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Short-acting Insulin Analogues for
Diabetes Mellitus: Meta-analysis of
Clinical Outcomes and Assessment
of Cost-effectiveness



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Canadian Agency for Drugs and Technologies in Health

**Short-acting Insulin Analogues for Diabetes Mellitus:
Meta-analysis of Clinical Outcomes and
Assessment of Cost-effectiveness**

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Conflicts of Interest

Dr. Michael Vallis has accepted speaking and consultation fees from Pfizer Inc., Roche, Novartis Inc., and Lifescan Inc. in the past two years for lectures on psychological issues in diabetes, but has had no involvement in the issue of analogue insulins.

Short-acting Insulin Analogues for Diabetes Mellitus: Meta-analysis of Clinical Outcomes and Assessment of Cost-effectiveness

Technology and Condition

Short-acting insulin analogues (SAIAs) for the treatment of type 1, type 2, and gestational diabetes mellitus (DM), including insulin lispro (ILis), insulin aspart (IAsp) and insulin glulisine (IGlu).

Issue

Over 2.25 million Canadians have DM. The annual cost of treating DM and its complications is more than \$9 billion. The successful management of diabetes often requires medications. SAIAs, which were developed to more closely mimic the natural pattern of endogenous insulin in non-diabetic individuals, cost more than human insulin (HI). There is uncertainty about whether the use of SAIAs is justified.

Methods and Results

A systematic review and a meta-analysis were undertaken to evaluate the clinical and economic implications of using SAIAs for the treatment of DM, relative to HI and to oral anti-diabetic agents (OADs). A total of 86 randomized controlled trials reporting clinical outcomes were included: 47 on type 1 DM, 26 on type 2 DM, 10 on types 1 and 2 DM (combined), and three on gestational DM. A review of economic studies and a budget impact analysis were performed.

Implications for Decision Making

- **For type 1 DM, treatment with ILis or IAsp significantly reduced HbA1c levels, compared to HI.** The episodes of overall and severe hypoglycemia were similar, but nocturnal hypoglycemia was less frequent with ILis than with HI.
- **For type 2 DM, treatment with SAIAs did not demonstrate differences in HbA1c levels, compared to HI.** SAIAs did not result in significant reductions in hypoglycemic episodes. When compared with OADs, improvements in HbA1c were seen with ILis and IAsp.
- **Publicly funding SAIAs would increase drug budgets.** For example, funding SAIAs in Ontario would be expected to cost an additional \$116 and \$240 yearly per patient switched. There is some evidence suggesting that these costs will be offset by other health care costs in the first 12 months.
- **Uncertainty remains regarding long-term impact and use in gestational DM.** No differences in patient mortality or quality of life have been demonstrated in patients with DM. The impact on health care costs beyond 12 months is unknown. Patients with gestational DM did not experience significant differences in overall hypoglycaemia rates with ILis, compared to HI, although post-meal glucose levels were improved.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Banerjee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, Campbell K, *Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness* [Technology Report no 87]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

EXECUTIVE SUMMARY

Issue

Insulin analogues are more expensive than conventional insulin. Because health care resources are limited, decision makers need to know if analogues are justified for all or some diabetic groups. This information will help determine their status in provincial drug plans.

Objectives

The aim is to evaluate the clinical and economic implications of short-acting insulin analogues [insulin lispro (ILis), insulin aspart (IAsp), and insulin glulisine (IGlu)] for the treatment of type 1, type 2, and gestational diabetes mellitus (DM).

Clinical review

Methods: A systematic review was conducted to identify randomized controlled trials (RCTs) that compared short-acting insulin analogues to conventional human insulin (HI) for the treatment of DM. The outcomes analyzed were glycated hemoglobin (HbA1c), blood glucose, hypoglycemia, adverse events, mortality, and quality of life (QoL). Meta-analysis was performed when appropriate.

Results: Eighty-six RCTs were included: 47 on type 1 DM, 26 on type 2 DM, 10 on types 1 and 2 DM, and three on gestational DM (GDM). Most were of low methodological quality (Jadad score ≤ 2). The number of patients in the trials varied between 10 and 1,070. Because of incomplete reporting of data, not all RCTs could be included in all meta-analyses.

Type 1 DM patients had significantly greater reductions in HbA1c levels with ILis than HI. The weighted mean difference (WMD) and 95% confidence interval (CI) was -0.09 ($-0.16, -0.01$). This difference was more pronounced [WMD (95% CI) $= -0.28$ ($-0.45, -0.12$)] in patients using continuous subcutaneous insulin infusion (CSII). Similar results were obtained with IAsp versus HI [WMD (95% CI) $= -0.14$ ($-0.22, -0.07$)] for all patients, and -0.31 ($-0.54, -0.08$) for patients using CSII. Post-meal blood glucose levels were generally lower, and pre-meal levels generally similar with ILis than HI. The rate of nocturnal hypoglycemia was less with ILis than HI [WMD (95% CI) $= -0.55$ ($-0.92, -0.19$)]. The rates of overall and severe hypoglycemia did not differ significantly between treatments. In five trials that reported on mortality, there were no detectable differences between treatments. In terms of QoL and well-being, limited evidence indicated that ILis was better than HI and that ILis was preferred over HI because of its convenience of use.

Type 2 DM patients experienced no significant difference in HbA1c levels with any of the insulin analogues compared to HI. Levels of HbA1c were improved with ILis and IAsp compared to oral anti-diabetic agents (OADs). ILis and IAsp achieved better control of postprandial blood glucose levels, but neither they nor IGlu had a significant difference in overall, severe, or nocturnal hypoglycemia. Mortality data were infrequently reported; 15 of 27 relevant reports made no mention of mortality. When such data were reported, mortality rates were low ($<5\%$) making between-treatment comparisons difficult. QoL data, noted in 25% of reports, suggest that there is no difference between ILis and HI in terms of treatment satisfaction or well-being. Compared to OADs, however, limited evidence suggests patient satisfaction is improved among those using an ILis formulation.

Unlike type 1 DM and type 2 DM, which have HbA1c as the treatment target, post-meal glucose is the treatment target for patients with GDM. Two studies have shown that post-meal glucose levels are significantly lower in GDM patients treated with ILis than in those treated with HI. The rates of overall hypoglycemia and HbA1c levels were similar in GDM patients treated with ILis, compared to HI. There is uncertainty, however, about the utility of these outcomes for this population.

Economic Review

Methods: Economic studies compared short-acting insulin analogues with conventional HI.

Results: Five economic studies were included: two cost comparisons and three willingness-to-pay (WTP). Two WTP studies included a cost-benefit analysis (CBA). All studies compared ILis (or Mix25) with HI (or HI 30/70). The two cost comparisons found no significant difference in total health-care payer costs between treatments. The higher pharmacy cost incurred with ILis was offset by the lower hospitalization cost. The European WTP study showed that patients would pay an extra C\$179 per month for Mix25 over HI 30/70. In the Australian WTP-CBA study, the net annual benefit of replacing HI with ILis was C\$352.90. The Canadian WTP-CBA study surveyed taxpayers, of whom 6% were DM patients, and found the net benefit of replacing HI 30/70 with Mix25 was C\$255.36 per year.

Health Services Impact

The number of people with DM in Canada has been increasing. All type 1 DM patients who seek care use insulin, and assuming that 10% of type 2 DM patients also use it, the estimated number of users for 1998 to 1999, 2000 to 2001, and 2003 were 164,523, 202,103, and 232,348 respectively. If increasing numbers of patients switch to short-acting insulin analogues, provincial drug plans will need to increase their budgets. If all patients switched, the budget impact over 2006 to 2008 was estimated to range from C\$1,565,574 to C\$52,882,768, depending on the province. Not all provinces were analyzed, and several assumptions were made that could limit the analysis. In terms of psychosocial outcomes such as social acceptability and ease of use, there is no evidence that insulin analogues are disadvantageous. The convenience of use provided by insulin analogues, compared to HI, may improve compliance.

Conclusion

In type 1 DM patients, treatment with ILis or IAsp significantly reduced HbA1c levels, compared to HI. The occurrence of overall and severe hypoglycemia was similar with the two treatments, but nocturnal hypoglycemia was less frequent with ILis compared with HI.

In type 2 DM patients, HbA1c levels, occurrences of hypoglycemia, and QoL were similar between those using HI and those using short-acting insulin analogues. Compared to OADs, improvements in HbA1c levels and patient satisfaction were noted among those treated with short-acting insulin analogues.

Uncertainty remains regarding the use of short-acting insulin analogues in GDM patients and pregnant women with diabetes. Two studies have shown that post-meal glucose levels are significantly reduced in GDM patients treated with ILis, compared to those treated with HI.

If users of HI switch to the more expensive insulin analogues, further increases in drug plan expenditures can be anticipated. There is evidence to suggest that these additional costs can be offset

by reductions in other health-care expenditures in a 12-month horizon. These findings are limited to study settings in the US. The available economic evidence also showed that patients preferred ILis to HI or Mix25 to HI 30/70.

High-quality long-term studies are needed to determine the benefit and harm of short-acting insulin analogues, compared to conventional insulin. Data on patient mortality and QoL are lacking. The impact on health care costs beyond 12 months is unknown.

ABBREVIATIONS

BG	blood glucose
BHI	biphasic conventional human insulin or HI Mix
BHI 30	biphasic conventional human insulin (30% HI, 70% NPH)
BIAsp	biphasic insulin aspart or aspartMix
BIAsp30	biphasic insulin aspart (30% aspart, 70% protamine insulin aspart)
BMI	body mass index
CBA	cost-benefit analysis
CI	confidence interval
CSII	continuous subcutaneous insulin infusion
d	day
DM	diabetes mellitus
DTSQ	diabetes treatment satisfaction questionnaire
FPG	fasting plasma glucose
GDM	gestational diabetes mellitus
Glib	glibenclamide (sulfonylurea)
Glim	glimepiride (sulfonylurea)
Glyb	glyburide (sulfonylurea)
HbA1c	glycated hemoglobin
HI	human insulin (conventional)
HI 30/70	biphasic conventional human insulin (30%HI, 70%NPH)
IAsp	insulin aspart
IGlu	insulin glulisine
ILis	insulin lispro
MDI	multiple daily injection
Mix25	biphasic insulin lispro (25% lispro, 75% NPL)
month	month
n	number
NPH	neutral protamine Hagedorn
NPL	neutral protamine lispro
NR	not reported
OAD	oral anti-diabetic agent
OGTT	oral glucose tolerance test
PG	casual plasma glucose
PIA	protamine insulin aspart
QoL	quality of life
RCT	randomized controlled trial
ROS	rosiglitazone
RR	relative risk
SD	standard deviation
Sfu	sulfonylurea
tx	treatment
wk	week
WBQ	well-being questionnaire
WMD	weighted mean difference
WTP	willingness to pay
y	year

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1 INTRODUCTION

1.1 Background

Diabetes mellitus (DM) comprises common metabolic disorders characterized by hyperglycemia (elevated blood glucose levels). It is a condition in which the body cannot produce enough insulin or cannot properly use the insulin that it produces. Insulin is a hormone secreted by β -cells from the islets of the pancreas in response to increased levels of glucose in the blood. Insulin helps the body's cells absorb glucose from the bloodstream so that it can be used as a source of energy.^{1,2} There are different types of diabetes (Table 1).

Table 1: Classification of diabetes	
Category	Description
type 1	body makes little or no insulin; previously classified as insulin-dependent DM (IDDM) or juvenile-onset diabetes
type 2	body makes insulin but cannot use it properly; previously classified as non-insulin dependent DM (NIDDM)
gestational diabetes mellitus (GDM)	body cannot use insulin properly during pregnancy
other	uncommon diabetic conditions, mainly associated with specific genetic defects, another disease, or drug use (e.g., genetic defects of beta cell function, genetic defects in insulin action, disease of pancreas, endocrinopathies, infections, uncommon forms of drug or chemical induced immune-mediated diabetes)

The diagnosis of diabetes is based on the criteria^{2,3} in Table 2.

Table 2: Diagnosis of diabetes	
Test	Criteria
fasting plasma glucose (FPG)	≥ 7.0 mmol/L (126 mg/dL); fasting defined as no caloric intake for at least 8 hours
casual plasma glucose (PG)	≥ 11.1 mmol/L (200 mg/dL) and symptoms of diabetes; casual signifies any time of day, without regard to interval since last meal; classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss
75 g oral glucose tolerance test (OGTT)	2-hour plasma glucose (2hPG) ≥ 11.1 mmol/L (200 mg/dL)

In the absence of symptoms, the finding of an abnormal glucose value has to be confirmed using a second test on a different day.²

DM is the seventh leading cause of death in Canada.⁴ Over 2.25 million Canadians are estimated to have diabetes. Of all diagnosed cases, 90% are type 2 DM and 10% are type 1 DM. The chronic nature of diabetes threatens many organs, and is responsible for most of the mortality and morbidity associated with the disease. The vascular complications are divided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery disease, peripheral artery disease, and cerebrovascular disease) complications. Other complications include gastroparesis, infections, and skin changes.³

The annual cost of treating diabetes and its complications is >C\$9 billion (this includes direct health care costs, and those arising from premature death and lost productivity).⁴ Type 2 DM is expected to continue to increase in Canada because of the aging population and rising obesity rates, which are recognized risk factors.

The successful management of diabetes is based on an educated and motivated patient with support from a multidisciplinary health care team. Combined with lifestyle measures such as diet modifications, weight control, and adequate exercise, medications are essential to survival for type 1 DM patients (i.e., insulin) and can assist in controlling blood glucose levels in people with type 2 DM (oral hypoglycemic agents and/or insulin) to reduce their risk of developing long-term complications.⁵ Maintaining glycemic levels near normal has been shown to reduce the risk of microvascular complications in types 1 and 2 DM.^{6,7} Medications may also be used in the primary prevention of complications, particularly cardiovascular disease, which is a cause of morbidity and mortality in diabetic patients.²

There are six classes of anti-diabetic drugs:

- sulfonylureas (including glyburide, gliclazide, glimepiride, chlorpropamide, and tolbutamide)
- biguanides (metformin)
- alpha-glucosidase inhibitors (acarbose)
- meglinitides (repaglinide and nateglinide)
- thiazolidinediones (rosiglitazone and pioglitazone)
- insulin and insulin analogues.

According to the Canadian Diabetes Association Clinical Practice Guidelines,² treatment for diabetes is aimed at the glycemic targets in Tables 3 and 4.

Targets	HbA1c Target (%)	Fasting or Pre-prandial Glucose Target (mmol/L)	2-hour Postprandial Glucose Target (mmol/L)
target for most patients	≤7	4.0 to 7.0	5.0 to 10.0
normal range*	≤6	4.0 to 6.0	5.0 to 8.0

*consider targets in normal range for patients for whom it can be achieved safely

Age (year)	HbA1c Target (%)	Preprandial Glucose Target (mmol/L)	Considerations
<5	≤9	6.0 to 12.0	extreme caution required to avoid severe hypoglycemia because of risk of cognitive impairment
5 to 12	≤8	4.0 to 10.0	targets should be graduated to child's age
13 to 18	≤7	4.0 to 7.0	appropriate for most patients
	≤6	4.0 to 6.0	consider for patients in whom it can be achieved safely

All patients with type 1 DM need insulin to stay alive. They require multiple daily injections of short-acting and an intermediate or a long-acting insulin to mimic normal insulin secretion that varies

with eating. Physiologic insulin secretion is a complicated process, with small amounts of insulin being secreted throughout the day (basal insulin) and with a significant increase in response to meals (bolus insulin). Bolus insulin is secreted mainly in response to changes in blood glucose concentration. This secretion is affected by incretins and neural control through the vagus nerve. The counter-regulatory hormones (growth hormones, cortisol, glucagons, and catecholamines) affect insulin dynamics. The amount of insulin secreted daily will depend, at least partly, on the individual's degree of insulin sensitivity or resistance.

Diabetic patients must coordinate the dosing and timing of their insulin injections with their meals and physical activity, to avoid hyperglycemia (related to insufficient insulin intake or excessive glucose ingestion) or hypoglycemia (related to excessive insulin intake or insufficient glucose ingestion). They must monitor their serum blood glucose levels to adjust the insulin dose or their caloric intake to prevent or identify episodes of hypoglycemia. Insulin is administered by subcutaneous injection into the abdomen, buttocks, upper arm, or thigh intermittently by syringe, pen-like injection device, or pump, which is known as a continuous subcutaneous insulin infusion (CSII).²

Patients with newly diagnosed type 2 DM are instructed to modify their diet and exercise to achieve a healthy weight and improve glycemic control. If these measures are insufficient, or if the degree of hyperglycemia at presentation is severe, ≥ 1 oral hypoglycemic agents or insulin can be used. The choice of agents is tailored to the individual, and depends on the comorbid conditions and underlying risk of developing hypoglycemia. Insulin is indicated for patients with type 2 DM who cannot achieve adequate glycemic control with other measures. There are many approaches to therapy for individuals with type 2 diabetes, from addition of intermediate- or long-acting insulin preparations as one dose — with or without oral hypoglycemic agents — to multiple daily insulin injection regimens and insulin pumps.² The goal of therapy should be the achievement of glycemic targets as close as possible to those in the non-diabetic population.

In patients diagnosed with GDM or those with existing diabetes who become pregnant, conventional treatment with human insulin is recommended. Most oral hypoglycemic agents cross the placenta and are not recommended during pregnancy.²

Hypoglycemia is the most common short-term adverse effect of insulin and some oral hypoglycemic agents. The more intensive glycemic targets are more of a risk for type 1 DM than type 2 DM.² If recognized early, hypoglycemia can be treated by ingestion of a carbohydrate (e.g. glucose tablets) followed by a protein and carbohydrate snack. If untreated, severe hypoglycemia can lead to confusion, coma, seizures, and death.²

The pharmacokinetic and pharmacodynamic features of conventional insulin are not always optimal, whether of animal origin (previously) or biosynthetic human origin (since the 1980s and currently prepared by recombinant DNA technology), and may cause hypoglycemia.⁸ Insulin analogues were developed to more closely mimic the natural pattern of endogenous insulin in non-diabetic individuals, i.e., rapid increase in circulating insulin levels soon after eating, with basal insulin between meals. The short-acting insulin analogues include insulin lispro (ILis), marketed as Humalog®; insulin aspart (IAsp), marketed as NovoLog® or NovoRapid®; and insulin glulisine (IGlu), marketed as Apidra.™ The long-acting insulin analogues include insulin glargine, marketed as Lantus®, and insulin detemir, marketed as Levemir®.

The registration of new pharmaceutical agents most often requires a demonstration of safety and efficacy equivalent to that of available medications (i.e., non-inferiority). Drug trials are performed before much experience with the optimal use of the agent has been acquired. The failure to demonstrate the superiority of a new agent may be impossible, until or unless it is tested after registration (high level of evidence) or through clinical experience (lower levels of evidence). This may be true of diabetes therapies, because the outcomes may depend on the blood sugar and HbA1c targets. Clinical trials rarely assess subjects' preferences or QoL as primary outcome measures. Both may be important to consider when choosing an appropriate diabetes treatment regimen.

1.2 Overview of Technology

Scientists originally isolated insulin from animal sources. In the 1980s, recombinant DNA technology allowed human insulin to be manufactured commercially. This technology made it possible to make new molecules with altered characteristics. Conventional insulin molecules tend to combine with themselves or self-associate to form dimers and hexamers that are less easily absorbed than monomers (single molecules). This is the main factor that limits the absorption of conventional human insulin.^{9,10}

To reduce the tendency for self-association, attempts were made to modify part of the insulin molecule.¹⁰ The insulin molecule is a polypeptide consisting of two chains: the A chain, with 21 amino acids, and the B chain, with 30 amino acids. The B26-30 region of the insulin molecule is not critical for its binding to the insulin receptor, but it is important for dimer and hexamer formation. Therefore, scientists focused on modifying the amino acid sequence in this part of the molecule. The development of short-acting insulin analogues was the result.^{8,11} Lis differs from conventional human insulin because the amino acid proline is substituted with lysine at position 28 and lysine with proline at position 29 of the insulin B chain. IAsp was designed by replacing the amino acid proline with aspartic acid at position 28 of the insulin B chain. In IGlu, the amino acid glutamine was replaced by lysine at position 29, and the amino acid lysine was replaced with asparagine at position 3 of the insulin B chain.

The pharmacokinetic profiles^{2,12} of conventional human insulin and the short-acting insulin analogues appear in Table 5.

Table 5: Pharmacokinetic profiles of insulin and short-acting insulin analogues			
Insulin (or Insulin Analogue) Preparation	Onset of Action (hours)	Peak Action (hours)	Duration of Action (hours)
conventional insulin (Humulin [®] -R, Novolin [®])	0.5 to 1	2 to 4	5 to 8
short-acting insulin analogue (Humalog, NovoRapid)	0.1 to 0.25	0.5 to 1.5	5
premixed conventional insulin (Humulin 70/30, Humulin 50/50)	0.5 to 1	Dual	10 to 16
premixed insulin analogues (Humalog Mix 75/25 [™] , NovoRapid Mix)	0.1 to 0.25	Dual	10 to 16

These timeframes are averages, may differ from one person to another, and in any individual from one injection to another. The variability in insulin analogues from day to day is less than that with conventional insulin preparations.^{13,14} The premixed preparations contain a short-acting insulin (or insulin analogue) and an intermediate-acting insulin (or insulin analogue) in a fixed ratio. The

premixed conventional insulin preparation contains neutral protamine Hagedorn (NPH) as the intermediate-acting insulin. The premixed insulin analogue preparation contains neutral protamine lispro or neutral protamine aspart as the intermediate-acting insulin.

ILis and IAsp are available in 10 mL vials and 3 mL cartridges. The strength in each is 100 units/mL. The cost of the insulin analogues and conventional human insulin appears in Table 6.

Health Canada issued notices of compliance for ILis (Humalog), IAsp (NovoRapid), and IGlu (Apidra) in 1996, 2001, and 2006 respectively.¹⁸⁻²⁰ The FDA approved ILis, IAsp, and IGlu for use in the US in 1996, 2000, and 2004 respectively.²¹⁻²³

Product	DIN	Package Size	Price* per Package (C\$)
Insulin analogues			
Humalog vial 10 mL, 100 units/mL	02229704	1 × 10 mL	25.14
Humalog cartridge 3 mL, 100 units/mL	02229705	5 × 3 mL	50.28
Humalog pre-filled pen 3 mL	02241283	5 × 3 mL	63.39
Humalog Mix25 cartridge 3 mL, 100 units/mL	02240294	5 × 3 mL	50.28
Humalog Mix25 pre-filled pen 3 mL	02240295	5 × 3 mL	63.39
NovoRapid vial 10 mL, 100 units/mL	02245397	1 × 10 mL	24.60
NovoRapid cartridge 3 mL, 100 units/mL	02244353	5 × 3 mL	49.23
Conventional human insulin			
Humulin R vial 10 mL, 100 units/mL	00586714	1 × 10 mL	16.72
Humulin R cartridge 3 mL, 100 units/mL	01959220	5 × 3 mL	34.67

*Prices for Humalog¹⁵ from Lilly indicate net price to wholesalers. Prices for NovoRapid¹⁶ from Novo Nordisk indicate price for all provinces excluding Québec. Prices for Humulin R from PPS® Pharma Publication.¹⁷

Tables 7 and 8 show utilization data from 2000 to 2005 for some insulin analogues and conventional human insulin in Alberta and Nova Scotia respectively.

Product	Category	2000	2001	2002	2003	2004	2005
Humalog 100 unit/mL injection (DIN 02229704)	number of persons	320	379	458	495	544	573
	quantity (units)	19,001	24,444	30,943	37,575	45,198	47,603
	expenditure (C\$)	36,601	43,457	54,917	68,235	81,830	92,568
Humalog 100 unit/mL injection cartridge (DIN 02229705)	number of persons	629	845	1,111	1,271	1,459	1,577
	quantity (units)	46,040	62,851	89,460	111,394	138,840	149,492
	expenditure (C\$)	122,986	168,958	244,731	309,367	395,315	432,734
NovoRapid 100 unit/mL injection (DIN 02245397)	number of persons	no data	no data	no data	16	40	93
	quantity (units)	no data	no data	no data	340	2,410	5,590
	expenditure (C\$)	no data	no data	no data	678	4,866	12,268
NovoRapid 100	number of	no data	no data	no data	99	363	659

Table 7: Utilization data for some insulin analogues and conventional human insulin formulation from provincial drug programs in Alberta*							
Product	Category	2000	2001	2002	2003	2004	2005
unit/mL injection cartridge (DIN 02244353)	persons						
	quantity (units)	no data	no data	no data	2,355	23,007	51,097
	expenditure (C\$)	no data	no data	no data	6,360	62,830	144,893
Humulin R 100 unit/mL injection cartridge (DIN 01959220)	number of persons	468	525	597	702	792	840
	quantity (units)	24,391	26,888	34,971	47,154	55,256	58,691
	expenditure (C\$)	45,184	50,003	66,489	83,206	105,395	120,094

*Data obtained from Alberta Ministry of Health (Chad Mitchell, Pharmaceutical Policy and Programs Branch, Alberta Health and Wellness, Edmonton: personal communication, 2006 Jan 30).

2 THE ISSUE

Insulin analogues are more expensive than conventional insulin. Because health care resources are limited, decision makers need to know if the use of analogues is justified for all or some diabetic groups. This information will help determine their status in provincial drug plans.

Table 8: Utilization data for some insulin analogues and conventional human insulin formulation from provincial drug programs in Nova Scotia*				
Product	Category	2003	2004	2005
Humalog 100 unit/mL injection (DIN 02229704)	number of persons	130	145	158
	expenditure (C\$)	42,936	46,939	53,530
Humalog 100 unit/mL injection cartridge (DIN 02229705)	number of persons	180	199	216
	expenditure (C \$)	72,379	82,335	100,695
NovoRapid 100 unit/mL injection (DIN 02245397)	number of persons	15	17	29
	expenditure (C\$)	2,766	4,154	8,231
NovoRapid 100 unit/mL injection cartridge (DIN 02244353)	number of persons	36	90	175
	expenditure (C\$)	7,369	26,168	64,104
Humulin R 100 unit/mL injection (DIN 00586714)	number of persons	1,116	1,057	947
	expenditure (C\$)	189,164	185,266	172,982
Humulin R 100 unit/mL injection cartridge (DIN 01959220)	number of persons	352	400	423
	expenditure (C\$)	74,440	99,301	107,746

*Expenditure indicates government amount paid at point of sale. Data obtained from Nova Scotia Ministry of Health (John A. Hoar, Department of Health and Pharmaceutical Services, Halifax: personal communication, 2006 Feb 8).

3 OBJECTIVES

Our objectives were to conduct a systematic review to evaluate the clinical efficacy of short-acting insulin analogues (ILis, IAsp, and IGlu), and to evaluate the economic implications of using these agents in the treatment of DM.

The objectives are accomplished by addressing the following questions.

1. What is the clinical efficacy of short-acting insulin analogues compared with conventional insulin or oral anti-diabetic agents (OADs) in the treatment of type 1, type 2, or gestational DM? What are the benefits and harms from a clinical and a patient perspective?
 - Are there subpopulations of diabetic patients (e.g., pregnant patients, patients using CSII) who may particularly benefit from treatment with insulin analogues in comparison to conventional human insulin or OADs?
 - What are the benefits and harms of combining insulin analogues with OADs, compared to combining conventional human insulin with OADs in the treatment of type 2 DM, from a clinical and a patient perspective?
 - Compared to conventional human insulin, do insulin analogues produce different clinical effects when used at the onset of the disease versus later, for patients with type 2 DM?
2. What is the evidence on the cost-effectiveness of using insulin analogues in the treatment of type 1 or type 2 DM?

4 CLINICAL REVIEW

4.1 Methods

A protocol for the systematic review was written a priori.

4.1.1 Literature search strategy

We obtained published literature by cross-searching MEDLINE[®], BIOSIS Previews[®], PASCAL, and EMBASE[®] databases from 1990 onwards, with no language restrictions. Because insulin analogues were approved for use starting in 1996, we limited our search to literature published since 1990. A broad search strategy with appropriate descriptors and keywords was used in combination with a filter to restrict results to controlled trials, meta-analyses, and systematic reviews. We ran a parallel search on PubMed and the Cochrane databases (Appendix 1).

The original search was performed in August 2005. We established regular alerts on MEDLINE[®], BIOSIS Previews[®], and EMBASE[®] databases to capture new studies until January 1, 2006, and updated searches on the Cochrane databases regularly. The last Cochrane updates for this report were performed on February 6, 2006.

Grey literature was obtained by searching the web sites of regulatory agencies, and health technology assessment and near-technology assessment agencies. Specialized databases such as the University of York NHS Centre for Reviews and Dissemination and the Latin American and Caribbean Center on Health Sciences Information were also searched. We used the Google[™] and Dogpile[®] search engines to find information on the internet. The web sites of professional associations such as the American Association of Clinical Endocrinologists, the Canadian Diabetes Association, the American Diabetes Association, and the European Association for the Study of Diabetes, and their associated conference sites were searched for additional information.

4.1.2 Selection criteria and method

a) Selection criteria

- study design: RCT
- population group: patients with DM (type 1, type 2, or GDM)
- intervention: short-acting insulin analogues (IAsp, ILis, or IGlu)
- comparator: conventional human insulin or OADs
- outcomes: glycemic control (HbA1c level and blood glucose level), hypoglycemic episodes, adverse events, mortality, QoL, and complications from diabetes.

b) Selection method

Study selection was done in two stages: screening based on title, keywords, and abstract; then full-text review of those citations identified as being potentially relevant. Two reviewers (SB, KT) independently selected trials for inclusion. Citations that were downloaded in Reference Manager 11 (bibliographic software) were exported into Microsoft® Excel® (spreadsheet software) to document the trial selection process. Differences in decisions between reviewers were resolved by consensus. For trials with multiple publications, only reports that included the outcomes of interest and had the longest follow-up were selected.

4.1.3 Data extraction strategy

Data from each included trial were extracted by two of three individuals (SB, KT, or KC) working independently and using a structured form (Appendix 2). Differences between reviewers were resolved by consensus.

4.1.4 Strategy for quality assessment

The quality of the included RCTs was evaluated using the Jadad five-point scale.²⁴ This scale rates trials on a scale of zero to five, with higher scores associated with better quality. Low quality trials (Jadad score ≤ 2) have the potential to contribute to overall increased estimates of benefit (i.e., exaggerate an intervention's effectiveness).^{25,26} The ratings are based on reporting of randomization, double blinding, and withdrawals and dropouts (Appendix 3). Information on concealment of allocation, blinding of assessors, and intention to treat analysis was also recorded.

4.1.5 Data analysis methods

We used Cochrane software Review Manager 4.2.3 to analyze data and generate forest plots. Where the quantitative pooling of results was appropriate, the random effects model was used to compute treatment efficacy. This decision depended on the statistical heterogeneity between the studies. Heterogeneity was determined using Higgins I^2 value, which indicates the extent of variation across studies due to heterogeneity rather than chance. $I^2=25\%$, 50% , and 75% indicate low, moderate, and high heterogeneity respectively. If $I^2 > 75\%$, the studies were not pooled. If $I^2=0$, then the random effects model provides the estimate that would result from a fixed effects approach. In cross-over trials, patients were counted twice for the meta-analysis because they participated in both treatment arms.

For the analyses of continuous data, when standard deviation (SD) values were not reported, they were calculated from the reported standard error ($SE=SD/\sqrt{N}$, where N =number of participants). In

trials where variances were reported but not specified as SD or standard error, they were assumed to be one or the other if the values were within the ranges reported in other trials.

For HbA1c and hypoglycemia, the negative values for WMD indicate better results with insulin analogues than conventional insulin or OADs. The WMD is statistically significant if the 95% CI excluded zero. For binary data, RR<1 indicates reduced risk with insulin analogues compared with conventional insulin or OADs, and this is statistically significant if the corresponding 95% CI excluded the value one.

The outcome data were analyzed according to the different groups of DM patients (i.e., type 1, type 2, types 1 and 2, and GDM). If RCTs including type 1 and type 2 DM patients reported outcomes for each group separately, the outcomes were considered accordingly in the type 1 or type 2 DM analysis. The trials were analyzed according to the type of short-acting insulin analogue used (i.e., ILis, IAsp, or IGlu) for each DM patient group.

4.2 Results

4.2.1 Quantity of research available

Figure 1 shows the trial selection process. A total of 841 citations were identified from the original literature search. The 706 excluded citations were mainly reviews, in vitro studies, pharmacokinetic or pharmacodynamic studies, and studies with comparisons and designs that were irrelevant for our review (e.g., modes of administration, non-randomized studies). Of the 135 potentially relevant reports, 80 were selected for inclusion. Nine reports²⁷⁻³⁵ were included from other sources (alerts and the pharmaceutical industry). Bott *et al.*³⁶ and Home *et al.*^{32,37} described the same trial but different outcomes or outcomes at different follow-up times. In two reports, Boehm *et al.*^{38,39} described the same trial, but provided outcome data for different follow-up times and different subsets of patients. There were 89 reports describing 86 unique trials.

4.2.2 Trial characteristics

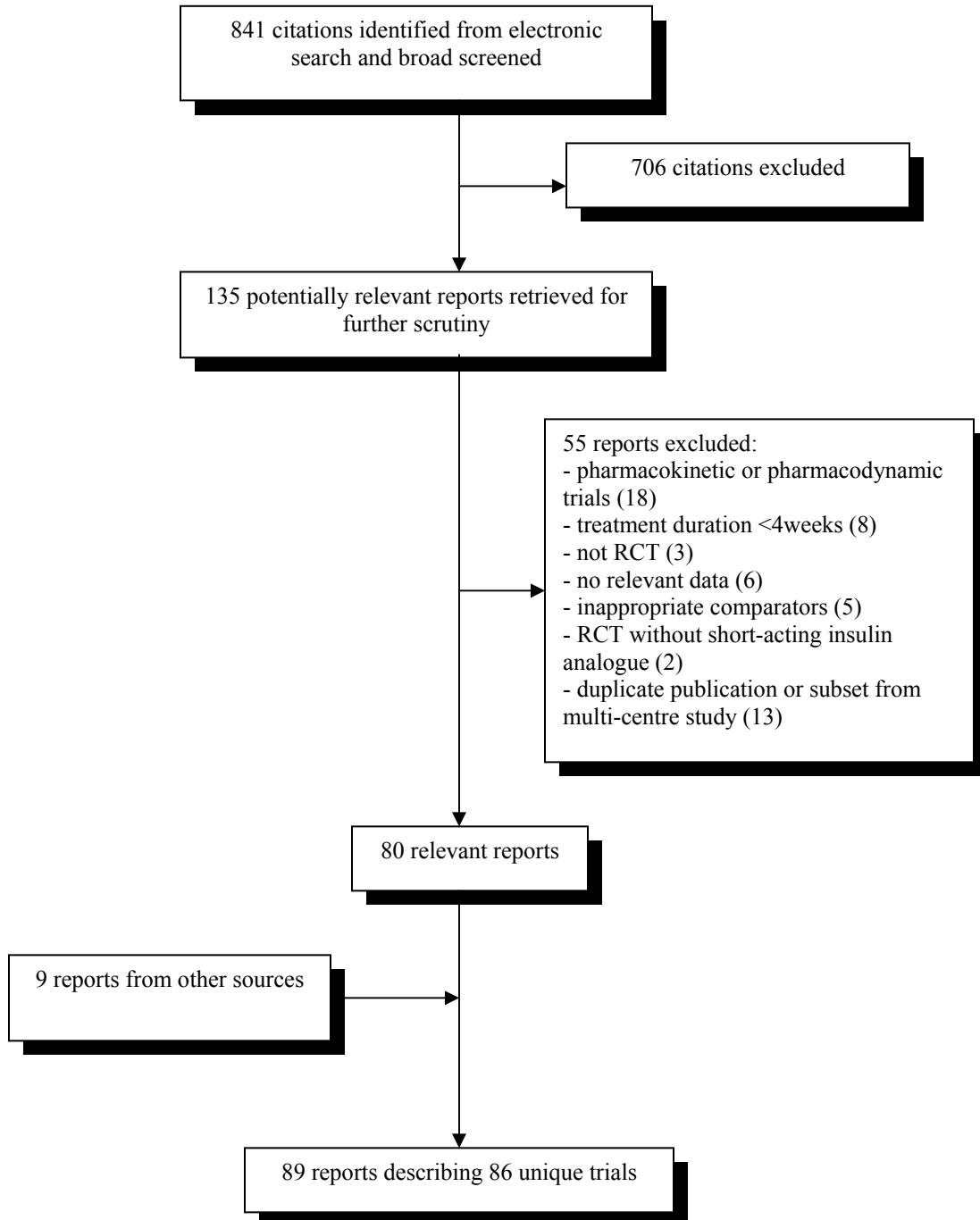
Characteristics of the RCTs comparing short-acting insulin analogues with conventional insulin or OADs in DM patients are shown in Appendices 4a to 4d.

Of all the reports, 49^{27,28,30-32,36,37,40-81} described 47 different RCTs on type 1 DM (Appendix 4a). Of these 49 reports, 44 (describing 42 RCTs) were journal articles, one was a poster, and four were conference abstracts. Of the 47 RCTs, 31 mentioned industry sponsorship, four had investigators from industry, two mentioned sponsorship from other organizations, and 10 did not report on sponsorship. Thirty-four RCTs were on ILis, 11 on IAsp, one on both ILis and IAsp, and one on IGlu. There were 29 crossover trials and 18 parallel trials. Patient numbers in the RCTs ranged between 10 and 1,070. Many of the RCTs were multicentre and multinational trials.

Twenty-seven RCT reports^{29,33-35,39,82-103} were on type 2 DM patients (Appendix 4b): one RCT report³⁹ was an extension study of an RCT³⁸ originally involving both types 1 and 2 DM patients; 24 were journal articles and three were conference abstracts; 19 mentioned industry sponsorship, three had investigators from industry, and five did not report on sponsorship. Sixteen reports were on ILis, nine on IAsp, and two on IGlu. There were seven reports on crossover trials and 20 on parallel trials. Patient numbers in the RCTs ranged between 21 and 876. Some of the trials were multi-centre and multinational.

Ten RCT reports^{38,41,104-111} were on types 1 and 2 DM patients (Appendix 4c). All 10 were journal articles: five mentioned industry sponsorship, two had investigators from industry, and three did not report on sponsorship. Nine reports were on ILIs, and one was on IAsp. Seven reports were on crossover trials, and three on parallel trials. The number of patients in the RCTs ranged between 14 and 942. Some trials were multi-centre and multinational.

Figure 1: Selection of clinical trials



Three RCT reports¹¹²⁻¹¹⁴ were on GDM patients (Appendix 4d). Two were journal articles, and one was a conference abstract. One mentioned industry sponsorship, and two did not report sponsorship. All the trials compared ILis with HI.

Most of the crossover trials did not have or did not mention a wash-out period.

The characteristics of the DM patient population in the RCTs appear in Appendices 5a to 5d. The inclusion and exclusion criteria for selecting patients for the trials appear in Appendix 6.

Of the 47 RCTs on type 1 DM patients, eight^{27,28,30,47,51,58,78,79} involved only pediatric populations (mean age ranged between eight and 15 years), and 39 involved mainly adults (mean age ranged from 23 to 48 years) (Appendix 5a). Of these 39 RCTs, 34 reported the number of males or females (one had only males, one had pregnant women, and the remaining 32 had 29% to 80% females). All 39 reported the duration of diabetes: 35 reported mean values ranging between four and 31 years, one reported as newly diagnosed (eight weeks), one reported as ≥ 1 year, one reported as ≥ 2 years, and one reported a range (two to 25 years). Of the eight reports on pediatric populations, all reported the number of males or females (for females, the range varied between 30% and 56%); and six reported the duration of diabetes (five reported mean values ranging between two and six years, and one reported >1 year).

Twenty-seven RCT reports were on type 2 DM patients (Appendix 5b). Of these reports, 25 reported mean age (between 54 and 68 years); 23 reported the number of males or females (for females, the range varied between 24% and 77%); and all 27 reported the duration of diabetes (26 reported mean values ranging between four and 16 years, and one reported ≥ 2 years).

Ten RCT reports were on types 1 and 2 patients (Appendix 5c). The mean age ranged between 32 and 64 years. The percentage of females included in these RCTs ranged between 28% and 59%. The duration of diabetes ranged between eight and 17 years.

Three RCT reports were on GDM patients (Appendix 5d). Of the three, two reported mean age (ranging between 30 and 35 years).

RCTs published as full reports were assessed for quality (Appendix 7). Of the 42 RCTs on type 1 DM patients, the mean Jadad score with SD was 1.8 ± 0.7 ; allocation concealment was adequate in two and unclear in the remainder; 52% reported intent to treat analysis. For the 24 reports on type 2 DM patients, the mean Jadad score with SD was 2.0 ± 0.6 ; allocation concealment was unclear in all, and 75% reported an intent to treat analysis. For the 10 reports considering types 1 and 2 DM patients, the mean Jadad score with SD was 1.8 ± 0.8 ; allocation concealment was unclear in all; 40% reported intent to treat analysis. For both reports on GDM patients, the Jadad score was 2, allocation concealment was unclear; neither reported intention to treat analysis.

4.2.3 Data analyses and synthesis

Because of incomplete reporting of data, we could not include all trials in the meta-analyses to derive summary estimates. For continuous data, RCTs could be pooled only if they reported SD values, or contained enough data to enable SD to be calculated. Most trials reported final values as opposed to change from baseline values at the end of treatment. Therefore, the analyses were performed with the final values. Summary estimates (WMD or RR) were computed using the fixed effects or random effects model. When heterogeneity was present, the random effects model was used. When there was

no heterogeneity (as indicated by Higgin’s $I^2=0\%$), the results obtained with the fixed and random effects model were similar. The results reported here were obtained using the random effects model. Pooling to derive summary estimates was not undertaken if $I^2 >75\%$. In crossover trials, patients were counted twice for the meta-analysis because they participated in both treatment arms.

a) HbA1c

Details of the HbA1c data for type 1, type 2, types 1 and 2, and GDM appear in Appendices 8a to 8d.

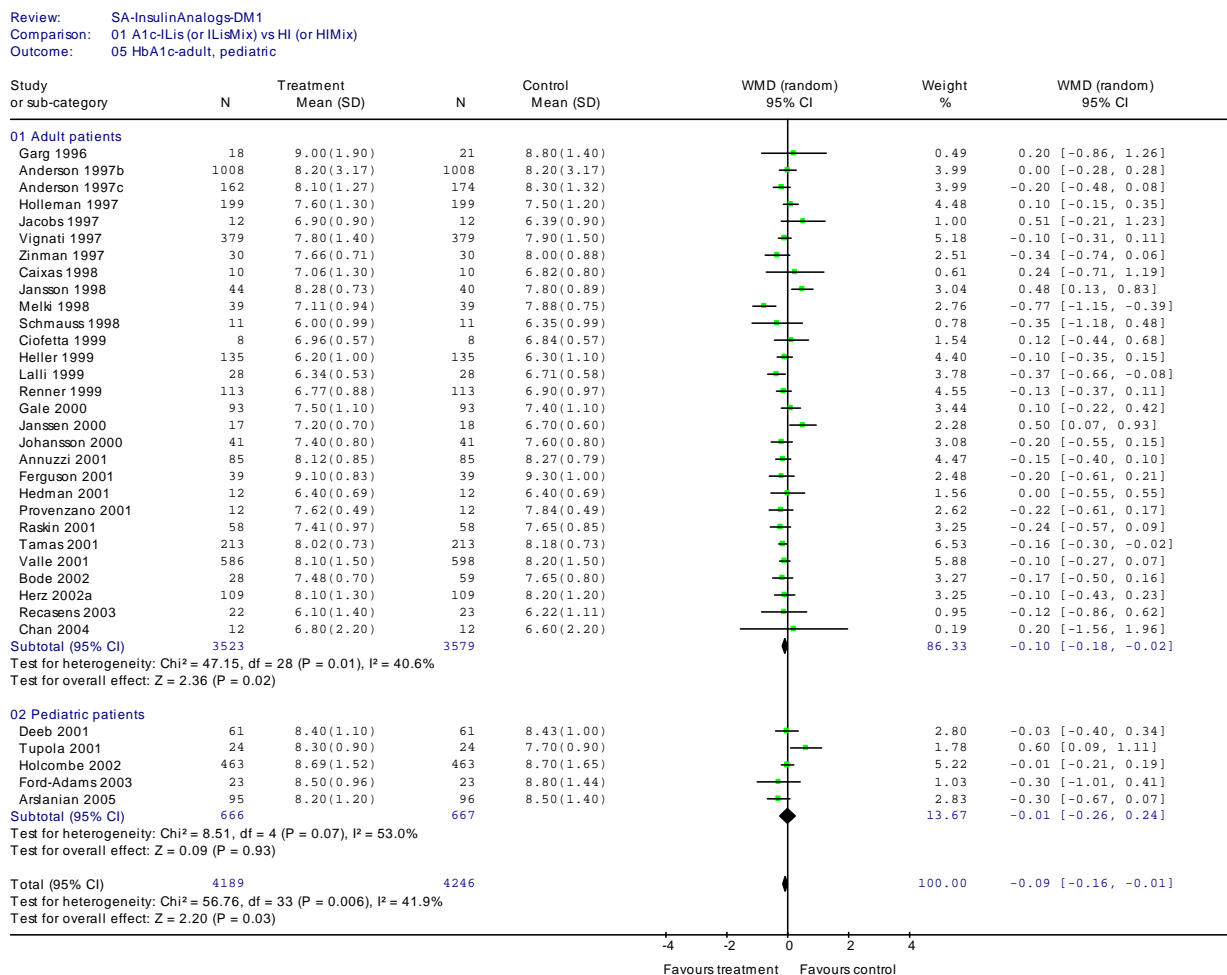
Type 1 DM: Results for the 41 RCTs that had HbA1c data on type 1 patients, which could be put through a meta-analysis, appear in Table 9. Of these, 33^{30, 40,41,44,45,47,50-54,56-59,62,64-67,69,71,72,74-77,79-81,104,111,115} used ILis, and seven^{30,32,43,49,55,61,73} used IAsp. One RCT⁴² compared ILis versus IAsp versus HI.

When all 34 RCTs — with a total of 8,435 patients and comparing ILis with HI — were pooled, the HbA1c level was found to be lower with ILis than with HI (Figures 2 and 3). This difference was small but statistically significant [WMD (95% CI)=-0.09 (-0.16, -0.01)]. The RCTs were grouped according to four criteria: treatment duration ≤ 3 months or >3 months, crossover or parallel design, drug administration by multiple daily injection (MDI) or CSII, and pediatric or adult patients. Each group was analyzed separately. The differences in HbA1c levels between treatments with ILis versus HI were significant for trials having a treatment duration >3 months, for adult patients, and for patients using CSII. The WMD (95% CI) values were -0.11 (-0.24, -0.01); -0.10 (-0.18, -0.02); and -0.28 (-0.45, -0.12) for trials with >3 month treatment duration, for adult patients, and for CSII patients respectively. The forest plots of the analyses by group (adult, pediatric, CSII, and MDI) appear in Figures 2 and 3 respectively. For pediatric patients, the reduction in HbA1c levels with ILis or HI was not significantly different [WMD (95% CI)=-0.01 (-0.26, 0.24)]. There was no significant difference in HbA1c between the two treatments for the remaining groups. The extent of variation among the RCTs is indicated by the I^2 values (Table 9).

Comparison	Category	Number of Trials	Number of Patients*	Random Effects Model	
				WMD (95% CI)	Heterogeneity I^2
ILis (or ILisMix) versus HI (or HIMix)	all	34	8,435	-0.09 (-0.16, -0.01)	41.9%
	≤ 3 month	22	6,051	-0.07 (-0.17, 0.03)	46.7%
	>3 month	12	2,384	-0.11 (-0.24, -0.01)	36.3%
	crossover	22	5,710	-0.09 (-0.19, 0.00)	34.2%
	parallel	12	2,725	-0.07 (-0.21, 0.06)	55.4%
	CSII	7	671	-0.28 (-0.45, -0.12)	31.2%
	MDI	27	7,764	-0.04 (-0.12, 0.04)	35.2%
	adult	29	7,102	-0.10 (-0.18, -0.02)	40.6%
	pediatric	5	1,333	-0.01 (-0.26, 0.24)	53.0%
IAsp (or IAspMix) versus HI or (HIMix)	all	8	2,948	-0.14 (-0.22, -0.07)	0%
	CSII	2	147	-0.31(-0.54, -0.08)	0%
	MDI	6	2,801	-0.12 (-0.20, -0.04)	0%

*in crossover trials, patients counted twice because they participate in all treatment arms and act as their own control.

Figure 2: HbA1c in type 1 DM patients in RCTs comparing ILis with HI by patient group (adult, pediatric)



When all eight RCTs^{30,32,42,43,49,55,61,73} — with a total of 2,948 patients and comparing IAsp with HI — were pooled, the HbA1c level was found to be lower with IAsp compared with HI (Figure 4). This difference was small but statistically significant [WMD (95% CI)=-0.14 (-0.22, -0.07)]. When the RCTs were grouped according to drug administration (MDI or CSII), the differences were significant [WMD (95% CI)=-0.12 (-0.20, -0.04) and -0.31 (-0.54, -0.08) for MDI and CSII respectively].

There was no heterogeneity across trials (I²=0%).

One RCT,³¹ with 564 patients and comparing IGlu with HI, showed no significant difference in HbA1c levels [WMD (95% CI)=0.10 (-0.06, 0.26)].

In summary, type 1 patients treated with ILis or IAsp had lower HbA1c levels than those treated with HI. This difference was small (between -0.09 to -0.14) but significant. The difference was more pronounced (between -0.28 to -0.31) in patients using CSII.

Figure 3: HbA1c in type 1 DM patients in RCTs comparing ILis with HI by mode of drug administration (CSII, MDI)

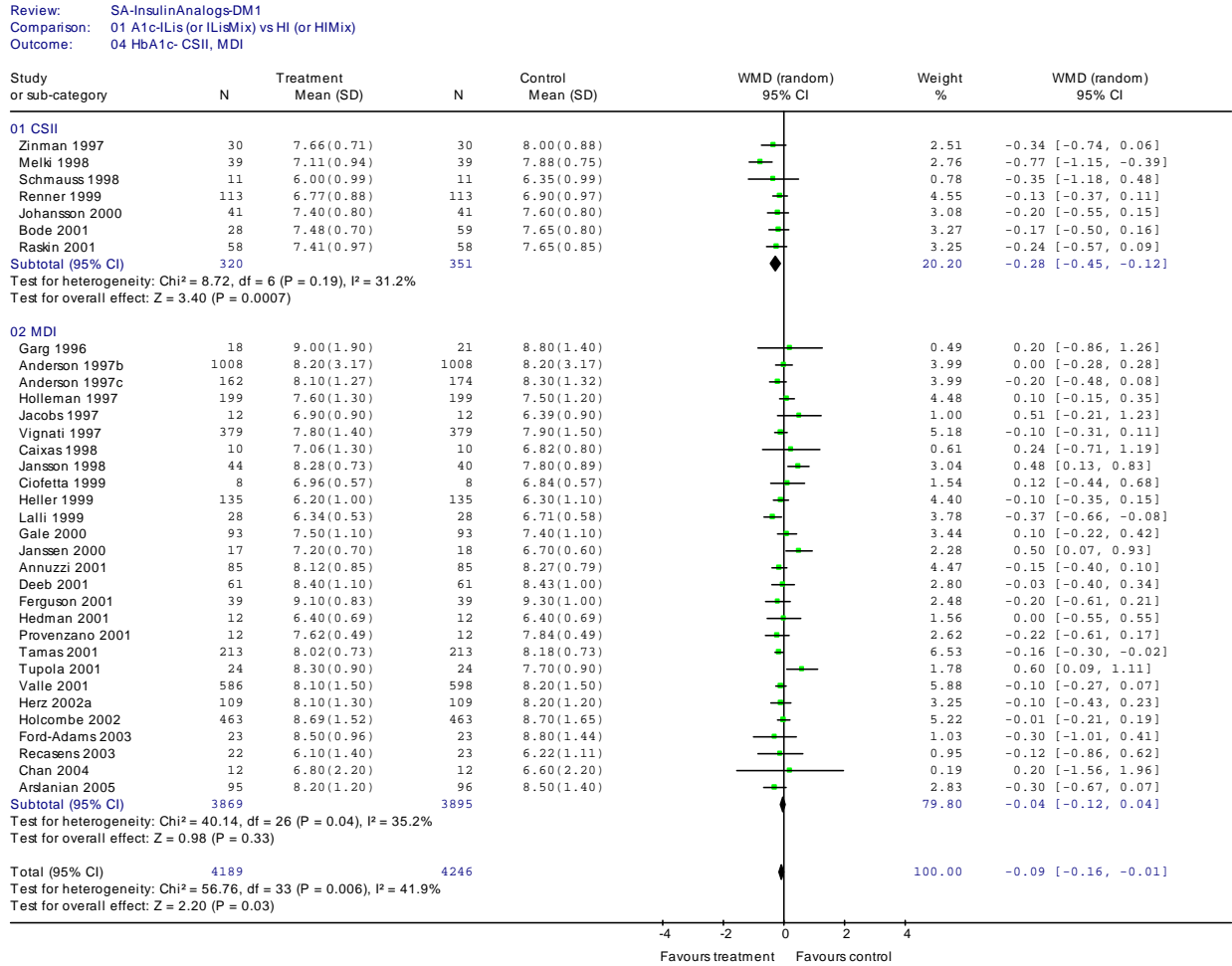
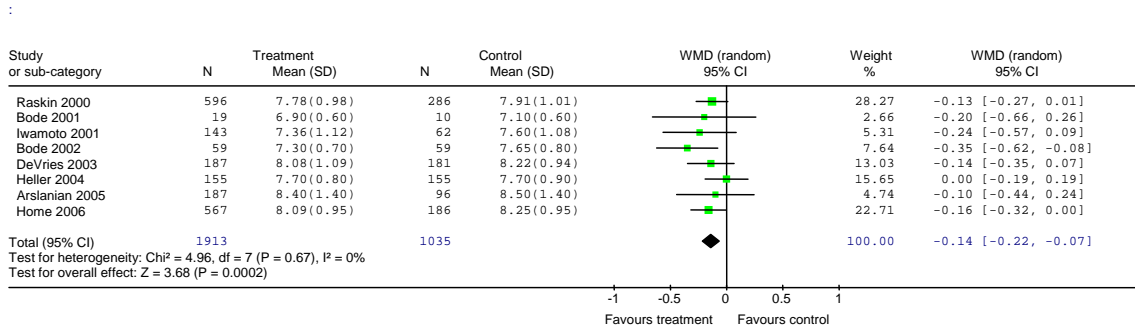


Figure 4: HbA1c in type 1 DM patients in RCTs comparing IAsp with HI



Type 2 DM: Of 12 trials examining the treatment effects of ILis and HI on HbA1c levels in type 2 diabetic patients, 10,^{41,82,83,96,101-104,107,111} with a total population of 2,844, could be pooled. Subgroup analysis included treatment duration ≤ 3 months versus >3 months and crossover versus parallel design.

The WMD for HbA1c (95% CI) from all 10 trials, with a total of 2,844 patients, was -0.11 ($-0.22, 0.00$), indicating no significant differences between ILis and HI treatments (Figure 5). There was no statistical heterogeneity across trials ($I^2=0\%$). There were two trials^{83,104} with a study duration of ≤ 3 months. The pooled results showed no statistically significant differences between treatments. The WMD of pooled data from eight trials^{41,82,96,101-103,107,111} with treatment duration >3 months showed a slight difference in favour of ILis, whereas six trials^{83,96,103,104,107,111} with crossover design and four trials^{41,82,101,102} with parallel design showed no significant differences between treatments. Thus, patients with type 2 DM on ILis or HI therapy had similar levels of HbA1c (Table 10).

Figure 5: HbA1c in type 2 DM patients in RCTs comparing ILis with HI

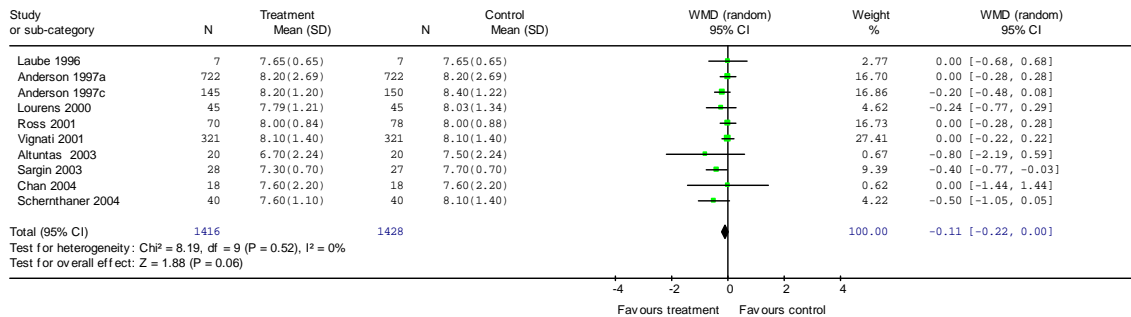


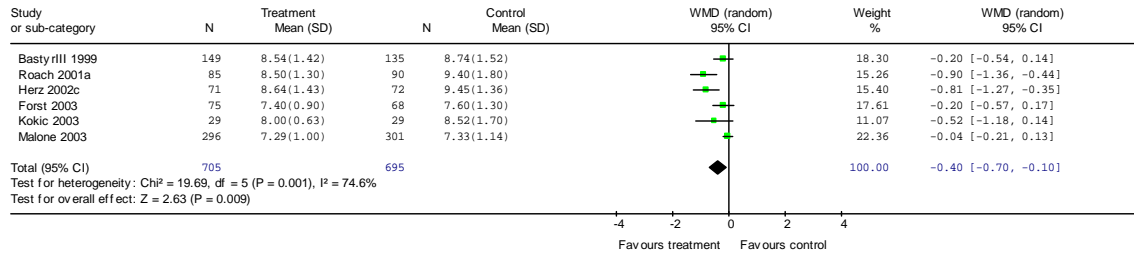
Table 10: HbA1c for type 2 DM

Comparison	Category	Number of Trials	Number of Patients*	Random Effects Model	
				WMD (95% CI)	Heterogeneity I ²
ILis (or ILisMix) versus HI (or HIMix)	all	10	2,844	-0.11 (-0.22, 0.00)	0%
	≤ 3 month	2	1,480	0.00 (-0.27, 0.27)	0%
	>3 month	8	1,364	-0.14 (-0.27, -0.01)	6%
	crossover	6	2,306	-0.06 (-0.21, 0.09)	0%
	parallel	4	538	-0.19 (-0.39, 0.02)	20.2%
ILis versus Sfu	all	6	1,400	-0.40 (-0.70, -0.10)	74.6%
IAsp versus HI	all	6	750	-0.09 (-0.23, 0.05)	0%
BIAsp versus Sfu	all	2	239	-0.63 (-1.04, -0.22)	0%
IGlu versus HI	all	2	1,768	-0.03 (-0.18, 0.11)	65.5%

*in crossover trials, patients counted twice, because they participate in all treatment arms and act as their own control.

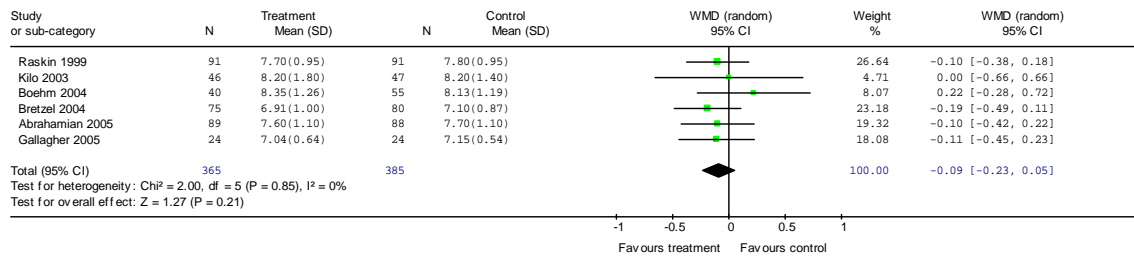
Six trials,^{85,88,92,95,97,99} with a total of 1,400 patients, examined the treatment effects of ILis and sulfonylurea (Sfu) – glibenclamide (Glib), glimepiride (Glim), glyburide (Glyb). The pooled WMD (95% CI) of these trials was -0.40 ($-0.70, -0.10$), indicating a significant reduction of HbA1c levels during ILis therapy compared with Sfu (Figure 6). There was heterogeneity across trials ($I^2=74.6\%$). Although the extent of the effect varied, the direction of effect (i.e., greater reduction in HbA1c values) was the same for all trials.

Figure 6: HbA1c in type 2 DM patients in RCTs comparing ILis with Sfu



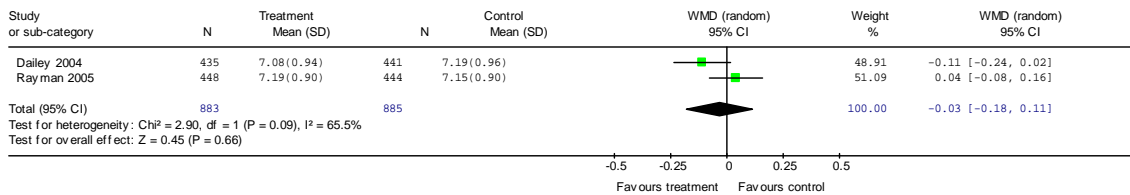
Six trials,^{33,34,39,86,89,94} with a total of 750 patients, compared the effects of treatments with IAsp [or biphasic insulin aspart or aspart Mix (BIAsp)] and HI (or biphasic conventional human insulin). The pooled WMD (95% CI), which was -0.23 ($-0.23, 0.05$), showed no significant differences (Figure 7). There was no heterogeneity across trials ($I^2=0\%$).

Figure 7: HbA1c in type 2 DM patients in RCTs comparing IAsp with HI



Two trials,^{35,98} with a total of 239 patients, compared the treatment effects of BIAsp and a Sfu. The pooled WMD (95% CI), which was -0.63 ($-1.04, -0.22$), showed a significant reduction in HbA1c levels during BIAsp therapy compared to Sfu. There was no heterogeneity across trials ($I^2=0\%$). Two other trials,^{29,87} with a total of 1,768 patients, compared the effects of treatment with IGlu and HI. The pooled WMD (95% CI), which was -0.03 ($-0.18, 0.11$), showed no significant differences (Figure 8). There was heterogeneity across trials ($I^2=65.5\%$).

Figure 8: HbA1c in type 2 DM patients in RCTs comparing IGlu with HI



There was no evidence showing significant differences in HbA1c levels for type 2 DM between ILis and HI, between IAsp and HI, or between IGlu and HI therapies. Type 2 patients with ILis therapy had significantly lower HbA1c levels than with Sfu therapy. BIAsp therapy significantly lowered HbA1c levels compared with a Sfu.

Types 1 and 2 DM: Of the 10 RCT reports in which the study population consisted of types 1 and 2 patients, five^{38,104,107,108,110} reported HbA1c data for combined type 1 and type 2 patients. Of these five, four^{104,107,108,110} compared ILis with HI in 378 patients, and one³⁸ compared IAsp with HI in 291 patients.

The HbA1c levels were lower with ILis and IAsp compared with HI, but the differences were not statistically significant. The WMD (95% CI) were -0.04 ($-0.37, 0.28$) and -0.01 ($-0.18, 0.16$) for ILis and IAsp respectively.

GDM: Of the three RCT reports¹¹²⁻¹¹⁴ on GDM patients, two^{113,114} reported HbA1c data. The two compared ILis with HI in 91 patients. The HbA1c level was higher with ILis treatment compared with HI, but the difference was not statistically significant. The WMD (95% CI) was 0.06 ($-0.11, 0.23$).

b) Blood Glucose

Investigators reported blood glucose data in two formats, as an eight-point blood glucose profile or as pre- and postprandial blood glucose levels (Appendices 9a to 9f).

Type 1 DM

Eight-point blood glucose profiles in type 1 patients

There are 27 trials^{30,42,45,47,48,50,52,56-59,62,64,65,67,69,70,74-76,78-81,109,111,115} comparing the effect of ILis and HI on the eight-point blood glucose profiles in patients with type 1 diabetes. Treatment with ILis significantly lowered blood glucose concentrations post-breakfast, post-lunch, and post-dinner in 19^{45,47,48,52,56,58,59,64,65,67,69,70,75,76,80,81,109,111,115} 12^{45,48,52,56,59,64,67,69,75,76,80,81} and 15^{30,45,47,48,57-59,67,69,75,76,80,81,111,115} trials respectively. Other trials did not report completely or showed no difference in blood glucose levels between ILis and HI patients at the time points. Conversely, treatment with ILis significantly increased blood glucose concentrations pre-breakfast, pre-lunch, pre-dinner, and at night in four^{45,52,58,79} two^{52,109} five^{45,52,58,59,62} and five^{42,45,50,58,78} trials respectively. Roach *et al.*¹⁰⁹ showed that blood glucose levels pre-lunch were significantly lower in patients treated with Mix50+Mix25 (biphasic ILis) than with those treated with HI50 + HI30 (biphasic HI). Ferguson *et al.*⁵⁰ showed that blood glucose levels at night were significantly lower in patients treated with ILis, compared with those treated with HI. Other trials did not report or showed no difference in blood glucose concentrations between ILis and HI at those times.

Ten trials^{30,37,42,43,49,55,60,61,73,77} compared the effect of IAsp and HI on the eight-point blood glucose profiles in patients with type 1 diabetes. Treatment with IAsp significantly lowered blood glucose concentrations post-breakfast, post-lunch, and post-dinner in six^{37,49,55,61,73,77} four^{37,49,60,73} and eight^{30,37,42,49,55,60,73,77} trials respectively. Other trials did not report completely or showed no difference in blood glucose levels between IAsp and HI at those times. For pre-breakfast and pre-dinner, Heller *et al.*,⁵⁵ Home *et al.*,³⁷ and Raskin *et al.*⁷³ showed a higher blood glucose level for IAsp than HI treatment. Other trials did not report or showed no difference in blood glucose concentrations between IAsp and HI at those times. Bode *et al.*⁴² and Heller *et al.*⁵⁵ showed that IAsp-treated patients had significantly higher night-time blood glucose concentrations than those of HI-treated patients.

Garg *et al.*³¹ compared the effect on blood glucose profiles of IGlu and HI that was given pre-meal or post-meal. Levels in the IGlu pre-meal group were significantly lower than those in the IGlu post-meal or HI group, both post-breakfast and post-dinner. No significant difference was found in post-lunch blood glucose values between IGlu and HI groups.

In summary, details of the blood glucose profile data showed that treatment with ILis or IAsp resulted in lower blood glucose levels after three meals compared with HI treatment. Blood glucose levels before meals were higher with the insulin analogues in some trials, but unchanged or lower than HI in other trials. One trial showed that IGlu lowered blood glucose post-breakfast and post-dinner, but not post-lunch, compared with HI.

Pre-prandial and postprandial blood glucose in type 1 DM patients

We derived summary estimates of pre-prandial and postprandial blood glucose levels from trials that could be pooled (Table 11).

Table 11: Pre-prandial and postprandial blood glucose for type 1 DM					
Comparison	Category	Number of Trials	Number of Patients	Random Effects Model	
				WMD (95% CI)	Heterogeneity I²
ILis (or ILisMix) versus HI (or HIMix)	fasting	4	233	-0.74 (-1.62, 0.13)	0%
	pre-prandial	3	2,014	0.27 (-0.10, 0.65)	27.5%
	1-hour postprandial	2	2,074	-1.06(-1.60, -0.52)	0%
	2-hour postprandial	6	2,210	-1.25 (-1.70, -0.79)	40.8%

Fasting and pre-prandial blood glucose levels were reported in four^{30,44,53,76} and three trials^{40,45,69} respectively. There was no statistically significant difference between ILis and HI treatments, except in the trial by Ciofetta *et al.*,⁴⁵ which showed significantly higher pre-prandial blood glucose levels in the ILis group than in the HI group. The WMD (95% CI) values for fasting and pre-prandial blood glucose were -0.74 (-1.62, 0.13) and 0.27 (-0.10, 0.65) respectively. The respective I² values were 0% and 27.5%, indicating no and little heterogeneity.

Seven trials^{40,44,45,68,69,72,76} compared the rise of postprandial blood glucose levels in patients receiving HI and ILis. The rise was significantly lower during treatment with ILis than with HI in six trials.^{40,45,68,69,72,76} One trial⁴⁴ showed no difference. The WMD (95% CI) values of one-hour and two-hour postprandial blood glucose levels were -1.06 (-1.60, -0.52) and -1.25 (-1.70, -0.79) respectively. The respective I² values were 0% and 40.8%, indicating no and some heterogeneity.

In conclusion, ILis therapy resulted in lower postprandial blood glucose levels, but showed similar fasting and pre-prandial blood glucose levels as HI.

Type 2 DM

Eight-point blood glucose profiles in type 2 DM patients

Eight trials^{82,96,100-103,109,111} compared the effects of ILis (or ILis mix) and HI (or HI mix) on the eight-point blood glucose profiles of patients with type 2 diabetes. In these trials, the blood glucose concentrations post-breakfast, post-lunch, and post-dinner of ILis-treated patients were significantly lower or not significantly different compared to those of HI-treated patients. For pre-meals, bedtime, and night-time blood glucose levels, there was heterogeneity between trials. Altuntas *et al.*⁸² showed that blood glucose levels were lower with ILis. Lourens *et al.*⁹⁶ and Vignati *et al.*¹¹¹ showed no significant differences between treatments at those times.

Four trials^{84,92,97,99} compared the effect of ILis and an OAD on the eight-point blood glucose profiles. ILis treatment significantly lowered blood glucose concentrations post-breakfast, pre-lunch, post-lunch, pre-

dinner, and post-dinner compared with the OAD. The pre-breakfast blood glucose level was higher with ILis than the OAD treatment in one trial,⁸⁴ but lower^{92,99} or not significantly different in the others.⁹⁷ Four trials^{33,34,89,93} on IAsp (BIAsp) versus HI and two^{35,98} on IAsp (BIAsp) versus Glib (an OAD from the sulfonylurea class) showed a significantly lower or no different blood glucose profile in the IAsp (BIAsp) group compared with the HI or Glib group.

Overall, patients with type 2 DM treated with ILis had lower blood glucose levels post-meals than those treated with an OAD. The differences in blood glucose levels between ILis and OAD patients pre-meals, at bedtime, and at night varied among trials. There was limited and inconclusive evidence for blood glucose profiles in patients treated with IAsp versus HI or ILis versus HI.

Pre-prandial and postprandial blood glucose levels in type 2 DM patients

One trial⁸³ reported pre-prandial and two^{83,91} reported postprandial blood glucose levels in type 2 patients treated with ILis or HI. The pre-prandial blood glucose levels were higher,⁸³ while the postprandial blood glucose levels were significantly lower^{83,91} with ILis compared with HI therapy. Gallagher *et al.*⁸⁹ showed that postprandial blood glucose levels were significantly lower with IAsp compared with HI therapy. Roach *et al.*⁹⁹ showed that patients treated with Mix25 had lower fasting and postprandial blood glucose levels than patients treated with the maximum dose of Glyb (an OAD from the sulfonylurea class).

Raz *et al.*⁹⁸ reported higher reductions in pre-prandial and postprandial blood glucose levels with BIAsp + rosiglitazone (Ros) (an OAD from the thiazolidinediones class) therapy, compared with Glib + Ros therapy; although it was not statistically significant. In another trial, Raz *et al.*³⁵ showed that BIAsp + pioglitazone (Pio) (another OAD from the thiazolidinediones class) therapy, resulted in lower fasting blood glucose levels than Glib + Pio therapy.

In summary, patients with type 2 DM treated with insulin analogues (ILis or IAsp) had a better control of postprandial blood glucose levels compared with conventional therapy such as HI or with OADs such as sulfonylurea. No conclusive evidence was obtained for fasting and pre-prandial blood glucose levels.

Types 1 and 2 DM

Eight-point blood glucose profiles in types 1 and 2 DM patients

Boehm *et al.*³⁸ and Roach *et al.*¹⁰⁸ reported eight-point blood glucose profiles in types 1 and 2 patients treated with BIAsp30 versus HI30 and ILis versus HI respectively. Both trials showed that blood glucose levels post-breakfast, pre-lunch, post-dinner, and at bedtime were significantly lower with insulin analogue treatment compared with HI. No significant treatment differences were noted for other times.

Pre-prandial and postprandial blood glucose levels in types 1 and 2 DM patients

The trials by Howorka *et al.*¹⁰⁵ and Skrha *et al.*,¹¹⁰ with study populations consisting of mixed types 1 and 2 patients, showed no differences between ILis and HI treatments. The rise of postprandial blood glucose levels was significantly lower in the ILis group versus the HI group in the Howorka *et al.* trial,¹⁰⁵ but Skrha *et al.*¹¹⁰ found no significant differences.

GDM

Pre-prandial and postprandial blood glucose levels in GDM patients

The fasting, pre-prandial and postprandial blood glucose levels of GDM patients treated with ILis and HI were from two trials.^{113,114} There were no differences in results for pre-prandial blood glucose

levels. Total one-hour postprandial blood glucose levels of patients treated with ILis were significantly lower than those of patients treated with HI.^{113,114} Jovanovic *et al.*¹¹³ showed that patients treated with ILis had lower plasma glucose, even two or three hours after meals.

c) Hypoglycemia

Hypoglycemia is the most common adverse effect of insulin therapy (Appendices 10a to 10d).

There were variations in the reporting of hypoglycemia data. Data were expressed in different units (e.g., episodes per patient per 30 days, patients with episodes) and were sometimes categorized (e.g., overall, severe, nocturnal). The definition of hypoglycemia varied between trials (Appendix 11a to 11d). We analyzed the data on the rate of overall hypoglycemia, severe or major hypoglycemia, and nocturnal hypoglycemia. When hypoglycemia was expressed as an episode rate, the WMD was calculated, and when hypoglycemia was expressed in terms of number of patients having episode(s), the RR was calculated. Because of insufficient data, not all RCTs could be used to derive summary statistics.

Type 1 DM

ILis versus HI: Of the 33 trials reporting on hypoglycemia, three^{40,48,67} showed a significant reduction in the overall hypoglycemia rate with ILis therapy compared with HI. Nineteen trials reported overall hypoglycemia rates expressed as episodes per patient per 30 days. Sixteen of these trials showed no significant difference in incidence of overall hypoglycemia between the two treatments. Sensitivity analyses included adult versus pediatric patients, ≤ 3 months versus >3 months therapy, crossover versus parallel, and CSII versus MDI (Table 12, Figures 9 and 10). With high heterogeneity ($I^2 > 75\%$), the pooling of RCTs to derive summary estimates was not undertaken for adult patients, for >3 months of therapy, for parallel trials, and for MDI. Of the 19 trials, four^{47,51,58,78} had a study population consisting of pediatric patients with ages ranging from two to 18 years. The WMD (95% CI) for overall hypoglycemia was -0.38 ($-0.94, 0.18$) for pediatric patients (Figure 10), indicating no significant difference between the treatments.

Figure 9: Hypoglycemia (overall) in type 1 DM patients in RCTs comparing ILis with HI by patient group (adult, pediatric)

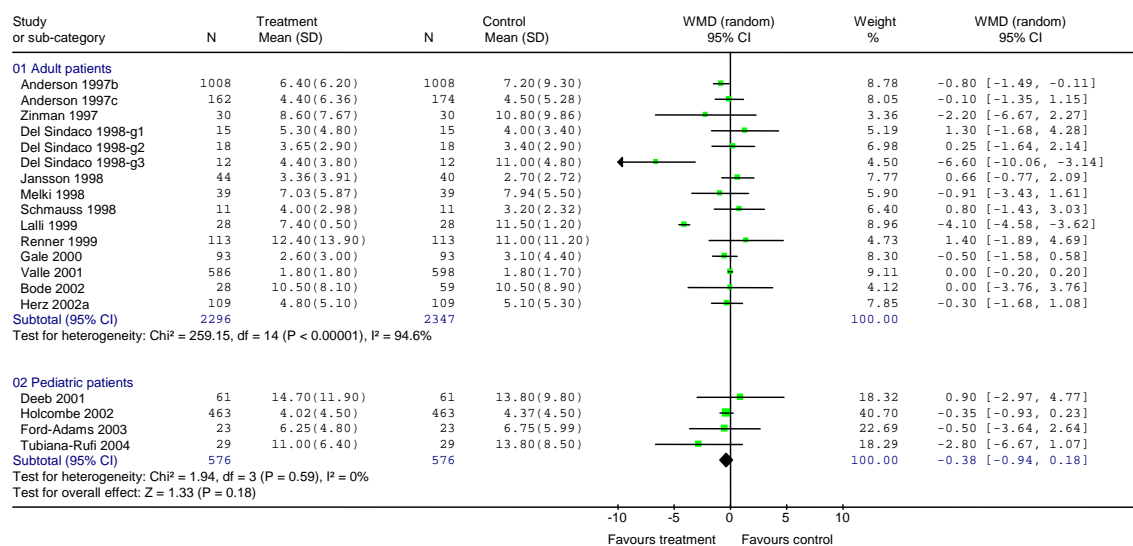
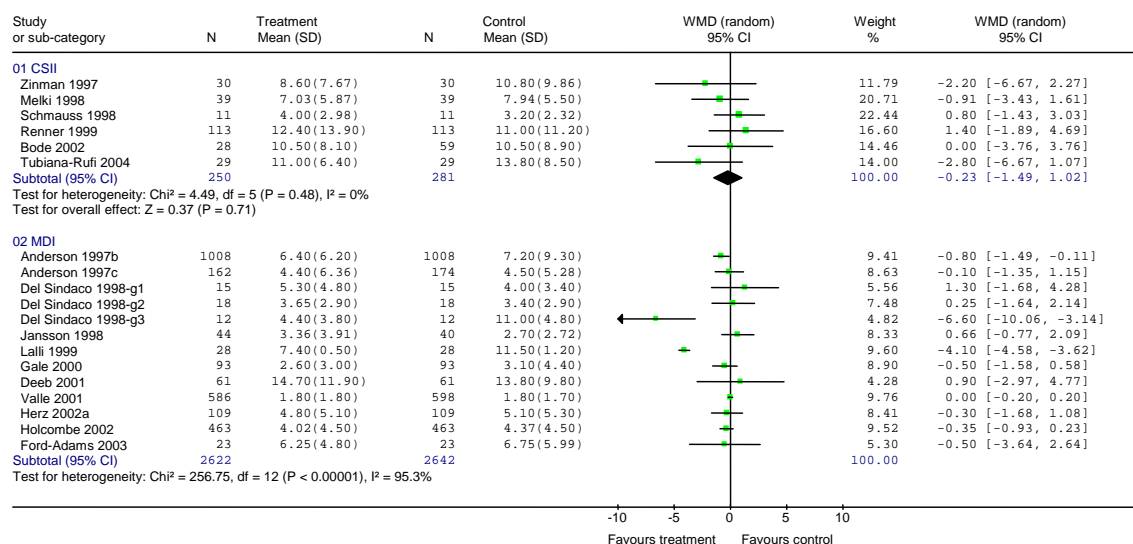
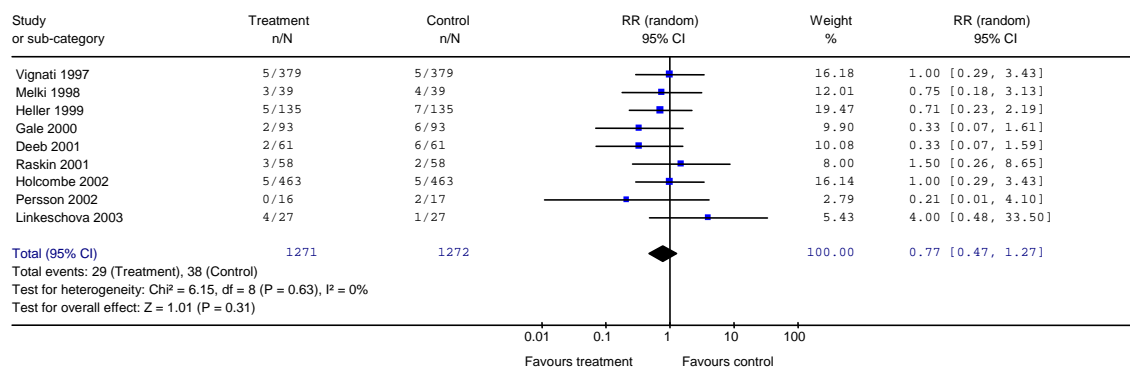


Figure 10: Hypoglycemia (overall) in type 1 DM patients in RCTs comparing ILIs with HI by mode of administration (CSII, MDI)



Of 16 trials reporting severe or major hypoglycemia, nine^{47,52,56,58,68-70,72,111} showed the actual number of patients who had an episode of hypoglycemia. Summary estimates revealed no statistically significant differences [RR (95% CI) 0.77 (0.47, 1.27)] between ILIs and HI treatments (Figure 11).

Figure 11: Relative risk of severe hypoglycemia in type 1 DM patients in RCTs comparing ILIs with HI



A subgroup analysis showed that the difference was not significant for adult or for pediatric patients [RR (95% CI) were 0.82 (0.46, 1.46) for adults and 0.64 (0.22, 1.85) for pediatric patients]. Among the 16 trials, a trial by Holleman *et al.*⁵⁹ and one by Valle *et al.*⁸⁰ showed that ILIs therapy significantly reduced severe hypoglycemia, i.e., 0.06 ($p=0.037$) versus 0.10 episodes per patient per 30 days and 13.8% ($p<0.001$) versus 18.7% of total episodes respectively. The remaining trials reported similar rates of severe or major hypoglycemia between treatments.

Of eight trials reporting nocturnal hypoglycemia, four,^{52,56,58,59} with a total population of 1,780 patients, showed significant differences between ILIs and HI treatments. Four trials,^{42,50,51,57} with a

total population of 427 patients, showed no significant differences. Among the four trials^{42,52,57,58} reporting the incidence rate of nocturnal hypoglycemia with variants, two trials,^{42,57} with a total population of 265 patients, showed no significant differences between treatments. Two trials,^{52,58} with a total population of 1,112 patients, showed significant differences. The pooled estimate from these four trials showed that the WMD (95% CI) for nocturnal hypoglycemia was -0.55 (-0.92 , -0.19), indicating that ILis significantly reduced the incidence rate of nocturnal hypoglycemia compared with HI (Table 12).

Table 12: WMD in overall and nocturnal hypoglycemia (expressed as episodes per patient per month) for type 1 DM						
Comparison	Category	Type of Hypoglycemia	Number of Trials	Number of Patients*	Random Effects Model	
					WMD (95% CI) [†]	Heterogeneity I ²
ILis (or ILisMix) versus HI (or HIMix)	all	overall	19	5,795	NP	93.1%
	adult patients	overall	15	4,643	NP	94.6%
	pediatric patients	overall	4	1,152	-0.38 (-0.94 , 0.18)	0%
	≤3 months	overall	12	4,034	-0.46 (-1.09 , 0.17)	53.9%
	>3 months	overall	7	1,761	NP	95.5%
	crossover	overall	14	4,048	-0.49 (-1.07 , 0.09)	35.1%
	parallel	overall	5	1,747	NP	98.3%
	CSII	overall	6	531	-0.23 (-1.49 , 1.02)	0%
	MDI	overall	13	5,264	NP	95.3%
ILis (or ILisMix) versus HI (or HIMix)	all	nocturnal	4	1,377	-0.55 (-0.92 , -0.19)	56.0%

*for crossover trials, patients counted twice, as they participate in all treatment arms and act as their own control; [†]with high heterogeneity (I² >75%), pooling to derive summary estimates not performed; NP=not pooled.

Overall, there was no evidence showing significant differences in the overall and severe incidence rate of hypoglycemia between ILis and HI groups. It appears that ILis therapy resulted in a lower rate of nocturnal hypoglycemia than HI therapy.

IAsp versus HI: Of 11 relevant trials, five^{27,42,43,60,61} reported overall hypoglycemia, seven^{30,32,49,55,60,73,77} reported severe or major hypoglycemia, and three^{32,42,55} reported nocturnal hypoglycemia. For overall hypoglycemia, one trial⁴² out of five showed a significant reduction of incidence rate with IAsp therapy (6.7 ± 5.4 versus 10.5 ± 8.9 episodes per patient per 30 days, $p=0.034$). Of the seven trials reporting severe or major hypoglycemia, one⁶⁰ showed that IAsp therapy resulted in a significantly lower rate than HI (20 episodes in 16 patients versus 44 episodes in 24 patients, $p<0.002$). There were no significant differences between treatments for the remaining trials.

For nocturnal hypoglycemia, two of three trials,^{42,55} with a total population of 273 patients, showed a significant reduction in incidence with IAsp therapy, 0.5 ± 0.83 versus 0.9 ± 0.97 ($p=0.004$) episodes per patient per 30 days and 0.80 versus 2.70 ($p=0.001$) episodes per patient per year respectively. Home *et al.*³² examined the long-term (three years) effects of IAsp and HI in 753 patients and found

no statistically significant differences in major nocturnal hypoglycemia between the two groups, although the percentage of patients experiencing at least one major nocturnal hypoglycemic event was lower in the IAsp group than in the HI group. Thus, patients in the IAsp and HI groups had the same incidence rate for overall, severe, and nocturnal hypoglycemia.

IGlu versus HI: Garg *et al.*³¹ compared the effects of IGlu given pre-meal and post-meal, and HI given pre-meal. There were no significant differences between treatments for symptomatic and nocturnal hypoglycemia. There was a higher rate, though not statistically significant, of severe hypoglycemia in the HI group (0.13±0.96 episodes per patient per 30 days) compared to the other two groups (0.05±0.24 and 0.05±0.23 episodes per patient per 30 days).

Type 2 DM

Of the 28 RCTs reporting hypoglycemia data for type 2 DM, 13 compared ILis with HI, six compared ILis with OADs, six compared IAsp with HI, one compared IAsp with OADs, and two compared IGlu with HI. Only trials with enough data could be included in the meta-analyses. The results appear in Tables 13a and 13b respectively.

Table 13a: WMD in hypoglycemia (expressed as episodes per patient per month) for type 2 DM					
Comparison	Type of Hypoglycemia	Number of Trials	Number of Patients*	Random Effects Model	
				WMD (95% CI) [†]	Heterogeneity I ²
ILis (or ILisMix) versus HI (or HIMix)	overall	7	2,762	-0.16 (-0.39, 0.07)	0%
	nocturnal	2	1,570	-0.24 (-0.39, -0.08)	0%
ILis versus Sulfonylurea	overall	3	912	NP	86.8%
	severe	1	597	-0.01 (-0.03, 0.01)	NA
	nocturnal	2	881	-0.06 (-0.11, -0.02)	0%
ILis versus Metformin	overall	1	81	0.40 (-0.23, 1.03)	NA

*For crossover trials, patients counted twice, as they participate in all treatment arms and act as their own control. [†]With high heterogeneity (I² >75%), pooling to derive summary estimates not performed. NA=not applicable, NP=not pooled.

Table 13b: Relative risk of hypoglycemia in type 2 DM					
Comparison	Type of Hypoglycemia	Number of Trials	Number of Patients*	Random Effects Model	
				RR (95% CI) [†]	Heterogeneity I ²
ILis or ILisMix versus HI or HIMix	overall	3	384	1.24 (0.90, 1.71)	0%
	severe	2	1,622	0.43 (0.08, 2.37)	0%
	nocturnal	1	178	1.63 (0.71, 3.73)	NA
ILis versus sulfonylurea	overall	2	315	NP	90.9%
IAsp (or IAspMix) versus HI or (HIMix)	overall	3	676	1.02 (0.87, 1.20)	0%
	severe	1	218	0.32 (0.09, 1.07)	NA
	nocturnal	1	93	0.65 (0.28, 1.53)	NA
IAsp versus sulfonylurea	overall	1	184	2.24 (1.28, 3.91)	NA
IGlu (or IGlu Mix) versus HI (or HI Mix)	overall	1	812	0.95 (0.85, 1.08)	NA
	severe	2	1,704	0.67 (0.24, 1.86)	45.4%
	nocturnal	2	1,704	0.77 (0.57, 1.03)	47.6%

*For crossover trials, patients counted twice, as they participate in all treatment arms and act as their own control. [†]With high heterogeneity (I² >75%), pooling to derive summary estimates not performed. NA=not applicable; NP=not pooled.

ILis versus HI: Seven RCTs^{41,83,91,96,101,102,111} involving 2,762 patients and reporting overall hypoglycemia as episodes per patient per 30 days were pooled. The rate of overall hypoglycemia was less for ILis compared with HI, but the difference was not significant (Figure 12). The WMD (95% CI) was -0.16 ($-0.39, 0.07$). Three RCTs,^{100,103,109} involving 384 patients and reporting overall hypoglycemia as the number of patients having episodes, were pooled. The RR was higher with ILis compared with HI, but the difference was not statistically significant. The RR (95% CI) was 1.24 ($0.91, 1.71$). On pooling data from two RCTs^{83,100} involving 1,622 patients, it was found that the RR of severe hypoglycemia was lower with ILis compared with HI, but the difference was not statistically significant (Figure 13). The RR (95% CI) was 0.43 ($0.08, 2.37$). When two RCTs^{83,109} involving 1,570 patients were pooled, there was a decrease in the rate of nocturnal hypoglycemia (episodes per patient per 30 days) with ILis compared to HI. The WMD (95% CI) was -0.24 ($-0.39, -0.08$). One RCT¹⁰⁰ involving 178 patients showed that the RR of nocturnal hypoglycemia was higher with ILis compared with HI. The difference was not significant. The RR (95% CI) was 1.63 ($0.71, 3.73$).

Figure 12: Hypoglycemia (overall) in type 2 DM patients in RCTs comparing ILis with HI

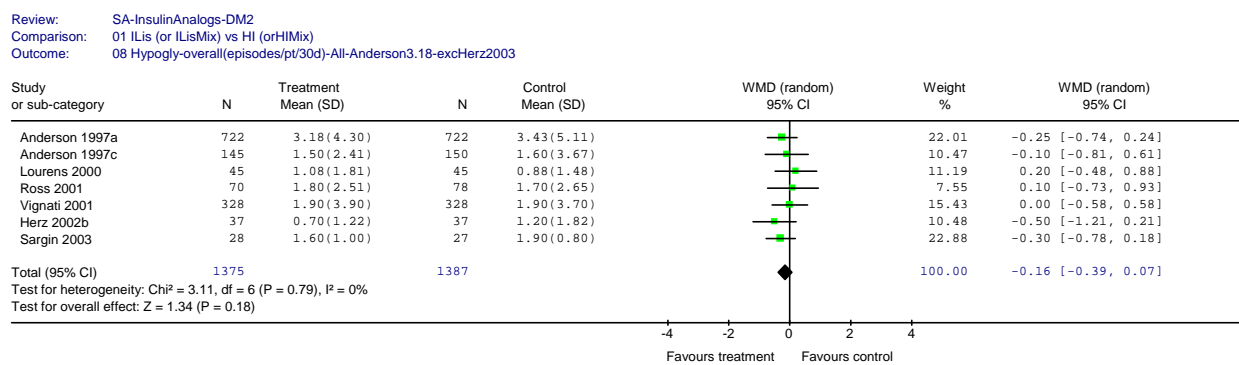
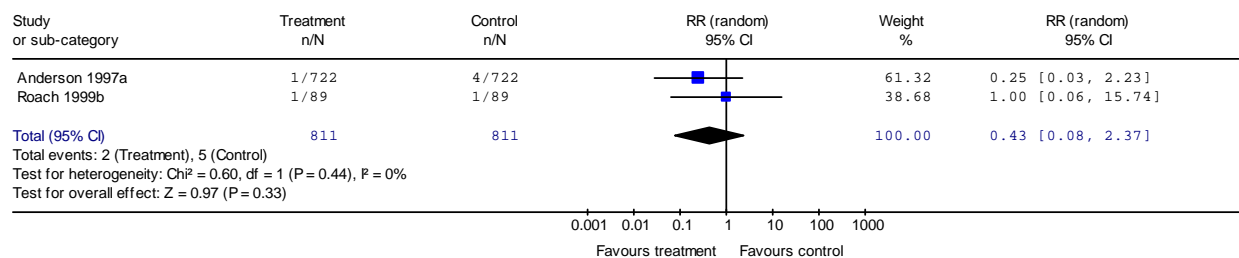


Figure 13: RR of hypoglycemia (severe) in type 2 DM patients in RCTs comparing ILis with HI



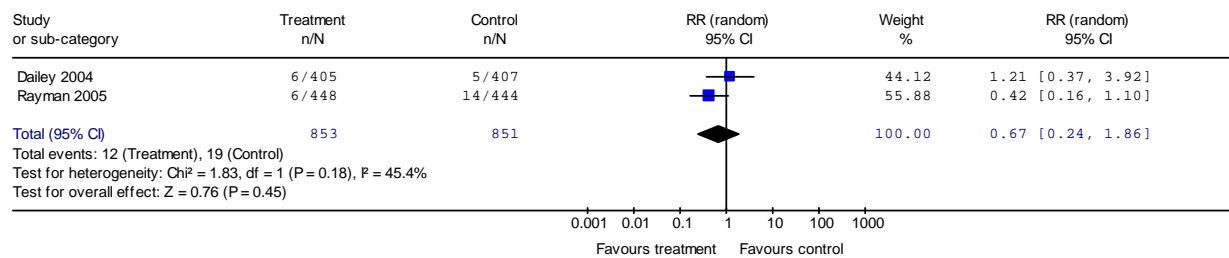
ILis versus OAD: Three RCTs,^{92,97,99} comparing ILis with Sfu, showed inconsistent results for overall hypoglycemia (episodes per patient per 30 days). The WMD (95% CI) values were 0.3 ($-0.11, 0.71$), -0.17 ($-0.35, 0.01$), and 0.25 ($0.13, 0.37$). Two RCTs,^{88,99} comparing ILis with Sfu, showed opposing results for the risk of overall hypoglycemia. The RR (95% CI) values were 0.45 ($0.14, 1.44$) and 4.32 ($2.23, 8.38$). One RCT,⁹⁷ involving 597 patients, showed that the rate of severe hypoglycemia was less with ILis than OAD, but the difference was not statistically significant. The WMD (95% CI) was -0.01 ($-0.03, 0.01$). Pooling data from two RCTs^{85,97} that involved 881 patients showed that there was a statistically significant decrease in nocturnal hypoglycemia with ILis compared with OAD. The WMD (95% CI) was -0.06 ($-0.11, -0.02$).

IAsp versus HI: Three RCTs,^{86,93,94} involving 676 patients and reporting overall hypoglycemia (as the number of patients having hypoglycemia), were pooled. There was no significant difference in the risk of overall hypoglycemia with IAsp compared with HI. The RR (95% CI) was 1.02 (0.87, 1.20). Boehm *et al.*³⁹ showed a decreased risk of severe hypoglycemia with IAsp compared with HI, but it was not statistically significant. The RR (95% CI) was 0.32 (0.09, 1.07). Two RCTs^{94,98} did not observe severe hypoglycemia with IAsp or HI therapy.

IAsp versus OAD: One RCT³⁵ with 184 patients showed the RR of overall hypoglycemia was significantly higher with IAsp than OAD. The RR (95% CI) was 2.24 (1.28, 3.91).

IGlu versus HI: Dailey *et al.*⁸⁷ showed no significant difference in the risk of overall hypoglycemia with IGlu compared with HI. The RR (95% CI) was 0.95 (0.85, 1.08). Pooling data from two RCTs^{29,87} involving 1,704 patients showed decreased risks for severe hypoglycemia (Figure 14) and for nocturnal hypoglycemia with IGlu compared with HI, but they were not statistically significant. The RR (95% CI) values were 0.67 (0.24, 1.86) and 0.77 (0.57, 1.03) respectively (Table 13b).

Figure 14: RR of hypoglycemia (severe) in type 2 DM patients in RCTs comparing IGlu with HI



There appears to be no significant difference in overall, severe, or nocturnal hypoglycemia between treatments with HI or any of the insulin analogues (ILIs, IAsp, or IGlu). In comparing the effects of insulin analogues and OADs on hypoglycemia, treatment with ILIs resulted in a statistically significant decrease in nocturnal hypoglycemia, whereas treatment with IAsp was found, in one study, to increase the risk of overall hypoglycemia relative to SFu.

Types 1 and 2

Skrha *et al.*¹¹⁰ reported overall hypoglycemia data for types 1 and 2 DM patients together. The risk of hypoglycemia was not significantly different with ILIs compared with HI therapy. The RR (95% CI) was 1.05 (0.81, 1.37).

GDM

In one RCT¹¹³ involving 42 patients, the RR for overall hypoglycemia was higher for ILIs than for HI, but it was not significant; WMD (95% CI)=1.32 (-0.44, 3.08).

d) Adverse events

Adverse events (i.e., adverse events excluding hypoglycemic episodes) that were associated with the use of conventional insulin or insulin analogues were sparsely documented in the RCT reports. Of the 49 reports on type 1 DM patients, 26 did not report on adverse events. Of the 24 reports on type 2 DM patients, six did not report on adverse events. Of the 10 reports on types 1 and 2 DM patients, seven did not report on adverse events. Of the three reports on GDM, none reported on adverse

events. When adverse events were reported, they were mostly described qualitatively. They included headache, pharyngitis, rhinitis, upper respiratory infection, flu syndrome, pain, and injection site reactions. Most were judged to be unrelated to treatment. There appeared to be no difference between the treatments with HI or the short-acting insulin analogues (Appendices 12a to 12c).

e) **Mortality**

Type 1 DM

Of the 49 relevant RCT reports, five^{32,37,49,56,59} provided mortality data, 28^{27,28,30,31,36,40,42,44,45,48,55,57,58,60-65,67,68,70,73-75,77,80,115} did not, and 16^{43,46,47,50-54,66,69,71,72,76,78,79,81} mentioned that there were no deaths (Appendix 13a). Two RCTs^{56,59} compared ILis with HI: one⁵⁹ reported one death, but did not specify the treatment arm, and the other⁵⁶ reported zero and one (0.7%) death in the ILis and HI arms respectively. Three reports^{32,37,49} described two RCTs comparing IAsp with HI. Home *et al.*³⁷ reported one (0.1%) death in the IAsp treatment arm and none in the HI arm from their RCT, which lasted six months and involved 1,065 patients. This trial³² was extended by 30 months, with 74% of the patients continuing to participate. During this period, there was no death in the IAsp treatment arm and two (1%) deaths in the HI arm. DeVries *et al.*⁴⁹ reported no deaths in the IAsp arm and two (1%) deaths in the HI arm. None of the deaths in these two RCTs were treatment-related.

Type 2 DM

Of the 27 relevant reports, 15^{29,33-35,57,83-86,88,93-95,100,101} did not provide mortality data, seven^{89-92,96,98,102} mentioned that there were no deaths, and five^{39,87,97,99,103} included mortality data (Appendix 13b). Boehm *et al.*³⁹ reported three (5.2%) and one (1.5%) deaths in the IAsp and HI treatment arms respectively. Malone *et al.*⁹⁷ reported one and zero deaths in the ILis and OAD treatment arms respectively. Dailey *et al.*⁸⁷ reported one and two deaths in the IGlu and HI treatment arms respectively. Roach *et al.*⁹⁹ and Scherthan *et al.*¹⁰³ reported one death each but did not specify the treatment arm. There was no consistency in the reporting of mortality data and in the results.

f) **Quality of life (QoL)**

Type 1 DM

ILis versus HI: Sixteen trials^{46,50,52,59,63-66,68,69,75,76,78,79,106,115} of ILis versus HI reported QoL data, which were measured using a diabetes treatment satisfaction questionnaire (DTSQ) or well-being questionnaire (WBQ) scales. All 16 trials reported full or partial DTSQ results, and seven trials^{52,63,64,66,68,69,106} reported full or partial WBQ results.

Of 16 trials conducting DTSQ, five^{50,52,64,66,68} showed no significant difference between treatments on the total scale; QoL and treatment satisfaction variables were comparable. Fergurson *et al.*⁵⁰ showed that ILis treatment was unassociated with improved QoL despite a lower incidence of severe hypoglycemia. Schmauss *et al.*⁷⁶ noted no significant differences in treatment satisfaction. All patients elected to continue with ILis because of its greater flexibility.

Five trials^{59,63,69,75,115} reported a significant dominance of ILis compared with HI on the total scale. Six trials^{46,59,65,69,106,115} showed a significant preference for ILis on the satisfaction scale, five^{59,63,69,78,115} on the convenience scale, six^{59,69,76,78,106,115} on the flexibility scale, and eight^{46,59,63,69,76,78,79,115} on the willingness-to-continue scale.

Of those trials conducting WBQ, Janes *et al.*⁶³ showed a significant preference for ILis when dealing with depression, anxiety, and energy, but not with positive well-being. Melki *et al.*⁶⁹ noted that

patients taking ILis felt better and had their glycemia best balanced. Four trials^{52,64,66,68} found no treatment effects on the total scores of WBQ.

Overall, type 1 patients prefer ILis compared with HI because of its convenience. Like other short-acting analogues, ILis has a faster onset of action than HI and can be used immediately before a meal. Patients on HI need to plan to take it half an hour to an hour before eating. In terms of well-being, there was limited evidence showing that ILis is better than HI.

IAsp versus HI: There were four trials of IAsp versus HI^{27,36,49,77} where QoL was measured using DTSQ. Three^{27,36,49} showed a significant superiority of IAsp over HI on the total scale. One trial⁷⁷ showed no significant difference between treatments, although IAsp gave more flexibility than HI. WBQ scores were not reported for these trials (Appendix 14a).

Type 2 DM

ILis versus OAD: There were four trials of ILis versus OAD and two trials of ILis versus HI, where QoL was measured using DTSQ or WBQ scales. Two trials^{92,99} of Mix25 (biphasic ILis) versus Glyb (an OAD) showed that patients using Mix25 were more satisfied and more willing to continue. In the Malone *et al.* trial,⁹⁷ most of the patients in both treatment groups were satisfied. Significantly more patients receiving Glib (an OAD) plus metformin (97%) elected to continue this treatment, compared with 92% of patients receiving Mix25 plus metformin ($p=0.016$). Patients receiving Mix25 plus metformin had fewer symptoms of hyperglycemia ($p=0.002$), greater well-being ($p=0.003$), lower thirst ($p=0.003$), and fewer trips to the bathroom at night ($p<0.001$).

ILis versus HI: Two trials by Kotsanos *et al.*¹⁰⁶ and Ross *et al.*¹⁰¹ demonstrated no significant differences between treatments on the satisfaction or flexibility scale, or on the WBQ subscales. The Bastyr *et al.*⁸⁴ trial on ILis+Glyb versus Metf+Glyb showed no significant differences between treatments on the total DTSQ scale.

Of four trials^{97,99,101,106} reporting WBQ results, two trials^{101,106} of ILis versus HI showed no significant differences between treatments. The Malone *et al.*⁹⁷ trial (Mix25 versus Glib) and the Roach *et al.*⁹⁹ trial (Mix25 versus Glyb) had higher scores on WBQ for ILis compared with sulfonylurea.

In summary, treatment with ILis compared with HI did not show any differences in terms of treatment satisfaction or patients' well-being (Appendix 14b). Treatment with Mix25 showed higher satisfaction compared with sulfonylurea in some trials,^{92,99} but not in others.^{84,97}

Types 1 and 2 DM

One trial by Chan *et al.*¹⁰⁴ and one trial by Howorka *et al.*¹⁰⁵ reported QoL in types 1 and 2 patients who were receiving treatment with ILis or HI. On the DTSQ scale, both trials showed a preference for ILis over HI on the willingness-to-continue scale. Howorka *et al.*¹⁰⁵ showed a preference for ILis over HI on every scale of DTSQ, but showed no significant differences on any subscales of WBQ (Appendix 14c).

4.3 Discussion

Of the 86 included RCTs, 47, 26, 10, and three were on type 1, type 2, types 1 and 2, and GDM patients respectively. For type 1, there were 34 RCTs on ILis versus HI, 11 on IAsp versus HI, one

on ILis versus IAsp versus HI, and one on IGlu versus HI. For type 2, there were 15 RCTs on ILis versus HI, nine on IAsp versus HI, and two on IGlu versus HI. For types 1 and 2 patients, there were nine RCTs on ILis versus HI and one on IAsp versus HI. For GDM patients, there were three RCTs on ILis versus HI.

In type 1 DM patients, treatments with ILis or IAsp resulted in lower HbA1c levels than treatment with HI. The difference was small and statistically significant. The difference was more pronounced in patients using CSII. This was evident from our meta-analyses of seven trials using ILis and two trials using IAsp. Post-meal blood glucose levels were generally lower and pre-meal blood glucose levels were generally higher with ILis compared with HI. There was no significant difference in overall or severe hypoglycemia between the two. The occurrence of nocturnal hypoglycemia was significantly lower with ILis than HI in some trials but not in others. The summary estimate from the four trials that could be pooled showed a significant reduction in nocturnal hypoglycemia with ILis compared to HI. Few trials provided mortality data. The mortality rates were not different for the different treatments. In terms of well-being, there was limited evidence indicating that ILis was better than HI. Type 1 DM patients preferred ILis compared with HI, because of its convenience of use.

In type 2 DM patients, there were no significant differences in the HbA1c levels after treatment with any of the three short-acting insulin analogues compared to treatments with HI. HbA1c levels were significantly reduced with ILis and IAsp compared with an OAD (sulfonylureas). In comparison to treatment with HI or an OAD (sulfonylureas), treatment with the insulin analogues (ILis or IAsp) achieved better control of postprandial blood glucose levels. Trials comparing insulin analogues with OAD excluded a comparison with HI. As a result, comparisons among the three treatment modalities were not possible. There was no significant difference in overall, severe, or nocturnal hypoglycemia between treatments with HI or any of the insulin analogues (ILis, IAsp, or IGlu). Mortality data were sparsely reported and inconsistent between trials. QoL data were sparse. Neither ILis nor HI produced greater satisfaction than the other in terms of treatment.

Among GDM patients, there was no significant difference in HbA1c levels or overall hypoglycemia rates with ILis compared with HI therapy. Post-meal glucose levels were lower with ILis treatment than with HI treatment.

Three reports^{6,7,116} on two studies demonstrated the importance of intensive glycemic control in delaying the onset and slowing the progression of long-term complications in diabetes patients. In the Diabetes Control and Complications Trial,⁷ 1,441 type 1 DM patients were randomly assigned to receive intensive insulin therapy or conventional insulin therapy. They were followed for a mean of 6½ years. A greater reduction in HbA1c levels was achieved with intensive therapy compared with conventional therapy. This difference was statistically significant ($p < 0.001$). Intensive therapy was found to delay the onset and slow the progression of retinopathy, nephropathy, and neuropathy in the range of 35% to 70%.

The UK Prospective Diabetes Study¹¹⁶ analyzed 3,642 type 2 DM patients for risk of microvascular and macrovascular complications. This observational study showed that a reduction in HbA1c of 1% is associated with a 37% decrease in risk of microvascular complications, a 21% decrease in the risk of death related to diabetes, and a 14% decrease in the risk of myocardial infarction. The lower HbA1c levels achieved with ILis or IAsp compared with HI in type 1 DM suggests greater benefit with these insulin analogues. Long-term data are unavailable to confirm whether this translates into fewer complications.

Any decrease in nocturnal hypoglycemia is important, as this is when it may progress undetected to dangerous levels without the patient being able to take appropriate action.¹⁰⁹ In type 1 DM, there appeared to be a decrease in nocturnal hypoglycemia with the insulin analogues, but this was inconsistent among the trials.

The insulin analogues offer greater convenience of use because they can be given immediately before meals. This is likely to result in better compliance.

This systematic review and meta-analysis has limitations. Not all reports documented data on all the outcomes of interest. This can introduce bias. It has been shown that significant results are more likely to be reported than non-significant results.¹¹⁷ Also, not all RCTs could be included in the meta-analyses of all outcomes, thereby reducing power.

The comparability of the treatment arms was difficult to determine because of the variation in treatments and dose adjustments according to patients' needs. Even in trials designed to have perfectly matched treatment arms, doses or frequency needed to be adjusted according to patients' needs. To determine comparable treatment arms, we used broad inclusion criteria. We included trials where the doses or frequencies were imperfectly matched. For example, in the study by Sargin *et al.*, which compared Iis + NPH with HI + NPH, the NPH was given at lunch and bedtime in the Iis arm, and at bedtime for the HI arm. The total dose was reported to be the same in both arms. Some RCTs had three treatment arms e.g., insulin analogue (pre-meal), insulin analogue (post-meal), and conventional insulin (pre-meal). In such cases, we considered only the pre-meal treatment arms in the meta-analysis.

There was heterogeneity among trials in some cases, as indicated by the high I^2 value. The heterogeneity may have resulted from variations in patient population and variation in methods.

During the selection of relevant trials, we discovered that there were multiple publications of the same trials. Duplicate publication can lead to biased results. For example, it has been reported that the inclusion of duplicated data in a meta-analysis of ondansetron led to a 23% overestimation of ondansetron's antiemetic efficacy (Tramer *et al.*).¹¹⁸ We have tried to exclude duplicate publications of the same trial, but this is difficult to determine. It would be useful if trials were identified using, for example, a number, so that duplicate publications could be excluded.

Allocation concealment was not mentioned in most trials. Inadequate allocation concealment can introduce bias.²⁶ Low-quality trials can contribute to increased estimates of benefit.^{25,26} Most trials were of limited quality. As a result, the results should be viewed cautiously.

Although QoL is important in the treatment of DM patients, not all trials addressed this issue. Those that addressed the issue did not always use the same QoL scale, making comparison difficult.

There was variation in the way that investigators defined hypoglycemia and in the way that they characterized the different types of hypoglycemia. In trials where hypoglycemia type was unspecified, we assumed it to be overall hypoglycemia. Overall and symptomatic hypoglycemia were put in the same group.

Because of lack of data, it was difficult to determine if there are differences in the clinical effects of insulin analogues compared with conventional human insulin, as a result of when treatment begins (at the onset of disease versus later). There was one RCT⁷⁴ involving type 1 patients who were newly diagnosed (eight weeks) with diabetes and no RCTs on newly diagnosed DM2 patients.

The patient-selection criteria for the trials were restrictive. As a result, it may not be possible to generalize the results to all DM patients. Most trials excluded patients with complications from diabetes. None of the RCTs described the effects of conventional human insulin and short-acting insulin analogues on the complications associated with diabetes.

Most of the reported RCTs lasted ≤ 6 months, targeted the non-inferiority of these analogues in comparison to conventional insulin preparations, and were performed with little or no prior experience with their use. These limitations suggest the need for trials of longer duration (≥ 1 year) targeting intensive diabetes management. Trials of longer duration are necessary to determine if there are long-term adverse events, such as progression of microvascular complications and carcinogenic effects associated with the insulin analogues.

Our systematic review included more trials than were included in published systematic reviews,¹¹⁹⁻¹²² because of broader inclusion criteria and the availability of newly published trial data. We corroborated the findings of two systematic reviews^{119,120} that concluded there was a minor benefit of lower HbA1c values in adult type 1 patients and no additional benefit in type 2 or GDM patients from treatment with short-acting insulin analogues compared with HI. Our report confirms findings in two systematic reviews^{121,122} that showed the use of short-acting insulin analogues resulted in a modest but significant reduction in HbA1c levels in type 1 DM compared with conventional insulin when used in CSII.

5 ECONOMIC REVIEW

5.1 Methods

5.1.1 Literature search strategy

We obtained published literature by cross-searching MEDLINE, BIOSIS Previews, PASCAL, and EMBASE databases from 1990 onwards, with no language restrictions. A broad search strategy with appropriate descriptors and keywords was used in combination with an economic filter to restrict the results to relevant economic records. We ran a parallel search on PubMed and the Cochrane databases (Appendix 15).

The original search was performed in August 2005. We established regular alerts on MEDLINE, BIOSIS Previews, and EMBASE databases to capture new studies until January 1, 2006 and updated searches on the Cochrane databases regularly. The last Cochrane updates were performed on February 6, 2006. We ran a search on the Health Economic Evaluations Database (HEED) using a parallel strategy. We obtained supplementary cost information by searching formularies.

5.1.2 Selection criteria and method

a) *Selection criteria*

A study was eligible for inclusion if it met the following criteria:

- study design: full economic study including cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis; or partial economic study including cost analysis, cost comparison, cost-consequence analysis
- study indications: type 1 DM, type 2 DM, or GDM

- intervention: short-acting insulin analogues including ILis, IAsp, or IGlu
- comparator: conventional HI or OADs.

Studies were excluded if only the abstracts were available. Studies published as non-English reports were excluded.

b) Selection method

Two reviewers (HL, SB) independently selected studies for inclusion. Citations downloaded in Reference Manager 11 (bibliographic software) were exported into Microsoft Excel (spreadsheet software) to document the study selection process. Differences in decisions between reviewers were resolved by consensus.

5.1.3 Data extraction strategy

The data extraction form was designed by one reviewer (HL) and tested independently by two reviewers (SB and HL) on one economic study. After comparing the results, the form was modified and used for data extraction. For the remaining studies, data were extracted by one reviewer (HL) and checked by another reviewer (SB or KT). Differences were resolved by consensus.

5.1.4 Strategy for quality assessment

We applied the 35-item *British Medical Journal* (BMJ) checklist (Appendix 16) to assess the quality of included economic studies. This tool was originally developed as a checklist for referees, authors, and journal editors to improve the quality of economic evaluations. This checklist is probably the most widely used instrument for assessing study quality. Deficiencies in quality, identified using the checklist, were used to help guide comments on the appropriateness of the methods in relation to the goal of the economic evaluation.

Two reviewers (SB and HL) piloted the BMJ checklist on one study. The results were discussed. After understanding the application of each item in the checklist, the same reviewers independently assessed each included economic study. Differences were resolved by consensus.

5.1.5 Data analysis methods

We performed a qualitative systematic review to address four questions.

- What are the main findings in the identified economic studies?
- Is there any significant variation in study results?
- What is the potential cause for variation or similarity?
- What limitations of these studies are noteworthy for decision makers?

5.2 Results

5.2.1 Quantity of research available

Figure 15 shows the study selection process. We identified 303 citations from the economic literature search, after citations that had been identified in the clinical search were removed. Of these, 296 citations were excluded. These were mainly reviews or studies with no comparisons or with comparisons that were irrelevant for our review. Of the seven potentially relevant reports, one¹²³ was selected for inclusion. Two economic studies^{124,125} were identified in the clinical search, and two^{126,127} were identified from other sources. Only five studies were identified, despite a broad search strategy and generous inclusion criteria.

5.2.2 Study characteristics

a) Study quality

The BMJ checklist-based quality-assessment results appear in Appendix 16. Some items of the checklist are inapplicable to the included studies.

We observed that the quality of the five studies was acceptable, because they met most of the applicable items of the checklist. The assessment results also showed the weakness of these studies. For instance, only one study, by Dranitsaris *et al.*,¹²⁵ described the alternative strategies. The remaining four did not detail the comparators. None of the included studies discussed productivity changes. Three studies¹²³⁻¹²⁵ did not state the quantities of resources and their unit costs separately, while two studies^{126,127} only gave unit costs. Three studies¹²³⁻¹²⁵ did not identify the study limitations adequately, nor did the authors discuss how potential limitations would affect the findings.

For the data collection section in the BMJ checklist, not all items were applicable to all studies or study performance. This could be because of study quality or study heterogeneity. None of the studies discussed the relevance of productivity changes to the study question.

In the last section of the checklist (Analysis and Interpretation of Results), the studies had similar assessment results.

b) Study design

Of the five included economic studies:¹²³⁻¹²⁷ two were cost comparisons,^{126,127} one was a WTP analysis,¹²⁴ and two were WTP-based CBAs.^{123,125} In the two cost-comparison studies,^{126,127} subjects using the insulin analogue were matched to conventional insulin users using a propensity score technique. Propensity scores are mathematical models that are used to estimate the probability that a subject will receive one of two treatment options based on selected characteristics.

The remaining three studies¹²³⁻¹²⁵ used a WTP technique to value the benefits of insulin analogue use. The effect of WTP was evaluated based on different demographic characteristics.

c) Time horizon

Two cost-comparison studies^{126,127} estimated total cost within a 12-month period. The WTP study of Aristides *et al.*¹²⁴ evaluated monthly costs. The other two WTP-based cost benefit studies, by Davey *et al.*¹²³ and Dranitsaris *et al.*,¹²⁵ presented survey results of peoples' preferences for one-month treatment that were extrapolated to obtain annual estimations.

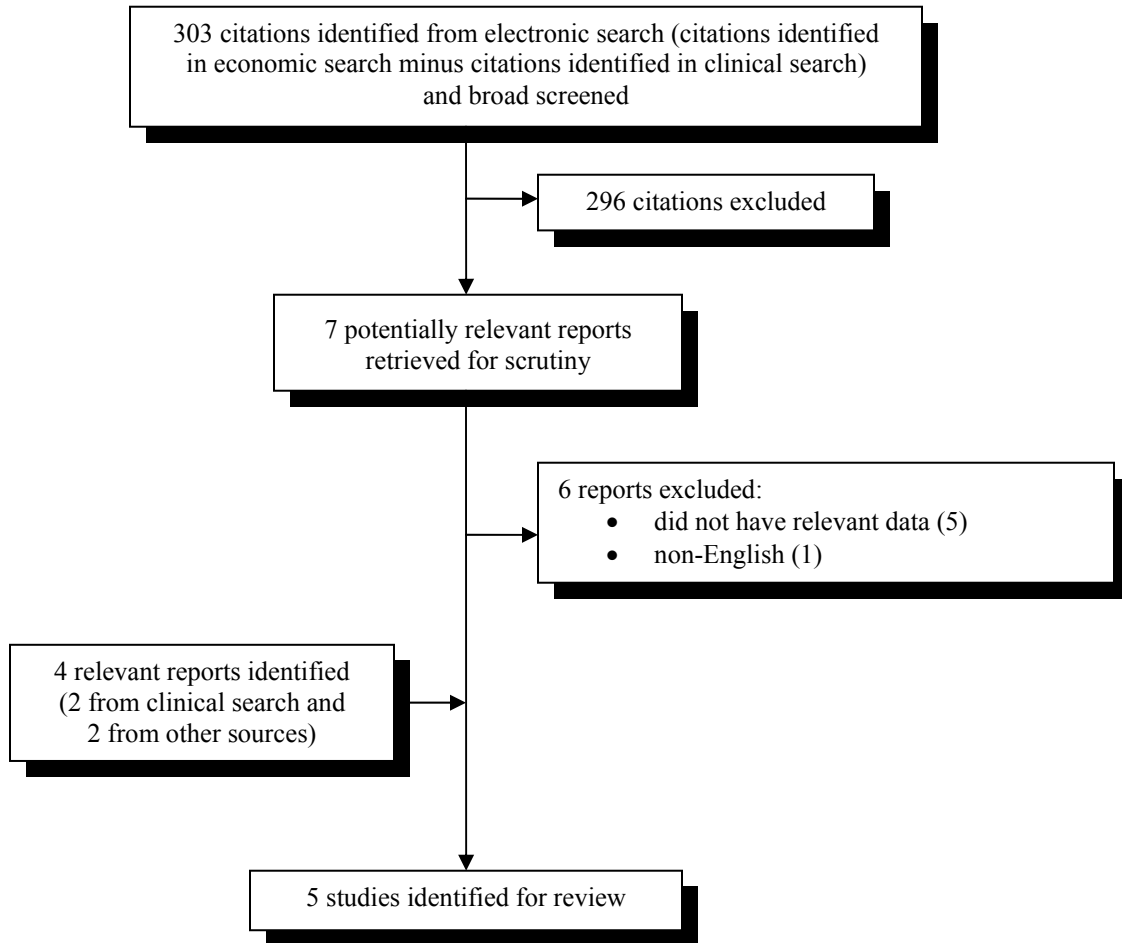
d) Study perspective

The perspectives of the studies by Hall *et al.*,¹²⁷ Aristides *et al.*,¹²⁴ and Dranitsaris *et al.*¹²⁵ were that of health plan member, individual patient, and individual Canadian taxpayer respectively. Neither Chen *et al.*¹²⁶ nor Davey *et al.*¹²³ stated the perspective.

e) Study population

The two cost-comparison studies^{126,127} and the WTP study by Davey *et al.*¹²³ enrolled types 1 and type 2 DM patients. Davey *et al.*¹²³ included patients who had participated in RCTs on ILIs. The Aristides *et al.*¹²⁴ study included type 2 DM patients only. The Dranitsaris *et al.* study¹²⁵ surveyed Canadian taxpayers, among whom 6.2% were diabetic patients.

Figure 15: Selection of economic studies



f) Intervention and comparator

Three studies^{123,126,127} compared ILis with HI, and two^{124,125} compared Mix25 (biphasic insulin lispro) with HI 30/70.

g) Economic outcomes

Two cost-comparison studies^{126,127} examined total health care costs. One study¹²⁴ explored the patients' WTP. Two studies^{123,125} also evaluated WTP and analyzed the net benefit of intervention over comparator by calculating the difference between incremental cost and incremental benefit.

h) Funding sources

Eli Lilly (manufacturer of ILis) sponsored all five included studies, and at least one investigator in all five studies was affiliated with the company.

The study characteristics appear in Appendix 17.

5.2.3 Study results

a) **Baseline results**

In the Chen *et al.* study,¹²⁶ the mean cost difference (ILis minus HI) per patient for the 12-month follow-up period was +C\$79 (p<0.001) for diabetes-related pharmacy costs, +C\$212 (p<0.001) for total pharmacy costs, -C\$75 (p<0.857) for diabetes-related medical costs, -C\$2,386 (p<0.011) for non-diabetes medical costs, and -C\$2,327 (p<0.072) for total costs.

In the Hall *et al.* study,¹²⁷ the mean cost difference (ILis minus HI) per patient for the 12-month follow-up period was +US\$447 (p<0.0001) for pharmacy costs, +US\$106 (p=0.0237) for office visits, +US\$8 (p=0.6433) for emergency visits, -US\$54 (p=0.7077) for outpatient hospital costs, -US\$769 (p=0.0277) for in-patient hospital costs, -US\$18 (p=0.4200) for laboratory costs, and -US\$280 (p=0.5266) for total costs.

These two cost-comparison studies showed that there was no significant difference in total health care costs between ILis and HI users. The higher pharmacy costs incurred with ILis seemed to be offset by the lower in-patient hospitalization cost.

In the Aristides *et al.* study,¹²⁴ the type 2 DM patients surveyed in the UK and Europe showed a preference toward the use of Mix25 over HI 30/70. If both treatments had a similar cost, 90% of the sample population would prefer Mix25. In terms of WTP, patients were willing to pay an extra €111 (C\$179) per month for Mix25.¹²⁸ The Australian study by Davey *et al.*¹²³ showed that 92% of the patient population preferred ILis over HI; 87% were happy with their current regimen, yet 95% were willing to try a new therapy if it offered advantages. As 41% of the subjects were taken from a recently completed clinical trial of ILis, the WTP estimation may be biased to favour ILis. The incremental WTP per month was estimated at A\$37.68 (C\$34.8), and the extrapolated annual incremental WTP was A\$452.16 (C\$417.9). ILis was listed on the Australian national formulary at a 36% premium over HI, so the additional cost per year would be A\$70.32 (C\$65.0). Therefore, the net benefit of replacing HI with ILis would be A\$381.84 (C\$352.9) per year, considering the drug costs only.

Dranitsaris *et al.*¹²⁵ found that 84% of the sample population preferred Mix25 over HI 30/70. Only 6% of the sample had diabetes, and the proportion using insulin was not stated. The WTP per month was estimated as C\$37.40 for Mix25 and C\$2.12 for HI 30/70. The incremental WTP per month was C\$35.28. The incremental monthly cost for Mix25 was C\$14. Therefore, the net benefit of Mix25 over HI 30/70 was C\$21.28 per month or C\$255.36 per year. This subject group does not represent the target population of potential users of short-acting insulin analogues. Therefore, it does not provide an appropriate estimate of their WTP.

b) **Sensitivity analysis results**

The simple sensitivity analysis by Aristides *et al.*¹²⁴ indicated that WTP was sensitive to the convenience of dosing, two-hour postprandial blood glucose level, and the rate of nocturnal hypoglycemic events. The most important was the frequency of nocturnal hypoglycemic events, followed by convenience of dosing, and then by the extent of two-hour postprandial blood glucose level. Their regression analysis demonstrated that the two demographic factors that significantly influenced WTP were access to private insurance and duration of diabetes. Patients with private health insurance were willing to pay more than those without private insurance. The longer a patient had diabetes, the greater the WTP.

The Davey *et al.* study¹²³ examined WTP between patients with or without prior exposure to ILis. People who had previously participated in a clinical trial were willing to pay on average A\$51.04 per month for ILis (95% CI: A\$34.81 to A\$67.28), while people without prior exposure recorded a WTP of A\$28.41 per month (95% CI: A\$15.95 to A\$40.87). Investigators found that patients' age was significantly associated with WTP for ILis therapy. Middle-aged patients had the strongest preference for ILis. Other factors, such as income and education, may be associated with WTP but were not statistically significant.

Dranitsaris *et al.*¹²⁵ showed that the baseline net benefit estimations of Mix25 over HI 30/70 were insensitive to extremes in the maximum WTP. A multivariate logistic model was used to identify independent predictors for an individual's WTP an additional cost for ILis. This model identified that age and income were significantly associated with WTP, while the number of children in the family and current diagnosis were not.

Despite the heterogeneities that stemmed from differences in objectives, study population, outcomes considered, and quantitative results, the two cost-comparison studies concluded that ILis and HI were similar. The three WTP studies concluded that ILis or ILis-based Mix was more favourable than HI or HI-based Mix.

The results appear in Appendix 18.

5.3 Discussion

Only five economic studies were identified, despite a thorough literature search and generous inclusion criteria. These studies compared ILis or ILis-based mixtures with conventional insulin. In the absence of economic data for IAsp, this report can only make observations on one short-acting insulin analogue. The limited amount of data restricts our ability to explore the cost implications associated with the use of these agents. Full economic evaluations — beyond a WTP design — are needed to help inform decisions about coverage.

The cost-comparison studies by Chen *et al.*¹²⁶ and Hall *et al.*¹²⁷ used retrospective cohort designs to compare 12-month claim data for subjects using ILis versus HI. The two studies used propensity scores in different ways to control for differences between groups. Both studies included costs of other health care resources (e.g., hospitalization, office visits, laboratory tests) and pharmacy costs. In each study, pharmacy costs were higher for the ILis group compared to HI, but the overall health care costs were similar. Chen *et al.* suggested that the higher product cost of ILis could be offset by lower non-diabetes medical costs. There was no significant difference in the hospitalization rates or physician visits between the two groups. Hall *et al.* observed significantly fewer hospitalizations and attributed costs in the ILis group compared to the HI group. It is unclear from these two studies how much the differences in hospitalization costs can be attributed to the different insulin regimens. For example, in both studies, subjects in the ILis group could also use HI during the observation period.

Hall *et al.*¹²⁷ indicated that flexible dosing and timing of meals with ILis accounted for fewer incidents of severe hypoglycemia, which may have resulted in fewer in-patient hospitalizations. Chen *et al.*¹²⁶ stated that the decrease in hospitalizations was unrelated to diabetes, and those that were related did not differ significantly between the two treatment groups.

The Australian WTP-CBA study¹²³ reported that ILis had a net economic benefit compared with HI, while the Canadian WTP-CBA study¹²⁵ showed a net benefit with Mix25 over HI 30/70. The UK-Europe WTP study¹²⁴ reported that patients preferred Mix25 over HI 30/70, and that the reduced risk of nocturnal hypoglycemic events and the pre-meal dosing convenience were the primary driving forces for the WTP value.

Several characteristics of the study population could affect the WTP estimation and the net benefit of the intervention of interest. The Australian study¹²³ reported middle-aged patients had a stronger preference for ILis relative to younger or older patients. This is consistent with the findings of Aristides *et al.*¹²⁴ and of Dranitsaris *et al.*¹²⁵ The former showed that the WTP estimate was C\$179 for patients whose average age was 51.3 years, and the latter showed that the WTP estimate was C\$35 for an average age 31.8 years. This WTP difference of C\$144 may arise from several factors, including differences in socioeconomic characteristics and disease status of the study subjects. Subjects in the Aristides *et al.* study¹²⁴ had DM for an average of 11 years, while the survey of Canadian taxpayers by Dranitsaris *et al.*¹²⁵ included only five (62%) subjects with diabetes.

Compared with a relevant review,¹²⁹ our review included two additional cost-comparison studies^{126,127} and one WTP study¹²⁴ that were published after 2002. The published review concluded that the available cost-benefit data favoured the inclusion of ILis and ILis-based Mix in formularies, but that more research was needed to investigate the pharmacoeconomic implications of ILis use in the long term. Although our review included three additional studies, we still lacked enough data to bridge the knowledge gap on long-term implications.

The cost-comparisons and WTP studies included in our review have limitations. First, all studies were funded by the company marketing the insulin analogue, and at least one author of each report was an employee of the company. Observations from these studies should be interpreted cautiously. Second, the propensity score method adopted by both cost-comparison studies^{126,127} has drawbacks. For example, it fails to control the bias incurred by covariates that are excluded in propensity score modelling. Hall *et al.*¹²⁷ indicated that compliance with therapy was not comparable across ILis and HI groups, possibly because of patients switching between therapies during the study period. The Chen *et al.* study¹²⁶ stated that covariates, such as socioeconomic status, HbA1c values, duration of diabetes, disease severity, and degree of medication adherence, which were unavailable in the claims database, might affect the propensity score. Third, neither study differentiated between types 1 and 2 DM status or age-related groups. Because these factors could affect the way that health care resources are used and the benefit of ILis, economic studies that consider them are essential to understand the implications of including ILis in the health care system. Finally, because the two studies are based on 12-month claim data, their findings should be verified with a longer follow-up period.

Two potential limitations are associated with the three WTP studies. First, the clinical results presented to patients in the WTP survey could be biased because they were derived from a limited number of trials. The source of the clinical data varied in the three studies. Dranitsaris *et al.*¹²⁵ used clinical data from one trial, Aristides *et al.*¹²⁴ used data from three trials (two full-length articles and one abstract), and Davey *et al.*¹²³ used data from their meta-analysis of six trials. Second, the study sample in each included study may not be representative of the population in the real world, where policy decisions are made. Dranitsaris *et al.*¹²⁵ justified their choice of study population (general taxpaying public) by stating that members of the public are potential candidates for the new therapy and indirectly finance the Canadian health care system through taxation. Aristides *et al.*¹²⁴ and Davey *et al.*¹²³ directly recruited diabetic patients. Therefore, it may be impossible to generalize the WTP estimations from these studies.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

The number of people affected by DM in Canada is increasing. For 1998 to 1999, 2000 to 2001, and 2003, there were 865,908, 1,063,698, and 1,222,882 people respectively who had DM.¹³⁰⁻¹³² The prevalence varied depending on province, age, sex, and year¹³³ (Table 14).

Of all the diagnosed diabetes cases, 90% are type 2 and 10% are type 1.¹³⁴ Therefore, the estimated numbers of type 1 DM patients for 1998 to 1999, 2000 to 2001, and 2003 were 86,591, 106,370, and 122,288 respectively. The estimated numbers of type 2 DM patients for the same years were 779,317, 957,328, and 1,100,594 respectively.

All type 1 DM patients are insulin users, and insulin is indicated for those type 2 DM patients who cannot achieve adequate glycemic control using other measures. Assuming that 10% of type 2 DM patients are on insulin therapy (based on the Boucher *et al.* report),¹³⁵ the estimated number of insulin users in Canada for these years were 164,523, 202,103, and 232,348 respectively.

Country or Province	1998 to 1999		2000 to 2001		2003	
	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)
Canada	3.0	3.9	3.9	4.4	4.3	4.9
Newfoundland and Labrador	5.8	4.5	6.1	5.4	5.7	7.2
Prince Edward Island	3.1	3.2	3.8	6.3	3.7	6.5
Nova Scotia	3.0	5.9	5.3	5.1	5.2	5.8
New Brunswick	4.4	2.2	4.8	5.3	5.2	5.7
Québec	2.9	3.4	4.0	4.2	4.4	4.7
Ontario	3.2	4.2	3.8	4.6	4.4	4.8
Manitoba	4.3	3.6	4.0	4.0	4.1	6.6
Saskatchewan	2.6	3.7	3.3	4.8	4.6	4.9
Alberta	2.7	3.5	3.4	3.3	3.2	4.0
British Columbia	2.3	4.6	3.6	4.2	3.8	5.3
Yukon	no data	no data	2.9	3.5	3.7	3.7
Northwest Territories	no data	no data	1.6	3.9	3.5	3.5
Nunavut	no data	no data	F	F	F	F

Data obtained from Statistics Canada reports;¹³⁰⁻¹³² data with coefficient of variation >33.3% suppressed (F) because of extreme sampling variability.

This estimation is only as reliable as the ratio of 1:9 between DM1 and DM2. The proportion of types of DM among all DM patients varies according to age. Type 1 DM most commonly develops before the age of 30 years, and type 2 DM typically develops with increasing age.³ Our result is likely to overestimate the number of DM2 patients, underestimate the number of DM1 patients in the younger age group, and vice versa for the older age group. The impact of these biases on the estimation of total insulin users is difficult to determine because of the lack of data.

6.2 Budget Impact

We undertook this budget impact analysis to estimate the financial implications of giving short-acting insulin analogues “open listing” on provincial drug plans. Given time constraints and limited data, we intended to give decision makers a general indication of how this would affect the future budget for insulin products. For precise values, drug planners would need to conduct a budget estimation with specific and sufficient data.

In Canada, there is no national guideline for doing a budget impact analysis. Alberta, Manitoba, and Ontario give templates to manufacturers for budget impact information and require different levels of detail.¹³⁶ In this analysis, we used patient claim data to forecast future budget impact, based on several assumptions.

First, we estimated each province’s budgets for future years, using the scenario where the current formulary statuses of insulin analogues stay the same. Then, we forecasted the budget in another scenario where no justification is required for the reimbursement of insulin analogues in provincial drug programs. Finally, by subtracting the former from the latter, we evaluated the potential impact of changing the formulary status of insulin analogues.

In the first scenario, where the current formulary status of short-acting insulin analogues continued, the total budget was the sum of expenditures on all insulin products of interest. That equalled the product of the derived number of insulin users and the corresponding per person per year cost of that insulin product. The simple regression equation for deriving the number of insulin users has several independent variables, including the number of patients over the past years and during the year, while its dependent variable is the number of patients in the future year of interest. For instance, given the insulin-user data for 2003 to 2005 ($N_{2003}, N_{2004}, N_{2005}$), the regression function for the insulin user in 2006 was $N_{2006}=f(N_{2003}, N_{2004}, N_{2005}, 2003, 2004, 2005, 2006)$. When some products showed declining utilization over the years, the regression results were negative. For those cases, we adjusted the values to zero, to be realistic.

In the second scenario, where patients received reimbursement for insulin analogues without providing any justification, we first estimated the number of potential users for each type of insulin product and then calculated the expenditures in a similar way as in the first scenario. The regression analysis in the first scenario generated the increasing or decreasing number of potential users with each type of insulin over the years. We added these yearly changes into subsequent calculations, to incorporate the original growth or reduction of the insulin-user pool over time, because of reasons other than the insulin analogues being listed. To calculate the budget for future years, we assumed that a proportion of conventional insulin users switched to the insulin analogues, and that switching from insulin analogue to conventional insulin did not occur. We assumed that patients who were newly initiated on insulin would be treated first with conventional insulin. In the first future year, (N^*_{2006}), the number of users for any insulin product equalled the number of users from the previous year (obtained from drug utilization data) (e.g., N_{2005}) plus (if an insulin analogue) or minus (if conventional insulin) the number switching to insulin analogues, based on an assumed switching rate (e.g., $N_{2005}*\text{switching rate}$) plus the number due to annual growth during that year, estimated from the linear regression analysis (e.g., $N_{2006}-N_{2005}$). The equation was $N^*_{2006}=N_{2005} \pm N_{2005}*\text{switching rate}+N_{2006}-N_{2005}$. For subsequent years, the number of users for insulin analogues or conventional insulin was similarly calculated as for the first year, except that the number for the corresponding previous year was estimated from the previous step instead of from the collected data. The equation was $N^*_{2007}=N^*_{2006} \pm N^*_{2006}*\text{switching}$

rate+ $N_{2007}-N_{2006}$. We programmed the calculation by using Excel, conducting its validation by testing if the budget impact is negligible when no patient switched to insulin analogues.

As the yearly switching rate is unknown, we varied the variable in the analyses from 10% to 25%, 50%, 75%, and 100% (i.e., all conventional insulin users switching). For instance, if the switching rate is assumed to be 10% yearly, 10% of the beneficiaries in the conventional insulin-user pool in the previous year would switch to an insulin analogue in the following year.

Our analysis was undertaken from a provincial drug plan perspective and tends to reflect cost to a government drug plan only, which may exclude part of the pharmacy mark-up and dispensing fees, depending on the province.

The budget impact was first analyzed by year, from 2006 to 2008. Then, the yearly results were summed for the three-year budget impact estimation. The inflation rate used was 3%. The formulary status of the insulin products appears in Table 15.

Formulary data as of September 2005 were used except for following jurisdictions: British Columbia, Alberta (October 2005), Saskatchewan, Manitoba (products available through Part III of Manitoba Formulary that have not been announced excluded), Ontario, Newfoundland and Labrador, Nova Scotia, New Brunswick, Prince Edward Island (July 2003), First Nations and Inuit Health Branch, Yukon (November 2004). Information does not differentiate between plans and programs available in each jurisdiction. If product listed on >1 plan or program in jurisdiction with different benefit statuses, then both statuses listed, separated by a comma. For product with “B” status, no justification required for reimbursement; for product with “L” status, specific criteria should be met for reimbursement; for product with “R” status, formal case-by-case request and review needed for drug program reimbursement.

Description	DIN_PDIN	Brand Name	BC	AB	SK	MB	ON	NB	NS	PE	NL	YT	FNIHB
INSULIN (HUMAN)	01959220	HUMULIN R CARTRIDGE 100 U/mL sol	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	00586714	HUMULIN R INJ 100 U/mL sol	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02024233	NOVOLIN GE TORONTO INJ 100 U/mL sol	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02024284	NOVOLIN GE TORONTO PENFILL [®] INJ 100 U/mL sol	B	B	B	B	B	B	B	B	B	B	
INSULIN LISPRO	02229704	HUMALOG 100 U/mL sol	B	B	R	B	L	L	R	B	R	B	B
INSULIN LISPRO	02229705	HUMALOG CARTRIDGE 100 U/mL sol	B	B	R	B	L	L	R	B	R	B	B
INSULIN LISPRO	02241283	HUMALOG PENFILL 100 U/mL sol	B								R	B	B
INSULIN ASPART	02244353	NOVORAPID 100 U/mL sol	B	B	R	B	L	L	R	B	R	B	B
INSULIN ASPART	02245397	NOVORAPID VIAL 100 U/mL sol	B	B	R	B	L	L	R	B	R	B	B
INSULIN (HUMAN)	01962655	HUMULIN 20/80 susp	B	B	B	B	B	B		B	B	B	B
INSULIN (HUMAN)	00795879	HUMULIN 30/70 INSULIN HUMAN BIOSYNTH INJ sol	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	01959212	HUMULIN CARTRIDGE 30/70 susp	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02024292	NOVOLIN GE 10/90 PENFILL INJ susp	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02024306	NOVOLIN GE 20/80 PENFILL INJ susp	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02024217	NOVOLIN GE 30/70 INJ susp	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02025248	NOVOLIN GE 30/70 PENFILL INJ susp	B	B	B	B	B	B	B	B	B	B	
INSULIN (HUMAN)	02024314	NOVOLIN GE 40/60 PENFILL INJ susp	B	B	B	B	B	B	B	B	B	B	B
INSULIN (HUMAN)	02024322	NOVOLIN GE 50/50 PENFILL INJ susp	B	B	B	B	B	B	B	B	B	B	B
INSULIN LISPRO	02240295	HUMALOG MIX25 PEN susp	B			B						B	B
INSULIN LISPRO	02240294	HUMALOG MIX25 susp	B	B	R	B	L			B	R	B	B

Source: National Prescription Drug Utilization Information System (NPDUIS), Canadian Institute for Health Information (CIHI), 2005. B=benefit; L=limited; R=restricted; sol=solution; susp=suspension.

The insulin products in our analyses were insulin analogues or conventional insulin. The insulin analogues are Mix insulin analogues and short-acting insulin analogues. The conventional insulin group is conventional mix insulin or conventional short-acting insulin. Only those products available in a provincial drug plan and in the Canadian market are included in our analysis (Table 16).

The switching scenario in our analysis was assumed to be:

Humulin Mix	—————>	Humalog Mix
Conventional insulin	—————>	Insulin lispro or insulin aspart

Table 16: Included Insulin Products in Analysis*		
Insulin Analogues	Name	DIN
Mix insulin analogue	Humalog Mix25	2240294
	Stylo Humalog Mix25 Pen	2240295
Short-acting insulin analogues	Humalog	229704
	Humalog†	229705
	Stylo Humalog Pen	2241283
	NovoRapid	2245397
	NovoRapid	2244353
Conventional insulin group	Name	DIN
Conventional mix insulin	Humulin 30/70	795879
	Humulin 30/70 susp	1959212
	Humulin 20/80	1962655
	Novolin GE 50/50 Penfill	2024322
	Novolin GE 40/60 Penfill	2024314
	Novolin GE 30/70 INJ susp	2024217
	Novolin GE 30/70 Penfill	2025248
	Novolin GE 20/80 Penfill	2024306
	Novolin GE 10/90 Penfill	2024292
Conventional short-acting insulin	Humulin R	586714
	Humulin R	1959220
	Novolin GE Toronto	2024233
	Novolin GE Toronto Penfill	2024284

*Humulin 10/90, Humulin 20/80 vial, Humulin 30/70 vial only, Humulin 40/60 3mL vial, and Humulin 50/50 not considered in our analysis. According to formulary information provided by CIHI, these insulin products are only available as benefits in NL. We excluded them to maximize comparability of between-province budget estimation results; †As Humalog (DIN 229705) could be 1.5 mL or 3 mL, and most of the obtained provincial drug utilization data did not distinguish Humalog at dosage size, we combined both in our budget analysis.

The drug utilization data were obtained from the provincial drug benefit databases that included total annual expenditures, number of patients, unit price of each insulin product, and number of dosage form units reimbursed.

The unit cost information (Appendix 19) for conventional insulin came from published provincial drug benefit formularies (Alberta, Québec, Ontario, Saskatchewan, Newfoundland, Nova Scotia), PPS® Pharma (for provinces without a publicly accessible formulary), or the median value of an

available provincial drug benefit price (for insulin products with a unit price that is not indicated in a typical provincial drug plan or the PPS Pharma publication).

For our analysis, we used the daily dose defined by the World Health Organization (WHO) for all included insulin products.¹³⁷ We assumed that the use of the intermediate-acting insulin NPH was the same for patients using short-acting insulin analogues and for conventional insulin users. Therefore, the budget impact calculation excluded NPH.

In general, listing the short-acting insulin analogues led to increasing budgets for all the jurisdictions considered. Our results showed that the budget impact increased over the years and became more significant with the higher switching rate (Table 17).

Our analysis demonstrates that the provincial drug plans need to increase their budget for insulin reimbursement if they are considering giving short-acting insulin analogues open listing in formularies.

The higher cost of insulin analogues (Appendix 19) largely contributed to budget increases over the years and to a higher switching rate (from 10% to 100%) when the insulin analogues received open listing. In Ontario, the patient cost is C\$523.17 per year, on average, with Humalog Mix versus C\$294.09 per year with conventional Humulin Mix. The annual cost per product and per patient increased 1.78 times. If a patient switches from Humulin to Humalog, the annual cost increases from an average of C\$271.39 to C\$388.21 in Ontario.

Table 17: Budget impact estimation results by province and year

Province	Switching Rate	Budget Impact by Year (C\$)			Budget Impact for 3 Years (C\$)
		2006	2007	2008	
Alberta	10%	134,123	258,342	370,521	762,986
	25%	335,309	595,559	791,702	1,722,569
	50%	670,617	1,023,464	1,230,913	2,924,995
	75%	1,005,926	1,323,296	1,489,361	3,818,583
	100%	1,416,517	1,574,834	1,706,515	4,697,866
Manitoba	10%	41,087	74,729	101,519	217,335
	25%	102,718	171,415	214,218	488,351
	50%	205,436	291,471	352,762	849,670
	75%	308,154	397,969	459,933	1,166,057
	100%	463,104	521,948	580,522	1,565,574
New Brunswick	10%	57,667	141,778	179,614	379,059
	25%	124,500	302,363	361,169	788,031
	50%	183,440	475,115	542,812	1,201,366
	75%	195,960	575,484	632,647	1,404,090
	100%	191,967	665,250	719,681	1,576,897
Newfoundland and Labrador	10%	87,075	123,008	154,276	364,359
	25%	200,493	262,013	309,099	771,604
	50%	343,674	415,631	478,162	1,237,467
	75%	452,462	513,537	567,110	1,533,109
	100%	554,970	606,110	657,250	1,818,329
Nova Scotia	10%	74,973.60	141,635.30	200,840.40	417,449
	25%	187,434.00	325,973.10	428,463.20	941,870
	50%	374,868.00	558,657.10	661,551.90	1,595,077

Table 17: Budget impact estimation results by province and year

Province	Switching Rate	Budget Impact by Year (C\$)			Budget Impact for 3 Years (C\$)
		2006	2007	2008	
	75%	562,302.00	718,752.40	801,317.60	2,082,372
	100%	790,796.50	857,971.90	924,640.60	2,573,409
Saskatchewan	10%	155,652	291,676	408,996	856,324
	25%	389,129	670,821	869,336	1,929,286
	50%	778,258	1,147,077	1,361,404	3,286,739
	75%	1,167,388	1,494,315	1,666,993	4,328,695
	100%	1,660,048	1,814,731	1,959,132	5,433,911
Ontario	10%	2,095,300	6,158,943	4,046,096	12,300,339
	25%	4,835,053	13,227,122	8,198,044	26,260,219
	50%	8,340,234	20,497,250	12,002,258	40,839,741
	75%	10,737,500	23,975,550	13,639,622	48,352,672
	100%	12,267,783	25,827,810	14,787,175	52,882,768

*As shown in Table 15, all insulin products of interest in this analysis have “B” benefit status in BC and YT. We did not calculate budget for these provinces; accordingly, no budget impacts reported. We did not receive drug utilization data on time for PE, so we could not report them.

In addition to the higher unit cost of insulin analogues, the increasing number of diabetes patients over the years could explain part of the rising budget impact. With limited data, we roughly derived the number of insulin users from 2006 to 2008 (Appendix 20) as varying from 67,394 to 2,674, depending on the jurisdiction and year.

There are differences between the provinces, even if we assumed the same switching rate from conventional insulin to short-acting insulin analogues. For instance, given a 10% switching rate in 2006, the budget impact ranged from C\$2.10 million in Ontario to C\$0.04 million in Manitoba. The provincial drug benefit formulary (Table 15) could be another reason. The province where insulin analogues have been conditionally listed had less of a budget impact than those where insulin analogues have not been listed.

In the real world, insulin regimens and the insulin dose for individual diabetes patients needs to be adapted to the specific treatment goal, and to the specific health and behavioural characteristics. Our budget impact analysis did not take into consideration these variations. Using the daily defined dose for each insulin product published by the World Health Organization and assuming that patients did not change their insulin regimens over the time horizon of our analysis, resulted in overestimation of the government drug plan cost attributable to the insulin products of interest. The reasons for the overestimation are that people could switch between insulin types, may not always use a particular insulin type for the entire year, or may not use the same dose during the entire period considered for the analysis. Because the budget impact was determined from the difference between two future scenarios, it was not overestimated as much as the budget. When the switching rate was zero, our analysis model generated zero or a negligible result, which confirms the model’s validity.

As we could not find the unit listing prices for all insulin products of interest in all provinces, we referred to the PPS Pharma or median value of available prices during our budget forecast. That might bias our results in terms of reflecting the truth. For those products with available province-specific listing prices, the fact that the prices may exclude dispensing fees or patients’ co-payments, depending on the nature of the provincial drug plan, indicated that our budget impact results have to

be viewed in the context of each province. If the plan adjusted the listing prices, the budget impact evaluation would change accordingly.

Switching between insulin products is a complex issue in terms of direction and degree. To simplify this issue, we assumed that only conventional insulin users would switch to insulin analogue treatment, and that the reverse would not occur. We also assumed that switching between conventional insulin products did not occur. This may be untrue. With the available data, our approach seems to be the best scenario. Our treatment-switching assumption might overestimate the number of insulin analogue users and underestimate the number of conventional insulin users in the scenario where analogues have open listing. Therefore, our analysis is likely to overestimate the budget impact, given the higher unit costs of insulin analogues compared with conventional insulin. Alberta, New Brunswick, Nova Scotia, Ontario, and Newfoundland provided fiscal year data, while Manitoba and Saskatchewan gave calendar year data. Thus, the corresponding estimations for each province were fiscal year or calendar year results.

6.3 Ethical, Equity, and Psychosocial Issues

Universal access is a foundation of the Canadian health care system. This relates mainly to services covered by each provincial insurance plan, such as access to physicians and hospital care. It relates less to ambulatory treatments that are not covered equally by provincial health plans. In discussing access to newer or more expensive medications, the principle of universality is essential. The medications should be equally accessible to all individuals, independent of private drug insurance plans, after the demonstration of at least equivalent potency (non-inferiority) and safety profile compared to existing agents. Cost issues often pose an ethical dilemma. The benefits to the individual may be offset by the incremental costs to the health care system. This requires a careful assessment of the cost-effectiveness or benefit impact of the new agents.

The approaches to ethical issues involve justice, respect for persons, beneficence, and non-maleficence. Justice and respect for persons presuppose reasonable access to medications with demonstrated efficacy in the treatment of a disease. Beneficence implies that the medication has been shown to be efficacious, and non-maleficence means that it carries no incremental risk of minor or serious adverse events.

The potential benefits of short-acting insulin analogues (e.g., ILis and IAsp) include enhanced reproducibility of results,^{13,14} improved metabolic control (defined by lower HbA1c levels) that has been demonstrated in this review for type 1 DM but not type 2 DM, a lower risk of hypoglycemia (nocturnal in some studies) for type 1 DM patients receiving CSII, and convenience of injection with a potential for increased compliance and better health outcomes. Insulin analogues can be taken immediately before a meal (or after in some instances) as opposed to short-acting insulin preparations, which are taken 30 to 45 minutes before a meal. No deleterious effects of short-acting insulin analogues have been established. Although their use is widespread, they have not been on the market long enough to determine possible long-term effects, such as mitogenicity.

Another ethical issue is that of informed consent. Where these analogues have been approved for use in particular patients with diabetes, informed consent is unnecessary. In these circumstances, it is reasonable to suggest that health care professionals inform their patients about available treatment options and explain why they are recommending a specific approach. Where an agent has not been

approved for a particular indication, such as during pregnancy or in very young children, off-label use requires that informed consent be obtained from the patient or their surrogate.

DM is a psychologically and behaviourally demanding disease, and psychosocial factors play a role in almost all aspects of its management.^{2,138} Individuals with diabetes face challenges that affect virtually all aspects of their daily lives. They often feel frustrated trying to manage the disease and find the level of self-care burdensome, leading to “diabetes burn-out,” which is the inability to meet the ongoing demands for excellent self-care.¹³⁹ Attention has focused on the psychosocial concomitants of type 1 DM, particularly in children and teens. It has been shown, for example, that children from single-parent families and lower socioeconomic status present more often with diabetic ketoacidosis at disease onset, have more episodes of this condition during the course of their diabetes, attend clinics less frequently, and are less likely to achieve and maintain good diabetes control.¹⁴⁰ Nearly half of all teens with type 1 DM have a period of “pervasive non-compliance” with their diabetes routines such as insulin injections, monitoring, and nutritional planning. These teens were more likely to show significant psychopathology, particularly depression, as young adults.¹⁴¹ An increased prevalence of depression in adults with type 1 DM, compared to the general population, has been reported.^{3,142-144} Depression is associated with poor control and health complications in patients with type 1 and type 2 DM.¹⁴⁵

Emotional stress may provoke behavioural changes, resulting in a lack of adherence to a dietary, exercise, or therapeutic regimen with negative consequences. For example, the fear of hypoglycemia may interfere with an individual’s ability to achieve near normoglycemia. This may be based on previous episodes of severe hypoglycemia or it may be part of an anxiety about the diabetes.¹⁴⁶ Fear of hypoglycemia can influence patients’ blood glucose levels, and their awareness and control of their diabetes. It can result in self-modification of treatment and post-episode lifestyle changes.¹⁴⁷

Nearly a quarter of teenage and young adult females with type 1 DM may have a full-blown or sub-threshold eating disorder at some stage.¹⁴⁸ The presence of such eating disorders is often associated with insulin omission to control weight through induced glycosuria, poor glycemic control, and earlier onset of diabetes-related complications.¹⁴⁹ Short-acting insulin may increase flexibility in the carbohydrate intake, timing of meals, and variety of food intake for adolescents. This may offer the theoretical advantages of improving metabolic control and lessening the feelings of dietary restraint, a factor that is likely involved in the development of eating disorders.¹⁵⁰

Any consideration of the benefits or risks of short-acting insulin analogues must account for these psychosocial issues in addition to the clinical and economic issues. It should be determined whether patients will derive a psychosocial benefit because of the convenience of use, perceived QoL advantage, or personal preference. In defining psychosocial outcomes, the impact of diabetes and its management on family members should be considered. This is likely to be more important among those whose family members provide care, i.e., for children and the elderly.

A theoretical and demonstrated advantage of the short-acting analogues is their quick onset of action after their administration immediately before a meal, rather than 30 to 45 minutes before, as with conventional insulin. Among younger children, administration of the analogues immediately after a meal has been shown to cause no deterioration in glycemic control compared with conventional insulin.⁴⁷ This may be especially advantageous for the youngster with erratic food intake patterns. This feature makes insulin analogues more convenient than the alternatives. They are dispensed in vials and cartridges for use with syringes and insulin pens, the same way that conventional insulin preparations are sold. They can be mixed with intermediate-acting insulin, but not long-acting ones,

like conventional insulin. Some studies suggest that the mixing of short- and long-acting analogues may be possible without changing the pharmacological properties of either insulin.^{151,152}

Although less well studied with respect to short-acting insulin analogues, patients' preference (perceived QoL, social acceptability, ease of use) should be considered by diabetes health professionals and health care funders. Compliance with complicated regimens may be facilitated by improved convenience as perceived by the patient.

Some studies that compare short-acting analogues to conventional insulin have shown an improvement in perceived QoL.^{36,37,120,153,154} This relates partly to the convenience of using these analogues immediately before eating. Patients may be influenced by diabetes health care professionals who believe that analogues are preferable, but this has not been supported by data. While insulin analogues may be more convenient and give the perception of an improved QoL, they are more expensive. Although insulin constitutes a small expense in comparison to the cost of other diabetes supplies, especially that of glucose monitoring strips, this increased cost may lead to the selection of an alternative therapeutic choice for those without drug insurance.

There is no evidence that short-acting analogues exacerbate the psychosocial issues that sometimes affect individuals with DM, and they may have a positive influence.

7 CONCLUSIONS

In type 1 DM patients, treatment with ILis or IAsp significantly reduced HbA1c levels, compared to HI. The difference was more pronounced in patients using CSII. The occurrence of overall and severe hypoglycemia was similar with the two treatments, but nocturnal hypoglycemia was less frequent with ILis compared with HI.

In type 2 DM patients, HbA1c levels, occurrences of hypoglycemia, and QoL were similar between those using HI and those using short-acting insulin analogues. Compared to OADs, improvements in HbA1c levels and in patient satisfaction were noted among those treated with short-acting insulin analogues.

Uncertainty remains regarding the use of short-acting insulin analogues in GDM patients and pregnant women with diabetes. Two studies have shown that post-meal glucose levels are significantly reduced in GDM patients treated with ILis, compared to those treated with HI.

If users of HI switch to the more expensive insulin analogues, further increases in drug plan expenditures can be anticipated. There is evidence to suggest, however, that these additional costs can be offset by reductions in other health-care expenditures in a 12-month horizon. These findings are limited to study settings in the US. The available economic evidence also showed that patients preferred ILis to HI or Mix25 to HI 30/70.

High-quality long-term studies are needed to determine the benefit and harm of short-acting insulin analogues, compared to conventional insulin. Data on patient mortality and QoL are lacking. The impact on health care costs beyond 12 months is unknown.

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APPENDICES

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