with type 2 DM



DM=diabetes mellitus; ICER=incremental cost-effectiveness ratio; IGLar=insulin glargine; LE=life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life expectancy

Figure 12: CEAC of IGlAr, relative to insulin NPH, in the treatment of patients with type 1 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; IGlAr=insulin glargine; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year

Table 36 presents results from the univariate sensitivity analyses. Results were sensitive to changes in A1c and disability associated with fear of hypoglycemia. However, results were robust to changes in other parameters examined in the sensitivity analysis; ICURs > \$450,000 per QALY gained.

Table 36: Results from univariate sensitivity analyses comparing IGlAr, relative to insulin NPH, in the treatment of patients with type 2 DM	
	ICUR (C\$ Per QALY Gained)
Base-Case Analysis*	\$642,994
Variation in change in A1c	
No A1c difference between treatments	\$1,577,457
Variation in discount rates	
0% costs, 0% QALYs	\$532,760
3% costs, 3% QALYs	\$596,091
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	\$643,161
0.0000285 (15 minutes in a state with utility=0)	\$639,998
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	\$643,077†
0.00274 (1 day in a state with utility=0)	\$650,436†
Variation in cost of IGlAr	
15% decrease in cost	\$450,111
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	\$573,563
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$73,989

A1c=glycosylated hemoglobin; C\$=Canadian \$; DM=diabetes mellitus; ICUR= incremental cost-utility ratio; IGlAr=insulin glargine; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.01 (-0.19, 0.08)^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycemic episode⁵⁰, 0.000004767 QALYs lost for a mild to moderate hypoglycemic episode⁵⁰, and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹

† SA results derived from the mean values of 1,000 samples of 1,000 iterations; counterintuitive ICUR may be attributable to small A1c differences, in combination with an inadequate number of samples

5.4 IDet Versus Insulin NPH

5.4.1 Type 1 DM

a) Base-case analysis

Life expectancy and quality-adjusted life expectancy

Treatment of T1DM with IDet is estimated to increase life expectancy by 0.012 years, relative to treatment with insulin NPH. Patients using IDet are estimated to have a quality-adjusted life expectancy (QALE) of 11.045 years, compared to a QALE of 11.034 years for patients taking insulin NPH. Results from the base case are presented in Table 37.

	IDet	Insulin NPH	Difference Between IDet and Insulin NPH
Life Expectancy [years]*	14.529	14.517	0.012
Undiscounted life expectancy [years]	30.49	30.417	0.073
Quality-adjusted life expectancy (QALE) [years]*	11.045	11.034	0.011
Undiscounted QALE [years]	22.758	22.699	0.059
Total direct costs [C\$]*	72,714	68,370	4,344
ICER [• costs* / • LE*]			363,888†
ICUR [• costs* / • QALE*]			387,729‡

C\$=Canadian \$; ICER= incremental cost-effectiveness ratio; LE= life expectancy;

DM=diabetes mellitus; HI=human insulin; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; IDet=insulin detemir; LE= life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life-expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained

‡ Cost in C\$ per incremental quality-adjusted life-year gained

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for a patient with T1DM using IDet were estimated to be C\$4344 greater than the corresponding cost for a patient using insulin NPH. This yields an incremental cost of C\$387,729 per QALY gained, for patients taking IDet, relative to insulin NPH. Treatment costs comprised the largest cost differential (C\$ 4,874) of direct costs. Table 38 presents the mean discounted lifetime direct cost for each treatment strategy.

Costing Component	IDet	Insulin NPH	Cost Differential (C\$)
Treatment costs	7,619	2,745	4,874
Management costs†	15,652	15,637	15
Management of cardiovascular complications	7,627	7,624	3
Management of renal complications	18,091	18,120	-29
Management of neuropathy/ulcer/amputation	11,476	11,579	-103
Management of eye disease	9,158	9,158	0
Management of hypoglycemia	1,946	2,362	-416
Management of keto/lactic acidosis	1,145	1,145	0
Total direct costs (over lifetime)	72,714	68,370	4,344

C\$=Canadian \$; DM=diabetes mellitus; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; IDet=insulin detemir; LE= life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life-expectancy

*Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases¹⁴

Projection of diabetic complications over lifetime

Table 39 presents data on the predicted time-to-event in years for each diabetes-related complication by treatment, and difference (in days) between treatment strategies. Model simulations project that patients taking IDet will experience diabetes complications slightly later in life (22 to 51 days) compared with insulin NPH.

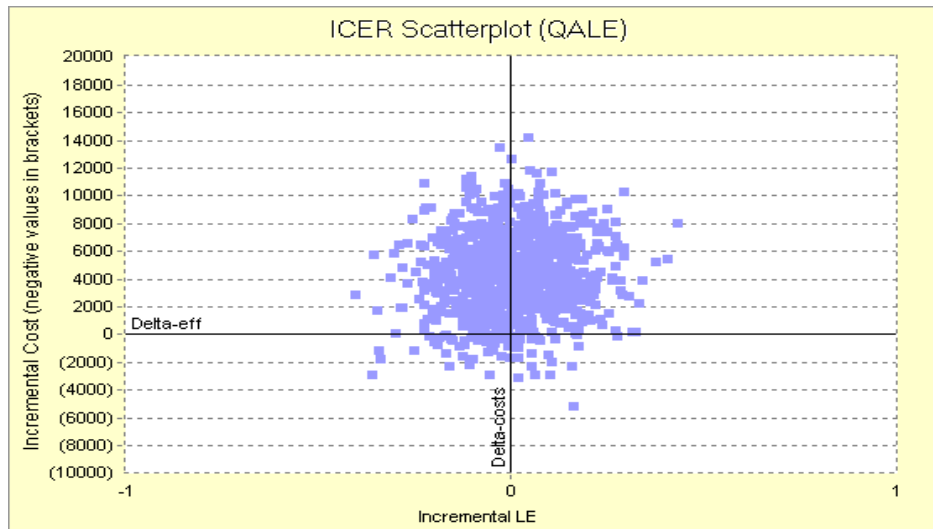
Table 39: Time free of diabetes complications (years) for each strategy			
Diabetes Complication	Time to Event (Years)		Difference (Days)
	IDet	Insulin NPH	
Severe vision loss/blindness	24.31	24.23	29
End-stage renal disease	29.7	29.63	26
Ulcer, first	24.95	24.86	33
Amputation, ulcer	28.84	28.76	29
Neuropathy	9.05	8.91	51
Peripheral vascular disease, onset	29.28	29.19	33
Congestive heart failure, first event	28.78	28.71	26
Angina	28.85	28.79	22
Myocardial infarction, event	29.15	29.08	26
Stroke, event	29.91	29.84	26

IDet=insulin detemir; NPH=neutral protamine Hagedorn

b) Sensitivity analyses

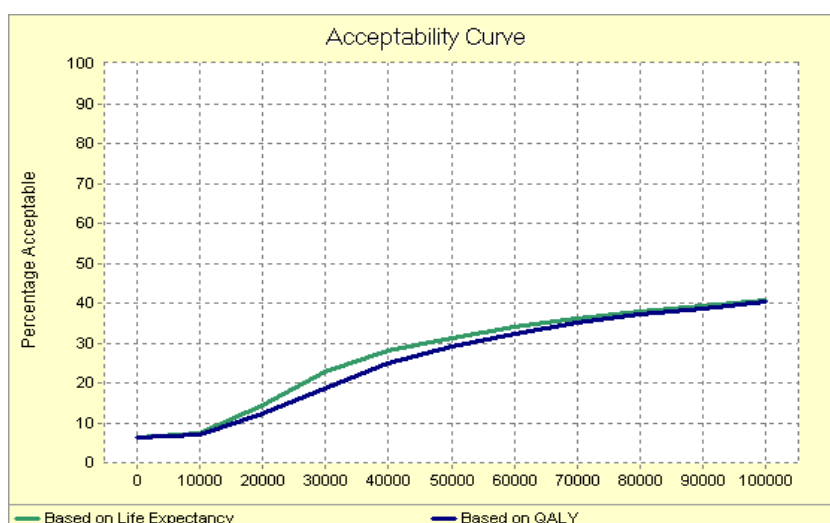
The ICER scatterplot (Figure 13) and CEAC (Figure 14) suggest that, relative to insulin NPH, and at WTP thresholds of C\$50,000 and C\$100,000 per QALY gained, IDet has a 29.2% and 40.5% chance of being cost-effective in patients with T1DM.

Figure 13: Incremental cost-utility scatter plot of IDet, relative to insulin NPH, in the treatment of patients with type 1 DM



DM=diabetes mellitus; ICER=incremental cost-effectiveness ratio; IDet=insulin detemir; LE=life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life expectancy

Figure 14: CEAC of IDet, relative to insulin NPH, in the treatment of patients with type 1 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year

Table 40 presents results from the univariate sensitivity analyses. Results were sensitive to changes in A1c and disutility associated with fear of hypoglycemia. However, results were robust to changes in other parameters examined in the sensitivity analysis; all ICURs > \$150,000 per QALY gained.

Table 40: Results from univariate sensitivity analyses comparing IDet, relative to insulin NPH, in the treatment of patients with type 1 DM	
	ICUR (C\$ Per QALY Gained)
Base-Case Analysis*	\$387,729
Variation in change in A1c	
No A1c difference between treatments	\$1,958,928
Variation in discount rates	
0% costs, 0% QALYs	\$161,243
3% costs, 3% QALYs	\$268,614
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	\$387,867
0.0000285 (15 minutes in a state with utility=0)	\$385,663
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	\$387,971†
0.00274 (1 day in a state with utility=0)	\$389,887†
Variation in cost of IDet	
15% decrease in cost	\$285,814
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	\$297,195
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$25,666

A1c=glycosylated hemoglobin; C\$=Canadian \$; DM=diabetes mellitus; ICUR= incremental cost-utility ratio; IDet=insulin detemir; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year

* Base-case analysis assumes an A1c difference of -0.05 (-0.13, 0.03).^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycaemic episode⁵⁰, 0.000004767 QALYs lost for a mild to moderate hypoglycemic episode⁵⁰, and the average management cost for a severe hypoglycaemic episode requiring assistance is C\$129⁷¹

† SA results derived from the mean values of 1,000 samples of 1,000 iterations; counterintuitive ICUR may be attributable to small A1c differences, in combination with an inadequate number of samples

5.4.2 Type 2 DM

a) Base-case analysis

Life expectancy and quality-adjusted life expectancy

Treatment of T2DM with IDet is estimated to decrease life expectancy^d by 0.042 years, relative to treatment with insulin NPH. Patients taking insulin detemir are projected have a quality adjusted life expectancy (QALE) of 5,944 years, whereas patients taking insulin NPH are projected to have a QALE of 5,978 years. Results from the base-case are presented in Table 41.

	IDet	Insulin NPH	Difference Between IDET and Insulin NPH
Life expectancy [years]*	7.945	7.987	-0.042
Undiscounted life expectancy [years]	11.807	11.895	-0.088
Quality-adjusted life expectancy (QALE) [years]*	5.944	5.978	-0.034
Undiscounted QALE [years]	8.772	8.841	-0.069
Total direct costs [C\$]*	65,749	59,228	6,521
ICER [• costs* / • LE*]			Dominated†§§
ICUR [• costs* / • QALE*]			Dominated‡

C\$=Canadian \$; DM=diabetes mellitus; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; IDet=insulin detemir; LE= life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life-expectancy

*Discounted at 5% per annum

† Cost in C\$ per incremental life-year gained; dominated refers to a strategy that is more costly and less effective

‡ Cost in C\$ per incremental quality-adjusted life-year gained; dominated refers to a strategy that is more costly and less effective

§ Results presented in the meta-analysis found that patients taking IDet had higher A1c values

Lifetime costs and cost-effectiveness

Total discounted lifetime costs for a patient with T2DM using IDet were estimated to be C\$6,521 greater than the corresponding cost for a patient using insulin NPH. Treating all patients with IDet is more costly and less effective (dominated)[‡]. Treatment costs comprised the largest cost differential (C\$6,368) of direct costs. Table 42 presents the mean discounted lifetime direct cost for each treatment strategy.

Costing Component	IDet	Insulin NPH	Cost Differential (C\$)
Treatment Costs	11,019	4,651	6,368
Management costs†	10,039	10,064	-25
Management of cardiovascular complications	23,203	23,144	59
Management of renal complications	5,981	5,744	237
Management of neuropathy/ulcer/amputation	9,982	9,962	20
Management of eye disease	4,963	4,935	28
Management of hypoglycemia	562	728	-166
Management of keto/lactic acidosis	0	0	0
Total direct costs (over lifetime)	65,749	59,228	6,521

C\$=Canadian \$; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn

* Discounted at 5% per annum

† Refer to medication and/or diagnostic tests; costs are derived from default CDM treatment/economic databases.¹⁴

^dResults presented in the meta-analysis found that patients taking IDet had higher A1c values (WMD, 0.14; 95% CI, -0.01,0.28)

Projection of diabetic complications over lifetime

Table 43 presents data on the predicted time-to-event in years for each diabetes-related complication by treatment, and difference (in days) between treatment strategies. Model simulations project that patients taking IDet will experience diabetes complications slightly earlier^e in life, compared with insulin NPH.

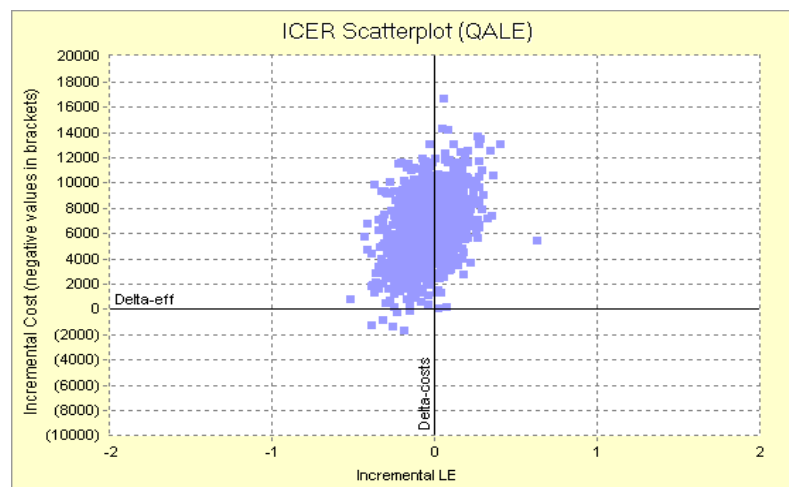
Table 43: Time free of diabetes complications (years) for each strategy			
Diabetes Complication	Time to Event (Years)		Difference(Days)
	IDet	Insulin NPH	
Severe vision loss/blindness	11.05	11.15	-36
End-stage renal disease	11.69	11.78	-33
Ulcer, first	9.64	9.73	-33
Amputation, ulcer	11.24	11.33	-33
Neuropathy	5.79	5.91	-44
Peripheral vascular disease, onset	9.94	10.05	-40
Congestive heart failure, first event	9.71	9.81	-36
Angina	9.68	9.75	-26
Myocardial infarction, event	10.05	10.14	-33
Stroke, event	10.46	10.53	-26

IDet=insulin detemir; NPH=neutral protamine Hagedorn

b) Sensitivity analyses

The ICER scatterplot (Figure 15) and CEAC (Figure 16) suggest that, relative to insulin NPH, and at WTP thresholds of C\$50,000 and C\$100,000 per QALY gained, IDet has a 10.8% and 22.6% chance of being cost-effective in patients with T2DM.

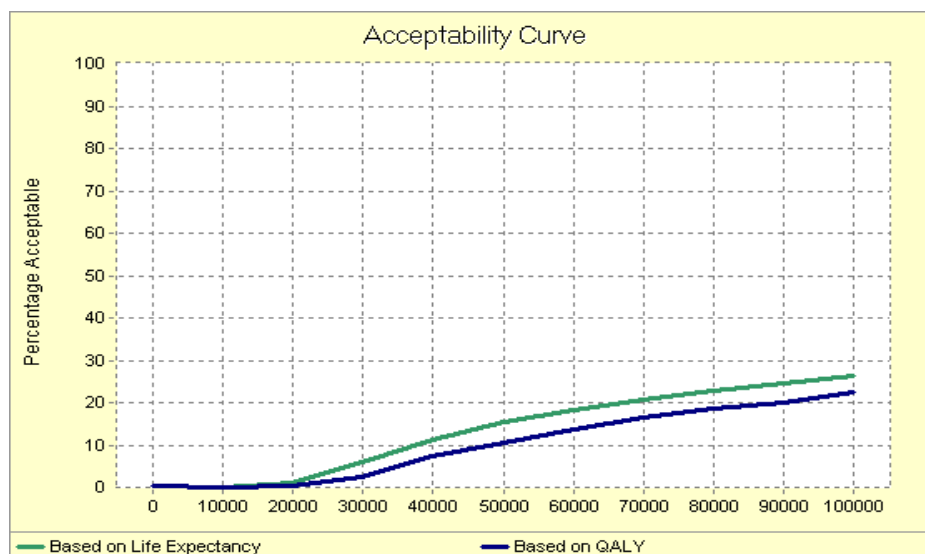
Figure 15: Incremental cost-utility scatter plot of IDet, relative to insulin NPH, in the treatment of patients with type 2 DM



DM=diabetes mellitus; ICER=incremental cost-effectiveness ratio; IDet=insulin detemir; LE=life expectancy; NPH=neutral protamine Hagedorn; QALE=quality-adjusted life expectancy

^e Results presented in the meta-analysis found that patients taking Idet had higher A1c values (WMD, 0.14; 95% CI, -0.01,0.28)

Figure 16: CEAC of IDet, relative to insulin NPH, in the treatment of patients with type 2 DM



CEAC=cost-effectiveness acceptability curve; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year

Table 44 presents results from the univariate sensitivity analyses. Results were sensitive to changes in A1c and disutility associated with fear of hypoglycemia.

Table 44: Results from univariate sensitivity analyses comparing IDet, relative to insulin NPH, in the treatment of patients with type 2 DM	
	ICUR (C\$ Per QALY Gained)
Base-case Analysis*	Dominated†
Variation in change in A1c	
No A1c difference between treatments	\$882,155
Variation in discount rates	
0% costs, 0% QALYs	Dominated†
3% costs, 3% QALYs	Dominated†
Variation in QALYs lost for a mild to moderate hypoglycemic episode	
0	Dominated†
0.000285 (15 minutes in a state with utility=0)	Dominated†
Variation in QALYs lost for a severe hypoglycemic episode	
0.00164 ⁴⁸	Dominated†
0.00274 (1 day in a state with utility=0)	Dominated†
Variation in cost of IDet	
15% decrease in cost	Dominated†
Variation in cost of a severe hypoglycemic episode	
\$440 ^{72,80,81}	Dominated†
Incorporation of disutility associated with fear of hypoglycemia	
0.0052	\$234,606

A1c=glycosylated hemoglobin; C\$=Canadian \$; DM=diabetes mellitus; ICUR= incremental cost-utility ratio; IDet=insulin detemir; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year
 * Base-case analysis assumes an A1c difference of 0.14 (-0.01,0.28)^{32,33}, discount rate of 5% for both costs and QALYs³⁷, 0.001503 QALYs lost for a severe hypoglycemic episode⁵⁰, 0.00004767 QALYs lost for a mild to moderate hypoglycemic episode⁵⁰, and that the average management cost for a severe hypoglycemic episode requiring assistance is C\$129⁷¹
 † Dominated refers to a strategy that is more costly and less effective

6 SUMMARY OF MAIN FINDINGS

6.1 Type 1 DM

6.1.1 Rapid-acting Insulin Analogues relative to regular HI

When meta-analytic estimates of drug efficacy were used in the CORE model, IAsp was less costly and more effective than regular HI for the treatment of T1DM in adults. This result did not change when fear of hypoglycemia was incorporated. However, when an A1c difference of zero was assumed, the ICUR for IAsp relative to regular HI increased to C\$104,598 (Table 45).

Using meta-analytic estimates of drug efficacy, the expected incremental cost for ILis compared to regular HI for the treatment of T1DM in adults was C\$28,996 per QALY gained. When fear of hypoglycemia was incorporated into the model, IAsp was less costly and more effective relative to regular HI. When an A1c difference of zero was assumed, the ICUR for ILis relative to regular HI, increased to C\$673,041.

6.1.2 Long-acting Insulin Analogues relative to insulin NPH

ICURs from base case analyses (i.e., using meta-analytic estimates of drug efficacy in the model), for IGlar and IDet for the treatment of T1DM in adults, each relative to insulin NPH, were C\$87,932 and C\$ 387,729 per QALY gained, respectively. Incorporation of fear of hypoglycemia decreased the ICURs to \$17,225, and \$25,666 for IGlar and IDet, respectively. When an A1c difference of zero was assumed, the ICURs for IGlar and IDet increased to \$916,401, and \$1,958,928, respectively (Table 45).

Table 45: Summary of results from economic evaluation of IAs compared with HI (regular and NPH) for the treatment of patients with type 1 DM in Canada

Comparators	Incremental Cost Per QALY Gained (ICUR)		
	Base-case	Fear of Hypoglycemia	HbA1c=0
IAsp versus regular HI	Cost Saving	Cost Saving	\$104,598
ILis versus regular HI	\$28,996	\$1,117	\$673,041
IGlar versus insulin NPH	\$87,932	\$17,225	\$916,401
IDet versus insulin NPH	\$387,729	\$25,666	\$1,958,928

DM= diabetes mellitus; HbA1c=glycosylated hemoglobin; HI= human insulin; IAs=insulin analogues; IAsp= insulin aspart; ICUR= incremental cost-utility ratio; IDet= insulin detemir; ILis=insulin lispro; IGlar= insulin glargine; IDet= insulin detemir; QALY=quality-adjusted life-year

6.2 Type 2 DM

6.2.1 Rapid-acting Insulin Analogues relative to regular HI

For adult patients with T2DM, treatment with IAsp and ILis, each relative to regular HI, was associated with ICURs of C\$22,488 and C\$130,865 per QALY gained, respectively. When fear of hypoglycemia was included in the model, ICURs decreased to \$4,429 and \$12,115 per QALY gained for IAsp and ILis, respectively. When an A1c difference of zero was assumed, ICURs for IAsp and ILis, each relative to regular HI, were C\$543,584 and C\$80,445, respectively (Table 46).

6.2.2 Long-acting Insulin Analogues relative to insulin NPH

For adult patients with T2DM, treatment with IGlar, relative to insulin NPH, was associated with an incremental cost of C\$642,994 per QALY gained. Treatment of T2DM with IDet was more costly and less effective (dominated). When fear of hypoglycemia was included in the analyses, ICURs decreased to \$73,989 and \$234,606 per QALY gained for IGlar and IDet, respectively. In contrast, when an A1c difference of zero was assumed, ICURs increased to C\$1,577,457 and C\$882,155, for IGlar and IDet, respectively (Table 46).

Table 46: Summary of results from economic evaluation of IAs compared with HI for the treatment of patients with Type 2 DM in Canada

Comparators	Incremental cost per QALY gained (ICUR)		
	Base-case	Fear of Hypoglycaemia	HbA1c=0
IAsp versus regular HI	\$22,488	\$4,429	\$543,584
ILis versus regular HI	\$130,865	\$12,115	\$80,445*
IGlar versus insulin NPH	\$642,994	\$73,989	\$1,577,457
IDet versus insulin NPH	Dominated†	\$234,606	\$882,155

* Base-case analysis assumes an A1c difference of -0.01 (-0.19, 0.08)^{32,33}; SA results derived from the mean values of 1000 samples of 1000 iterations; Counterintuitive ICUR may be attributable to small A1c differences, in combination with an inadequate number of samples

† Base-case analysis assumes an increase in A1c of 0.14 (-0.01, 0.28); Dominated refers to a strategy that is more costly and less effective DM= diabetes mellitus; HI= human insulin; IAs=insulin analogues; IAsp= insulin aspart; ICUR= incremental cost-utility ratio; IDet= insulin detemir; IGlar= insulin glargine; ILis=insulin lispro

7 DISCUSSION

In base case analyses, the use of IAsp for the treatment of T1DM in adults, compared to using regular HI, was cost saving while the use of ILis, relative to regular HI, was associated with a relatively low ICUR. For adults with T1DM, treatment with LAIA, compared to insulin NPH, was associated with relatively high ICURs. The use of IAsp for the treatment of T2DM in adults, compared to regular HI, was associated with a relatively low ICUR while the use of ILis was associated with a relatively high ICUR.

Results from sensitivity analyses indicated that the model was very sensitive to changes in two input variables; A1c effect estimates and the disutility associated with fear of hypoglycemia. Sensitivity analyses that assumed a zero A1c difference between comparators resulted in increased ICURs for both RAIAs and LAIA. In contrast, inclusion of fear of hypoglycemia in sensitivity analyses resulted in decreased ICURs for both RAIAs and LAIAs for patients with T1DM and those with T2DM.

Base-case results for IGlar are consistent with those reported by other international bodies.^{49,68} For example, in 2002, NICE estimated base-case ICURs of •32,000 and •120,000 per QALY for IGlar, compared to NPH, in patients with T1DM and T2DM, respectively.⁶⁸ Similarly, for patients with T1DM requiring intensive

treatment regimens (those who experienced unexplained severe hypoglycaemic episodes in the past 12 months), PHARMAC estimated an ICUR range of NZ\$34,500 to NZ\$58,000 in 2005.⁴⁹

However, results of the current base-case analyses for IGLar differ from those reported in a 2005 Canadian evaluation.⁸² Based on A1c reductions of 0.40% and 0.87% for IGLar relative to insulin NPH, Grima and colleagues⁸² estimated ICURs of C\$20,799 and C\$8,618 per QALY gained for adult patients with T1DM and T2DM, respectively. In contrast, the current analyses, which were based on an A1c differences of 0.11% and 0.05%, ICURs were C\$87,932 and C\$642,994 per QALY gained for IGLar, relative to insulin NPH, in the treatment of adults with T1DM and T2DM were estimated, respectively. It should be noted, however, that the A1c reductions used by Grima and colleagues were derived by taking the lower bound⁸³ of five trials (121 patients)⁸³⁻⁸⁷ and the results of a, then unpublished, abstract.⁸⁸ In contrast, the current analyses were based on A1c differences between IGLar and insulin NPH (that were derived from meta-analyses of 11 studies including 2,745 patients).^{32,33}

As noted above, results of the current analyses were extremely sensitive to changes in A1c effect size and the disutility for fear of hypoglycemia. Similar sensitivities have been reported by other authors.^{49,68} For example, in the evaluation by Grima and colleagues⁸² (discussed above) ICURs increased four-fold when A1c effect estimates were decreased from 0.40% to 0.20% for IGLar relative to NPH, resulting in an ICUR of C\$87,132.⁸² When NICE included fear of hypoglycemia in their analyses, ICURs for IGLar relative to insulin NPH for the treatment of T1DM and T2DM in adult patients decreased from •32,000 and •120,000 per QALY gained to •3500 and •32,500 per QALY gained, respectively.⁶⁸ Similarly, ICUR estimated by PHARMAC for LAIAs, relative to insulin NPH, in the treatment of adult patients with DM ranged from of NZ \$17,000 to NZ \$3.1 million; an extreme range that was largely driven by the impact of fear of further hypoglycaemic episodes on HRQoL.⁴⁹

However, it should be noted that the effect of fear of hypoglycaemic episodes on HRQoL remains unknown and estimates have varied considerably in the literature.^{14,48,49} Moreover, it should be noted that the CDM accommodates fear of hypoglycemia by applying a chronic utility decrement in the traditional insulin arm only, and that no decrement was applied in the IA arm. As hypoglycemia has been reported in patients using IAs,^{32,33} albeit less frequently than in patients using traditional insulin, results from sensitivity analyses examining the effect of fear of hypoglycemia should be interpreted with caution.

7.1 Limitations and Strengths of Approach

Decision-modelling is increasingly used to inform reimbursement decisions in health care settings.^{78,89} Nevertheless, use of decision-analytic modelling to forecast lifetime health outcomes and costs for patients with DM is a complex process. Thus, results of this economic evaluation should be interpreted with the following caveats in mind. First, model projections were based on data from clinical trials which were of short duration with highly selected populations that may differ from “real world” patients with respect to age, comorbidities, and concomitant medication use.

Second, A1c, a surrogate outcome, was used to forecast the occurrence of long-term diabetes complications. The validity of surrogate outcomes has been, and continues to be, extensively debated in the literature.⁹⁰⁻⁹³ Third, progression of diabetes-related complications was based on data from epidemiological studies^{14,94} that may not have accounted for all risk factors or unknown confounding variables.⁹⁵ Fourth, the effect of hypoglycemic episodes on quality of life is unknown and estimates have varied considerably.^{14,48,49} It was therefore assumed that the effect of a hypoglycaemic episode in the base-case would be reflected in the movement in the EQ-5D score against the dimensions of usual activities and anxiety/depression.⁵⁰ However, a sensitivity analysis was conducted to examine robustness of results to incorporation of a disutility associated with fear of hypoglycemia. However, it should be noted that the CDM accommodates fear of

hypoglycemia by applying a chronic utility decrement (e.g., 0.0052) in the traditional insulin (i.e., regular HI, insulin NPH) arm only. That is, no utility decrement was applied in the IA arm. As hypoglycemia has been reported in patients using IAs^{32,33}, albeit less frequently than in patients prescribed traditional insulin, results from sensitivity analyses should be interpreted with caution. Finally, the present economic analysis is not based on direct comparison of insulin analogues in head-to-head clinical trials. Therefore, decision makers should not draw any conclusions regarding the cost-utility of insulin analogues relative to one another.

There are, however, a number of strengths associated with our analyses. First, the well validated¹⁵ CORE Diabetes model was utilized.¹⁴ Second, disutility estimates for chronic states were obtained from an EQ-5D Catalogue in the United States.^{42,43} which has been recommended by the Washington Panel on Cost Effectiveness in Health & Medicine^{42,43} for use in cost-effectiveness analyses. Third, resource use and costing inputs specific to diabetes management in Canada were used in the analyses.²³ Finally, clinical inputs for the model were derived from meta-analyses that are up-to-date and robust.^{32,33}

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