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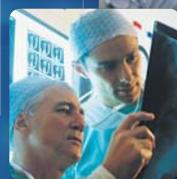
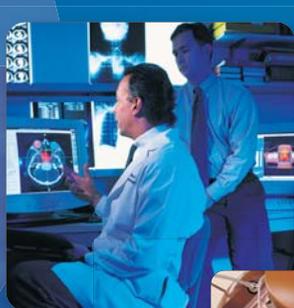


## T E C H N O L O G Y R E P O R T

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Long-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**

**Long-Acting Insulin Analogues for Diabetes Mellitus:  
Meta-analysis of Clinical Outcomes and  
Assessment of Cost-Effectiveness**

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October 2007

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Srabani Banerjee, overall research lead, co-ordinated the project.

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Huimin Li, the lead for economics, selected studies; extracted, tabulated, and analyzed data; and wrote the economic sections of the report.

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Scot H. Simpson provided economic expertise.

Kaitryn Campbell was responsible for the design and execution of the literature search strategies, for the associated appendix, and for the bibliographies.

All authors contributed to the revisions of the report.

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## **Conflicts of Interest**

Dr. Denis Daneman was co-chair of a satellite symposium at an International Diabetes Federation meeting in Cape Town, South Africa. He received partial funding from Eli Lilly Canada for a study of the role of pioglitazone in glycemic control among adolescents with poorly controlled type 1 diabetes. He is a member of the Hvidovre Study Group on Childhood Diabetes, which is funded by Novo Nordisk (Denmark). He was a speaker at a workshop on long-acting analogues of insulin for children (funded by Sanofi-Aventis).

Dr. Scot Simpson received honoraria for continuing education presentations on insulin use in type 2 diabetes (Sanofi-Aventis) and general management issues in type 2 diabetes (Merck Frosst).

The other authors of this report have no conflicts of interest.

Dr. Michael Vallis has received speaking fees from Pfizer, GlaxoSmithKline, and Eli Lilly, and sits on an advisory board of Sanofi-Aventis.

Dr. Jeffrey Johnson has been a consultant for Oxford Outcomes, which has a consulting agreement with Novo Nordisk for a project to assess the health utilities associated with hypoglycemia.

## Long-Acting Insulin Analogues for Diabetes Mellitus

### Technology and Condition

Long-acting insulin analogues used as basal insulin, insulin glargine (IGlar) and insulin detemir (IDet), for the treatment of type 1 and 2 diabetes mellitus (DM).

### Issue

More than 2.25 million Canadians have DM. The annual cost of treating DM and its complications is more than \$9 billion. The successful management of DM often requires medications. Insulin analogues cost more than human insulin (HI). There is uncertainty about whether the use of insulin analogues is justified.

### Methods and Results

A systematic review and a meta-analysis were undertaken to evaluate the clinical and economic implications of using long-acting analogues for the treatment of DM, relative to human insulin and to oral anti-diabetic agents. A total of 34 randomized controlled trials were eligible for review: 23 trials of patients with type 1 DM and 11 trials on type 2 DM. Meta-analysis was performed using trials that completely reported data. The budget impact to publicly funded provincial drug plans was also examined.

### Implications for Decision Making

- **Long-acting insulin analogues (LAIAs) have no demonstrated impact on blood sugar control, relative to HI.** The available evidence suggests that LAIAs have not demonstrated clinically important differences in glycated hemoglobin, a widely used marker of blood sugar control in types 1 and 2 DM.
- **Reduced complications from therapy can occur.** The evidence suggests IGlar can reduce the risk of severe hypoglycemia in type 1 DM patients taking human insulin. IGlar reduced the risk of nocturnal but not severe hypoglycemia in type 2 DM patients. IDet has demonstrated a reduced risk of severe and nocturnal hypoglycemia in type 1 DM. No reductions in complications with IDet were observed in patients with type 2 DM.
- **Funding decisions may require more compelling economic evidence.** Publicly funding LAIAs will require significant additional investment. Economic arguments for this investment are limited largely because they are based on unproven assumptions about the long-term benefit of therapy.

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Tran K, Banerjee S, Li H, Cimon K, Daneman D, Simpson S, Campbell K. *Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness* [Technology Report number 92]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

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# EXECUTIVE SUMMARY

## Issue

More than 2.25 million Canadians have DM. The annual cost of treating DM and its complications is more than \$9 billion. The successful management of DM often requires medications. Insulin analogues cost more than human insulin (HI). There is uncertainty about whether the use of insulin analogues is justified.

## Objective

The aim of this systematic review is to evaluate the clinical efficacy and economic implications of long-acting insulin analogues, specifically insulin glargine (IGlar) and insulin detemir (IDet), for the treatment of diabetes mellitus (DM).

## Clinical Review

**Methods:** Randomized controlled trials (RCTs) comparing long-acting insulin analogues with conventional human insulin were identified through electronic databases, web sites, and industry. In the systematic review approach that was taken, two reviewers independently identified trials that were eligible for inclusion, on the basis of eligibility criteria outlined a priori.

**Results:** Of the 841 originally identified citations, 34 RCTs were included: 23 on type 1 DM and 11 on type 2 DM patients. The number of patients ranged between 14 and 756. All studies were conducted in adults, except three RCTs in type 1 DM that involved pediatric or young adult populations. On average, the RCTs were of low quality as reflected by a mean score of 2.3 on the Jadad scale. Seven RCTs in type 1 DM and five RCTs in type 2 DM received a Jadad score of 3, which is suggestive of higher quality. This is of concern because the evidence suggests that low-quality RCTs result in exaggerated estimates of a treatment's benefit. In addition, because of the incomplete reporting of outcome data, some RCTs were excluded from certain meta-analyses. All, however, were included in the systematic review.

In type 1 DM patients, for glycated hemoglobin levels (HbA1c), the results were not pooled for IGlar in type 1 DM because of high statistical heterogeneity. Reductions in HbA1c levels were statistically significant with IGlar treatment compared with neutral protamine Hagedorn (NPH) treatment in five of 11 RCTs reporting such data. In no case, however, did such reductions achieve the minimal clinically important difference of a 1.0 reduction in HbA1c, which is a widely used marker of blood sugar control. The pooled estimates of all RCTs – regardless of bolus insulin type – showed no statistically significant differences between treatments for overall, severe, or nocturnal hypoglycemia; the relative risk (RR) (95% CI) values were 1.00 (0.95, 1.06), 0.78 (0.58, 1.05), and 0.92 (0.81, 1.04) respectively. A significant risk reduction (27%) in severe hypoglycemia was observed when the subgroup of RCTs using human insulin (HI) as the bolus were pooled, RR (95% CI)= 0.73, (0.55, 0.95).

For trials on type 1 DM patients using IDet, no statistically significant differences were seen in HbA1c levels compared with NPH [WMD (95% CI)=-0.05 (-0.12, 0.03)]. When insulin aspart (IAsp) was used as the bolus, the reduction in nocturnal and severe hypoglycemia (16% and 30% respectively) were statistically significant when IDet was compared with NPH [RR (95% CI)=0.84 (0.73, 0.95) and 0.70 (0.52, 0.95)].

In type 2 DM patients, no significant difference in HbA1c levels was seen with IGLar or IDet compared with NPH [WMD (95% CI)=0.05 (-0.07, 0.16) and 0.11 (-0.03, 0.26) for IGLar and IDet respectively]. The risk of nocturnal hypoglycemia was significantly reduced in IGLar patients compared with NPH patients [RR (95% CI)=0.57 (0.44, 0.74)], regardless of whether they received in addition HI or an oral anti-diabetic agent. The risk of severe hypoglycemia was found to be increased in type 2 DM patients on IGLar compared to those on NPH. This increase was not statistically significant [RR (95% (CI)=1.09 (0.56, 2.12)].

In types 1 and 2 DM patients, adverse events appeared to be similar with insulin analogues and conventional insulin. Mortality and quality of life (QoL) data were sparsely reported and inconclusive.

## Economic Review

**Methods:** Economic studies comparing long-acting insulin analogues with conventional human insulin were identified through electronic databases, web sites, and industry.

**Results:** A total of 303 citations were identified from the economic literature search. Three economic studies were included: one from the electronic literature search, one from the clinical review, and one from other sources. The two studies that compared IGLar with NPH suggested that the benefit gained from patients avoiding severe hypoglycemic events with the insulin analogue offset the increased cost of the drug and resulted in cost savings. The study comparing IDet with NPH in type 1 DM patients concluded that IDet-based basal and bolus therapy would result in an incremental cost equivalent to C\$51,427 per life-year gained and with an incremental cost of C\$44,130 per quality-adjusted life-year (QALY), is likely to be good value for money. Sensitivity analyses were conducted in two studies. All three studies had some limitations, including the fact that they were sponsored by or had authors affiliated with the company that developed the long-acting insulin analogues.

## Health Services Impact

The prevalence of diabetes is increasing in Canada, as is the number of people using insulin. All type 1 DM patients receiving care use insulin. Assuming that 10% of type 2 DM patients also use it, the estimated number of users has increased from 164,523 in 1998-1999 to 232,348 in 2003. Greater costs would be incurred if more patients switched to long-acting insulin analogues. We estimated the provincial budget impact over three years (2006 to 2008) would range from C\$605,708 to C\$13,921,951 (if 10% switched) and from C\$3,534,906 to C\$79,115,423 (if 100% switched), depending on the province. Two provinces and the three territories were not analyzed. Assumptions were made that might limit our evaluation.

## Conclusions

The evidence suggests that the use of long-acting insulin analogues does not result in the attainment of clinically important outcomes for all individuals with DM. In those individuals with type 1 DM, IGLar resulted in statistically significantly greater reductions in HbA1c levels compared with NPH in less than half of the trials reporting this outcome. In no case did the magnitude of the reductions reach the minimal clinically important level of a full point (i.e., 1.0) reduction. HbA1c levels in type 2 DM patients were similar when they were treated with NPH, IGLar, or IDet. IGLar reduced the risks of severe hypoglycemia in type 1 DM patients on HI (bolus), and IDet reduced the risks of severe and nocturnal hypoglycemia in type 1 DM patients on IAsp (bolus). IGLar reduced the risk of nocturnal but not severe hypoglycemia in type 2 DM patients.

Long-term comparative studies of high quality are needed to definitively determine the benefit and harm of long-acting insulin analogues compared with conventional insulins.

Three economic studies, which were sponsored by industry or had industry affiliation, showed results in favour of long-acting insulin analogues compared with NPH. These findings are limited to the specific study settings. Future studies should be conducted with a longer time horizon and be based on updated and more reliable clinical data.

The prevalence of diabetes and the number of insulin users are increasing in Canadians. This will result in increased expenditures for insulin products. If conventional insulin users switch to the more expensive insulin analogues, there will be further demands on drug plans. As long-term data on insulin analogues is unavailable, the impact on health care resources is difficult to predict.

# ABBREVIATIONS

12h	12-hour interval
ADDQoL	Audit of Diabetes-Dependent Quality Questionnaire
AE	adverse event
AEs	adverse events
BG	blood glucose
CEA	cost-effectiveness analysis
CHF	Swiss franc
CI	confidence interval
CNS	central nervous system
CUA	cost-utility analysis
DCCT	Diabetes Control and Complications Trial
DIN	drug identification number
DM	diabetes mellitus
DTSQ	Diabetes Treatment Satisfaction Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
FBG	fasting blood glucose
GDM	gestational diabetes mellitus
Glim	glimepiride (sulfonylurea)
HbA1c	glycated hemoglobin
HI	conventional human insulin
HRQL	health-related quality of life
HTA	health technology assessment
IAsp	insulin aspart
ICER	incremental cost-effectiveness ratio
IDet	insulin detemir
IGlar	insulin glargine
IGlar[30]	insulin glargine containing 30 µg/mL zinc
IGlar[80]	insulin glargine containing 80 µg/mL zinc
ILis	insulin lispro
i.v.	intravenous
LA	long-acting insulin analogues
LY	life-year
m + b	morning and bedtime
m + d	morning and before dinner
max	maximum dose
Metf	metformin
NA	not applicable
NHS	National Health Service
NNT	number needed to treat

NP	not pooled
NPH	neutral protamine Hagedorn
NR	not reported
NS	not significant
NSD	no significant difference
OAD	oral anti-diabetic agent
PG	plasma glucose
Pio	pioglitazone
pts	patients
pt-days	patient-days
pt-year	patient-year
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
Ros	rosiglitazone
RD	risk difference
RR	relative risk
SD	standard deviation
SE	standard error
Sfu	sulfonylurea
tx	treatment
UL	ultra lente
WBQ	Well-Being Questionnaire
WMD	weighted mean difference



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# 1 INTRODUCTION

## 1.1 Background

Diabetes mellitus (DM) is a complex health problem for individuals with the disease and a national health challenge. It is the seventh leading cause of death in Canada.<sup>1</sup> Over 2.25 million Canadians are estimated to have DM. Of all the diagnosed cases, 90% are type 2 DM and 10% are type 1 DM. It is estimated that the annual cost for health care for diabetes and its complications is more than C\$9 billion, which includes direct health care costs and those arising from premature death and lost productivity.<sup>1</sup> If present trends continue, the prevalence of type 2 DM will increase because of the aging population and rising rates of obesity. The total health care costs are projected to increase from C\$4.66 billion (in 2000) to C\$8.14 billion in 2016 (in 1996 C\$ values).<sup>2</sup>

DM comprises a group of 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 the beta cells from the islets of the pancreas, in response to increased levels of glucose in the blood. Insulin helps glucose to be absorbed from the bloodstream into cells where it can be used as a source of energy.<sup>3</sup> Table 1 shows the classification of different types of DM.

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	variety of uncommon diabetic conditions that are 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 immune-mediated diabetes that are drug or chemical induced).

The diagnosis of diabetes is based on the criteria<sup>4,5</sup> described in Table 2.

Test	Criteria
fasting plasma glucose (FPG)	FPG $\geq$ 7.0 mmol/L (126 mg/dL), fasting defined as no caloric intake for at least 8 hours
casual plasma glucose (PG)	PG $\geq$ 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) $\geq$ 11.1 mmol/L (200 mg/dL)

In the absence of symptoms, the finding of an abnormal glucose value requires confirmation by using a second test on another day.<sup>4</sup>

The chronic nature of DM threatens many organs and is responsible for most of the mortality and morbidity associated with the disease. These can be divided into vascular and non-vascular complications, with vascular complications subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery disease, peripheral artery disease, and cerebrovascular disease) complications. Non-vascular complications include gastroparesis, infections, and skin changes.<sup>5</sup>

The successful management of DM requires an educated and motivated patient with support from a multidisciplinary health care team. In combination with diet modifications, weight control, and adequate exercise, medications can assist patients in controlling blood glucose levels to reduce the risk of developing long-term diabetic complications.<sup>6</sup> Maintaining glycemic levels near normal has been shown to lower the risk of microvascular complications.<sup>7,8</sup> Medications may also be used in the primary prevention of complications, particularly cardiovascular disease, which is a cause of morbidity and mortality in patients with DM.<sup>4</sup>

There are six classes of anti-diabetic drugs available on the Canadian market:

- 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’s Clinical Practice Guidelines,<sup>4</sup> treatment for DM aims for the glycemic targets described in Tables 3 and 4.

<b>Table 3: Glycemic targets for adults</b>			
<b>Targets</b>	<b>HbA1c Target (%)</b>	<b>Fasting or Preprandial Glucose Target (mmol/L)</b>	<b>2-hour Postprandial Glucose Target (mmol/L)</b>
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

HbA1c=glycated hemoglobin; \* consider targets in normal range for patients for whom these can be achieved safely

<b>Table 4: Glycemic targets for children and adolescents</b>			
<b>Age (year)</b>	<b>HbA1c Target (%)</b>	<b>Preprandial Glucose Target (mmol/L)</b>	<b>Considerations</b>
<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 ≤6	4.0 to 7.0 4.0 to 6.0	appropriate for most patients; consider for patients in whom it can be achieved safely

HbA1c=glycated hemoglobin

All patients with type 1 DM need insulin to stay alive. They require multiple daily injections of a short-acting and an intermediate- or long-acting insulin to mimic normal insulin secretion. Physiologic insulin secretion is a complicated process in which small amounts of insulin are secreted throughout the day (“basal” insulin) with a significant increase in response to meals (“bolus” insulin).

The latter occurs mainly in response to changes in blood glucose concentration, but it is also affected by incretins and neural control through the vagus nerve. The counterregulatory hormones (growth hormones, cortisol, glucagons, and catecholamines) also affect insulin dynamics. Furthermore, the amount of insulin secreted per day will depend, at least partly, on an individual's degree of insulin sensitivity or resistance.

Patients with DM 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 also 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 (pen-like injection device), or pump, also known as a continuous subcutaneous insulin infusion (CSII).<sup>4</sup>

Patients with newly diagnosed type 2 DM are instructed to modify their diet and increase their level of physical activity to achieve a healthy weight and improve glycemic control. If these measures are insufficient or if the degree of hyperglycemia at presentation is severe, one or more oral hypoglycemic agents or insulin can be used. The choice of agent(s) is tailored to the individual and depends on his or her co-morbid conditions and underlying risk of developing hypoglycemia. Insulin is also indicated for patients with type 2 DM who cannot achieve adequate glycemic control with other measures. There are many approaches to insulin therapy in individuals with type 2 DM, from the 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.<sup>4</sup> In all approaches, the goal of therapy should be the achievement of glycemic targets that are as close as possible to those in the nondiabetic population, when these can be safely achieved.

In patients diagnosed with GDM or in those with pre-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.<sup>4</sup>

Hypoglycemia is the greatest 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.<sup>4</sup> If recognized early, hypoglycemia can be treated by the ingestion of carbohydrate (e.g., glucose tablets) followed by a protein and carbohydrate snack. If untreated, severe hypoglycemia can lead to confusion, coma, seizures, and death.<sup>4</sup>

The pharmacokinetic and pharmacodynamic features of conventional insulin, whether of animal origin (previously) or biosynthetic human origin (since the 1980s and currently prepared by recombinant DNA technology), may be suboptimal and may cause hypoglycemia.<sup>9</sup> 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 low level (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 (IGlar), marketed as Lantus, and insulin detemir (IDet), marketed as Levemir.

## 1.2 Overview of Technology

Insulin was originally isolated from animal sources. In the 1980s, recombinant DNA technology allowed biosynthetic human insulin to be manufactured commercially. This technology also made it possible to engineer novel molecules with altered characteristics. The main pharmacokinetic limitation of the conventional intermediate- and long-acting insulins is their inability to recreate the low, even insulin profile of normal physiology.<sup>10</sup> Instead, their absorption is characterized by a peak followed by a steady decline.<sup>10,11</sup> With the intent of circumventing this problem, long-acting insulin analogues were developed using the recombinant DNA technology.

The insulin molecule is a polypeptide consisting of an A chain with 21 amino acids and a B chain with 30 amino acids.<sup>12</sup> IGLar, a long-acting insulin analogue, was produced by substituting glycine for asparagine at position 21 of the A chain and by adding two arginine molecules at position 30 of the B chain. These changes led to a shift in the molecule's isoelectric point.<sup>9</sup> IGLar injection solution is formulated to a pH of 4.0, at which it is soluble.<sup>12</sup> After subcutaneous injection, the acidic IGLar solution is neutralized and forms microprecipitates.<sup>11</sup> This delays its absorption into the bloodstream and a relatively constant basal insulin supply is achieved. This is consistent with the secretion of insulin in those without diabetes.<sup>12</sup>

IDet is another long-acting insulin analogue, in which the amino acid threonine at position 30 of the B chain is removed and a 14-carbon, myristoyl fatty acid is acylated to lysine at position 29 of the B chain.<sup>10,12</sup> Hence, IDet can bind to albumin. This retards the absorption of IDet and prolongs its blood-glucose lowering effect.<sup>12</sup> IDet is soluble at neutral pH, so the subcutaneous depot remains liquid. Consequently, the IDet depot has a greater surface area, so absorption is expected to occur with reduced variability.<sup>10</sup>

The pharmacokinetic profiles<sup>10,13</sup> of conventional human insulin and the long-acting insulin analogues, used as basal insulin, appear in Table 5.

<b>Insulin Products Used as Basal Insulin</b>	<b>Onset of Action (hours)</b>	<b>Peak of Action (hours)</b>	<b>Duration of Action (hours)</b>
<b>Conventional insulin</b>			
isophane insulin (NPH, Humulin N, Novolin N)	1 to 2	5 to 7	13 to 18
zinc insulin (Lente, Humulin L, Novolin L)	1 to 3	4 to 8	13 to 20
extended zinc insulin (Ultralente, Humulin U)	2 to 4	8 to 10	18 to 30
<b>Long-acting insulin analogues</b>			
insulin glargine (Lantus)	1 to 2	none	20 to 24
insulin detemir (Levemir)	1 to 2	none	10 to 18

Time courses of action represent averages and may differ from one person to another and in any individual from one injection to another. NPH=neutral protamine Hagedorn.

The costs of the insulin analogues and conventional human insulin appear in Table 6.

Both IGLar and IDet are 2.3 to 4.4 times as expensive as NPH (Humulin N).

**Table 6: Product Information**

Product	DIN	Package Size	Price* per Package (C\$)
<b>Insulin analogues</b>			
Levemir (IDet), penfill cartridge, 100 units/mL	02271842	5 × 3 mL	109.86
Lantus (IGlar), cartridge, 100 units/mL	02251930	5 × 3 mL	109.87
Lantus (IGlar), vial, 100 units/mL	02245689	1 × 10 mL	55.07
<b>Conventional human insulins (NPH)</b>			
Humulin N, vial, 100 units/mL	00587737	1 × 10 mL	16.72
Humulin N, pen, 100 units/mL	02241310	5 × 3 mL	47.61
Humulin L, vial, 100 units/mL	00646148	1 × 10 mL	16.72
Humulin U, vial, 100 units/mL	00733075	1 × 10 mL	16.72

\*Price for Lantus provided by Sanofi-Aventis (Christine Chin, Sanofi-Aventis Canada Inc.: personal communication, 2007 May 25). Price for Levemir provided by Novo Nordisk<sup>15</sup> and indicates net price to wholesalers. Prices for conventional insulin taken from PPS.<sup>19</sup>

Health Canada issued Notices of Compliance for IGlAr and IDet in 2002 and 2005 respectively.<sup>14,15</sup> The FDA approved the use of IGlAr and IDet in the US in 2000 and 2005 respectively.<sup>16,17</sup>

## 2 THE ISSUE

More than 2.25 million Canadians have DM. The annual cost of treating DM and its complications is more than \$9 billion. The successful management of DM often requires medications. Insulin analogues cost more than human insulin (HI). There is uncertainty about whether the use of insulin analogues is justified.

## 3 OBJECTIVE

Our objective was to conduct a systematic review, to evaluate the clinical efficacy of long-acting insulin analogues (IGlar and IDet) and to evaluate the economic implications of using these agents in the treatment of DM.

This objective is accomplished by addressing the following:

- a) What is the clinical efficacy of the long-acting insulin analogues when compared with conventional insulin or anti-diabetic agents in the treatment of type 1, type 2, or gestational DM?
  - What are the benefits and harms from the clinical and the patient's perspectives?
  - Are there subpopulations of DM patients who may particularly benefit from treatment with long-acting insulin analogues, in comparison with conventional human insulins or oral anti-diabetic agents?
  - What are the benefits and harms of long-acting insulin analogues in combination with oral anti-diabetic agents compared with conventional human insulin in combination with oral anti-diabetic agents in the treatment of type 2 DM?
  - Compared with conventional human insulin, are there differences in the clinical effects of long-acting insulin analogues, when used at the onset versus later in the course of the disease, for patients with type 2 DM?

- b) What is the evidence of cost-effectiveness of using long-acting insulin analogues in the treatment of type 1 DM 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 searching Medline, BIOSIS Previews, PASCAL, EMBASE, PubMed, and the Cochrane Database of Systematic Reviews from 1990 onwards. The search strategy included long-acting and short-acting insulin analogues, because initially, one systematic review was to be conducted for both insulin types. A decision was made after the literature search to divide the project into two parts and perform separate systematic reviews on the short- and long-acting insulin analogues. The search was constructed using controlled vocabulary [e.g., the National Library of Medicine's Medical Subject Headings (MeSH)] and keyword terminology. Publication filters were used to identify specific publication types, namely controlled trials, meta-analyses, and systematic reviews (Appendix 1).

The original search was performed in August 2005. Alert searches were run from August 2005 forward. Alert search results from August 2005 to February 2006 are incorporated into this systematic review. Relevant results found between February 2006 and June 2007 have been noted in the conclusion but are excluded from the systematic review.

We obtained grey literature by searching the web sites of regulatory agencies, 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 searched the Internet using the Google and Dogpile search engines and found additional information on 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. Manufacturers were asked to provide relevant information.

#### 4.1.2 Selection criteria and method

##### a) *Selection criteria*

Study design: randomized controlled trials (RCT)

Population group(s): patients with DM (type 1, type 2, or GDM)

Intervention: long-acting insulin analogues (IGlar, or IDet)

Comparator: conventional human insulin or oral anti-diabetic agents

Outcomes: glycemic control [glycated hemoglobin (HbA1c) level, blood glucose level], quality of life (QoL), hypoglycemic episodes, adverse events (AEs), complications of diabetes, or mortality.

#### **b) Selection method**

Two of three reviewers (SB, KT, or KC) independently selected the 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. The differences in decisions between reviewers were compared and resolved by consensus.

#### **4.1.3 Data extraction strategy**

After the relevant trials were selected, one reviewer (KT or KC) extracted data from each trial using a structured form (Appendix 2), and another reviewer (KT, KC, or SB) checked the data independently. The 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 scale.<sup>20</sup> This scale is used to rate trials on a scale of zero to five, with higher scores associated with better quality. Low quality trials (Jadad score  $\leq 2$ ) have the potential to contribute to overall increased estimates of benefits (i.e., exaggerate an intervention's effectiveness).<sup>21,22</sup> The ratings are based on the reporting of randomization, double-blinding, and withdrawals and dropouts (Appendix 3). Information on the concealment of allocation, blinding of assessors, and intention to treat was also recorded.

#### **4.1.5 Data analysis methods**

We used the Cochrane software Review Manager 4.2.3 to analyze data and generate Forest plots. Computations were performed using the fixed effects and random effects model. Where the quantitative pooling of results was appropriate, summary estimates were computed. This decision depended on the statistical heterogeneity between the trials. Heterogeneity was determined using Higgin's  $I^2$  value, which indicates the extent of variation across trials due to heterogeneity rather than chance.  $I^2=25\%$ ,  $I^2=50\%$ , or  $I^2=75\%$  indicate low, moderate, or high heterogeneity respectively.<sup>23</sup> If  $I^2>75\%$ , the trials were not pooled. If  $I^2=0$ , then the random effects model provides the estimate that would result from a fixed effects approach. Whenever possible for our analyses, we used the number of patients who were randomized (i.e., intention-to-treat population). We used the weighted mean difference (WMD) for continuous data and relative risk (RR) and risk difference (RD) for binary data.

For the analyses of continuous data, when standard deviation (SD) values were not reported, they were calculated from the reported standard error (SE) ( $SE=SD/\sqrt{N}$ ), where N=number of participants).<sup>24</sup> In trials where variances were reported but unspecified as SD or SE, they were assumed to be one or the other, if the values were within the ranges reported in other trials.

For HbA1c, the negative values for WMD indicated better results with long-acting insulin analogues than with conventional insulin or oral anti-diabetic agents. The WMD was statistically significant if the 95% confidence interval (CI) excluded zero.

For binary data,  $RR<1$  indicated reduced risk with long-acting insulin analogues compared with conventional insulin or oral anti-diabetic agents. This was statistically significant if the corresponding 95% CI excluded the value of one.  $RD<0$  indicated reduced risk with long-acting insulin analogues compared with conventional insulin or oral anti-diabetic agents. This was statistically significant if the corresponding 95% CI excluded zero.

The outcome data were analyzed according to the different groups of DM patients (i.e., type 1 and type 2). For each patient group, the trials were analyzed according to the type of long-acting insulin analogue (i.e., IGl<sub>ar</sub> or ID<sub>et</sub>). Subgroups were also analyzed according to the substance used as the bolus. Decisions to perform subgroup analysis were made a priori.

## 4.2 Results

### 4.2.1 Quantity of research available

The flowchart in Figure 1 shows the trial selection process. A total of 841 citations were identified from the original literature search. Of these, 802 citations were excluded. These were mainly reviews, in vitro studies, pharmacokinetic or pharmacodynamic studies, and studies with comparisons and designs that were irrelevant for the review. Of the 39 potentially relevant reports selected for further examination, 24 were selected for inclusion. In addition, 12 reports were obtained from other sources (which included alerts set up after the original literature search was performed, industry, and the HTA checklist). The total number of included reports was 36. For two RCTs, there were two reports for each, and both were used for data extraction. As a result, there were 36 reports describing 34 unique RCTs.

### 4.2.2 Trial characteristics

The characteristics of the RCTs comparing long-acting insulin analogues with intermediate- or long-acting conventional insulins or oral anti-diabetic agents (OADs) in type 1 and type 2 DM patients appear in Appendices 4a and 4b respectively. No RCTs were available on long-acting insulin analogues in patients with GDM.

Of the 36 reports, 23 reports<sup>25-47</sup> were on type 1 DM patients. Of these, 19<sup>25,26,28-31,34-39,41-47</sup> were journal articles, two<sup>27,32</sup> were conference abstracts, and two<sup>33,40</sup> were posters. Nineteen<sup>25,26,28-31,33-36,38-41,43-47</sup> mentioned industry sponsorship, two<sup>37,42</sup> government sponsorship, and two<sup>27,32</sup> did not report sponsorship. Fourteen RCTs<sup>26,27,29,30,32,34,35,37-39,41,42,44,47</sup> were on IGl<sub>ar</sub> and nine<sup>25,28,31,33,36,40,43,45,46</sup> were on ID<sub>et</sub>. There were 19 parallel trials<sup>25-27,29-31,35-47</sup> and four crossover trials.<sup>28,32-34</sup> In the RCTs, the number of patients ranged between 14 and 749. Most of the trials were multi-centre, and many were also multinational.

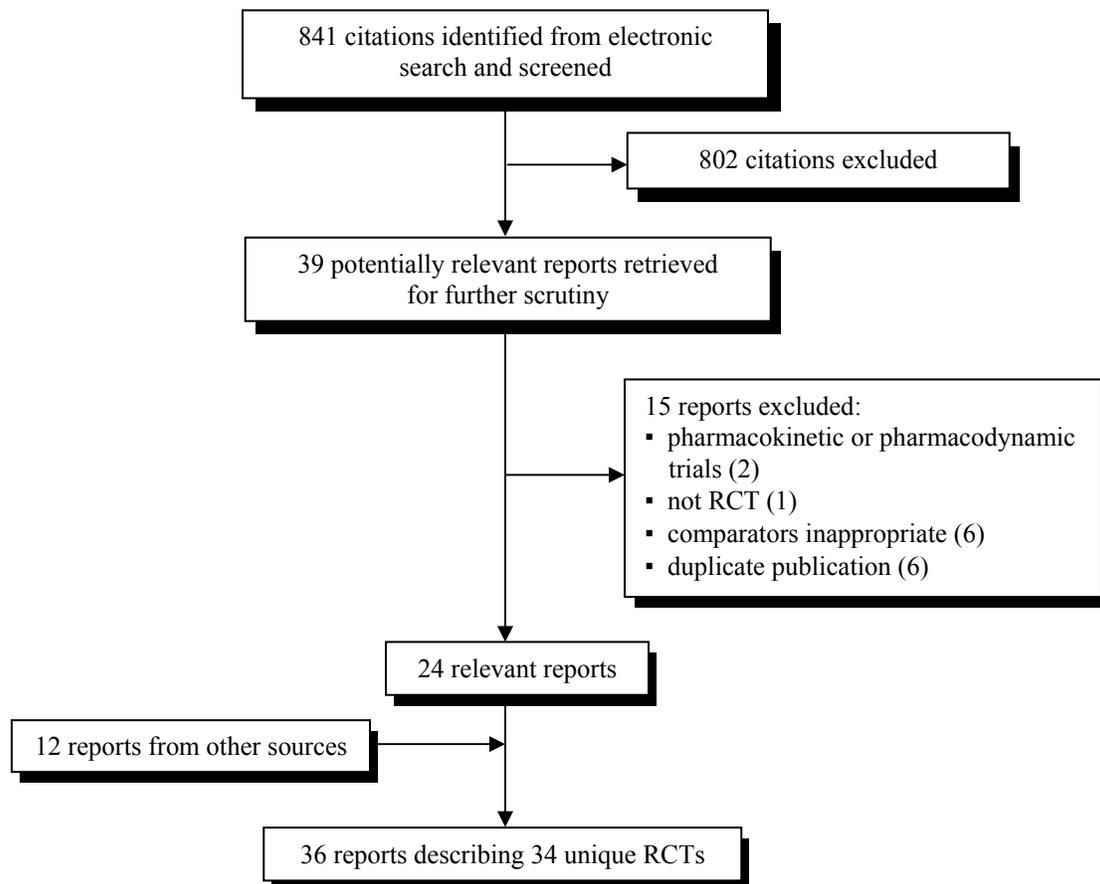
Thirteen reports<sup>48-60</sup> described 11 RCTs involving type 2 DM patients. Of these, 10<sup>48-50,53,55-60</sup> were journal articles, one<sup>54</sup> was a conference abstract, and two<sup>51,52</sup> were posters. Two journal articles<sup>48,56</sup> described the same trial, and two posters<sup>51,52</sup> described the same trial, but all were used for data extraction. Eleven reports<sup>48-53,55,57-60</sup> mentioned industry sponsorship, and two<sup>54,56</sup> did not report on sponsorship. Nine RCTs<sup>48,49,53-60</sup> were on IGl<sub>ar</sub>, and two<sup>50-52</sup> were on ID<sub>et</sub>. All were parallel trials. In the RCTs, the number of patients ranged between 110 and 756. Most of the trials were multi-centre, and many were also multinational.

The characteristics of the patients in the RCTs comparing long-acting insulin analogues with intermediate- or long-acting conventional insulins or oral anti-diabetic agents (OADs) in DM patients appear in Appendices 5a and 5b. The inclusion and exclusion criteria used in selecting patients for the trials appear in Appendix 6.

Twenty-three RCT reports were on type 1 DM patients whose characteristics appear in Appendix 5a. Of the 23 RCTs, 20<sup>25-31,33-39,41-43,45-47</sup> involved adult patients (mean age between 24 and 43 years;

one<sup>32</sup> involved pediatric and young adult patients (ages from eight to 21 years); and two<sup>40,44</sup> involved only pediatric patients (mean age 12 years). Of the 20 RCTs<sup>25-31,33-39,41-43,45-47</sup> on adult patients, 19<sup>25,26,28-31,33-39,41-43,45-47</sup> reported the number of males or females (the percentage of females ranged between 18% and 61%), and 19<sup>25-31,33-39,41-43,45,46</sup> reported the duration of diabetes (mean values between 10.7 and 18.6 years). The RCT<sup>32</sup> on pediatric and young adult patients did not report on the number of males or females or on the duration of diabetes.

**Figure 1: Selection of trials**



RCT=randomized controlled trial

For the two RCTs<sup>40,44</sup> on pediatric patients, the percentage of females ranged between 48% and 55%, and the mean duration of diabetes ranged between 4.8 and 5.0 years.

Eleven RCTs were on type 2 DM patients whose characteristics appear in Appendix 5b. The mean age ranged between 53 and 61 years. Of the 11 RCTs, 10<sup>49-51,53,55-60</sup> reported on the number of males or females (the percentage of females ranged between 36% and 49%). The mean duration of diabetes ranged between 8.5 and 13.8 years.

We assessed the quality of all the reports available as full texts. For the 19 RCT reports<sup>25,26,28-31,34-39,41-47</sup> on type 1 DM patients, the mean Jadad score with SD was 2.3±0.7; allocation concealment

was adequate in three<sup>31,37,46</sup> and unclear in the remainder; and 74% reported an intent-to-treat analysis.<sup>25,26,29-31,36,37,39,41,43-47</sup> For the 10 full reports<sup>48-50,53,55-60</sup> on type 2 DM patients, the mean Jadad score with SD was 2.4±0.7; allocation concealment was adequate in four<sup>53,55,58,60</sup> and unclear in the remainder; and 90% reported an intent-to-treat analysis. A summary of results from the quality assessment appears in Appendix 7.

### 4.2.3 Data analyses and synthesis

Because of incomplete reporting of data, not all trials could be included in the meta-analyses to derive summary estimates. No attempts were made to contact authors and investigators to obtain the missing information. For continuous data, the only RCTs that could be pooled were those that reported SD values or contained data enabling SD to be calculated. The results reported here were obtained using the random effects model. Pooling to derive summary estimates was not undertaken if  $I^2 > 75\%$ .

#### a) **HbA1c**

The HbA1c data for type 1 DM and type 2 DM appear in Appendices 8a to 8b. All HbA1c data are expressed as percentages.

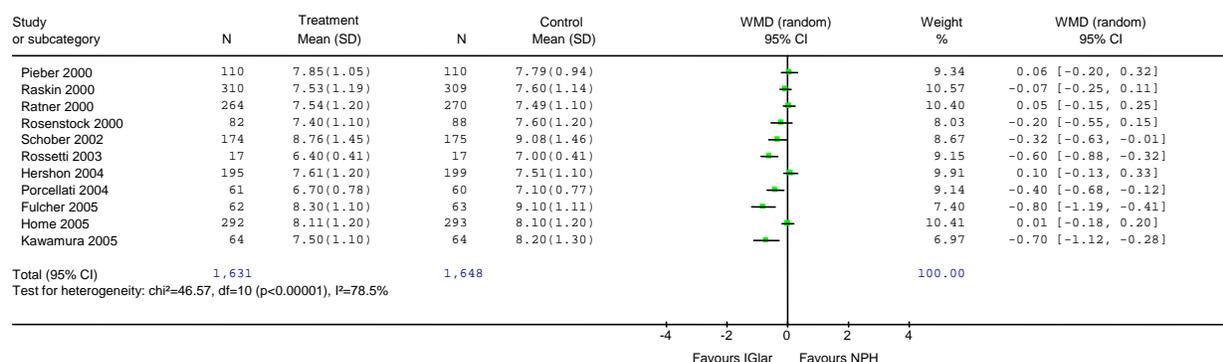
#### **Type 1 DM**

**IGlar versus NPH:** Of 12 RCTs<sup>26,27,29,30,32,35,37-39,41,42,44</sup> comparing IGLar with NPH reported end-point HbA1c data in type 1 DM patients, 11<sup>26,29,30,32,35,37-39,41,42,44</sup> that report end-point HbA1c levels with variants appear in Figure 2. One RCT<sup>27</sup> with 14 patients was excluded from the analysis because it lacked complete data. Of these 11 RCTs, seven<sup>26,32,37,38,41,42,44</sup> showed greater improvement with IGLar compared to NPH. The difference was statistically significant in five.<sup>26,32,37,42,44</sup> Four RCTs<sup>29,30,35,39</sup> showed the opposite effect, but the difference was not statistically significant. The difference was not considered to be clinically important in any of the 11 RCTs, because a difference in HbA1c of 1.0 is considered to be a minimal clinical change.<sup>61</sup> Because heterogeneity was high ( $I^2 > 75\%$ ), these trials were not pooled. Heterogeneity can result from clinical, methodological, or other differences among trials. For example, the classification of these 11 trials based on bolus type yielded six<sup>29,30,35,39,41,44</sup> with HI, four<sup>26,37,38,42</sup> with ILis, and one<sup>32</sup> with IAsp, so bolus type could be a source of heterogeneity (Table 7).

**IDet versus NPH:** Of eight trials<sup>25,31,33,36,40,43,45,46</sup> examining the effect of IDet versus NPH as basal insulin, on the HbA1c levels in type 1 diabetic patients, two<sup>43,45</sup> used HI as a bolus and six<sup>25,31,33,36,40,46</sup> used IAsp. The pooled estimate of all eight trials using the random effects model showed no statistically significant differences between treatments (Figure 3). The WMD (95% CI) was -0.05 (-0.12, 0.03). The difference was not clinically important, because a difference in HbA1c of 1.0 is considered to be a minimal clinical change.<sup>61</sup> The results were not significantly affected when the one cross-over trial<sup>33</sup> was excluded from the analysis. Subgroup analysis based on bolus type (i.e., IAsp or HI) also showed no significant differences between treatments (Table 7).

In summary, HbA1c levels were lowered to a greater degree in the IGLar group compared with the NPH group in some trials but not in others. None of the RCTs showed a clinically important difference between the two treatments. Overall, there were no statistically significant or clinically important differences for HbA1c levels between the IDet and the NPH group, regardless of whether the bolus insulin was IAsp or HI.

**Figure 2: HbA1c levels in type 1 DM patients (IGlar versus NPH)**



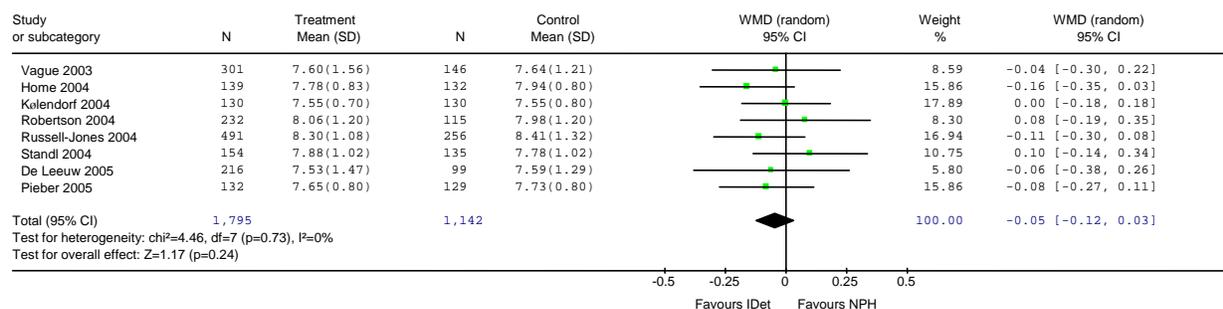
HbA1c=glycated hemoglobin; CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; SD=standard deviation, WMD=weighted mean difference

**Table 7: HbA1c for type 1 DM**

Comparison	Category	Number of Trials	Number of Patients*	Random Effects Model	
				WMD (95% CI) <sup>†</sup>	Heterogeneity $I^2$
IGlar versus NPH	bolus=all	11	3,279	NP	78.5%
	bolus=HI	6	2,252	-0.02 (-0.13, 0.10)	25.3%
	bolus=ILis	4	899	NP	82.6%
	bolus=IAsp	1	128	-0.70 (-1.21, -0.28)	NA
IDet versus NPH	bolus=all	8	2,937	-0.05 (-0.12, 0.03)	0%
	bolus=IAsp	6	1,901	-0.05 (-0.14, 0.04)	0%
	bolus=HI	2	1,036	-0.02 (-0.22, 0.19)	46.4%

HbA1c=glycated hemoglobin; CI=confidence interval; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NA=not applicable; NP=not pooled; NPH=neutral protamine Hagedorn; WMD=weighted mean difference. \*For crossover trials, patients are counted twice because they participate in all treatment arms and act as their own control. <sup>†</sup>In case of high heterogeneity ( $I^2>75\%$ ), pooling to derive summary estimates not performed.

**Figure 3: HbA1c levels in type 1 DM patients (IDet versus NPH)**



HbA1c=glycated hemoglobin; CI=confidence interval; IDet=insulin detemir; NPH=neutral protamine Hagedorn; SD=standard deviation; WMD=weighted mean difference.

## Type 2 DM

**IGlar versus NPH:** Seven RCTs<sup>49,53,55,56,58-60</sup> compared the treatment effects of IGlar and NPH on A1c levels in type 2 DM patients. The pooled estimate [WMD (95% CI)=0.05 (-0.07, 0.16)] from these RCTs revealed neither a statistically significant nor a clinically important difference in A1c

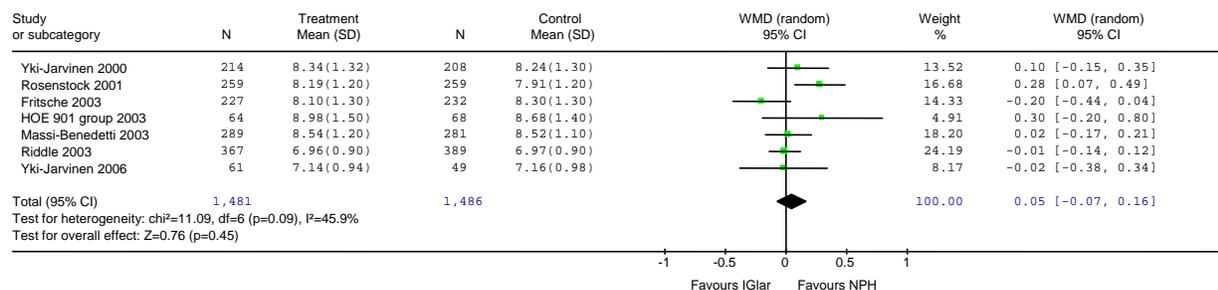
levels between treatments (Figure 4, Table 8). There was some heterogeneity between the trials ( $I^2=45.9\%$ ). Of these seven RCTs, six<sup>49,53,55,58-60</sup> included an OAD in all treatment arms.

The remaining RCT<sup>56</sup> also included HI in both treatment arms. The pooled estimate [WMD (95% CI) = -0.01 (-0.09, 0.08)] from these six trials with OADs revealed neither a statistically significant nor a clinically important difference in HbA1c levels between treatments with IGlAr or NPH. There was no heterogeneity among the trials ( $I^2=0\%$ ). The RCT<sup>56</sup> with HI showed that the HbA1c levels were significantly higher for IGlAr compared with NPH [WMD (95% CI)=0.28 (0.07, 0.49)]. Although this difference was statistically significant, its magnitude is insufficient to be clinically important.

**IDet versus NPH:** Two RCTs<sup>50,51</sup> compared the treatment effect of IDet versus NPH on HbA1c levels in type 2 DM patients (Figure 5). No difference of statistical significance or clinical importance was noted between treatments [WMD (95% CI)=0.11 (-0.03, 0.26)]. There was no heterogeneity among the trials ( $I^2=0\%$ ). Of these two RCTs, one<sup>51</sup> included an OAD, and the other<sup>50</sup> included IAsp in the treatment arms. Neither RCT showed a significant difference in HbA1c levels (Table 8).

Overall, there were no statistically significant or clinically important differences with respect to HbA1c levels between long-acting insulin analogues (i.e., IDet or IGlAr) and NPH treatments in type 2 DM patients.

**Figure 4:** HbA1c levels in type 2 DM patients (IGlar versus NPH)



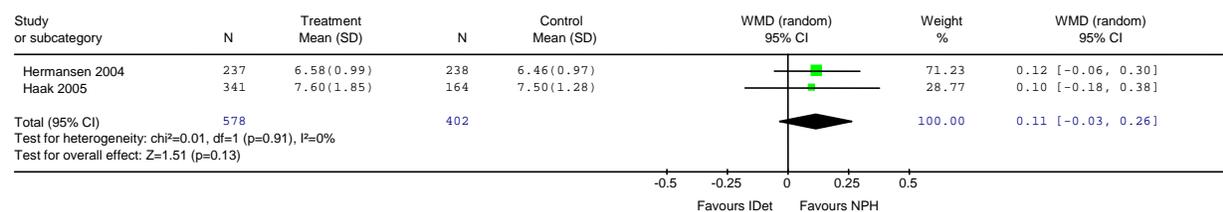
HbA1c=glycated hemoglobin; CI=confidence interval; IGlAr=insulin glargine; NPH=neutral protamine Hagedorn; SD=standard deviation; WMD=weighted mean difference

**Table 8:** HbA1c for type 2 DM

				Random Effects Model	
Comparison	Category	Number of Trials	Number of Patients	WMD (95% CI)	Heterogeneity $I^2$
IGlar versus NPH	all	7	2,967	0.05 (-0.07, 0.16)	45.9%
	OAD	6	2,449	-0.01 (-0.09, 0.08)	0%
	HI	1	518	0.28 (0.07, 0.49)	NA
IDet versus NPH	all	2	980	0.11 (-0.03, 0.26)	0%
	IAsp	1	505	0.10 (-0.18, 0.38)	NA
	OAD	1	475	0.12 (-0.06, 0.30)	NA

HbA1c=glycated hemoglobin; CI=confidence interval; IAsp=insulin aspart; IDet=insulin detemir; NA=not applicable; NPH=neutral protamine Hagedorn; OAD=oral anti-diabetic agent; WMD=weighted mean difference.

**Figure 5: HbA1c levels in type 2 DM patients (IDet versus NPH)**



HbA1c=glycated hemoglobin; CI=confidence interval; IDet=insulin detemir; NPH=neutral protamine Hagedorn; SD=standard deviation; WMD=weighted mean difference.

### b) Blood glucose

Investigators reported blood glucose data as an eight-point blood glucose profile or as fasting blood glucose levels (Appendices 9a to 9d).

#### Type 1 DM

##### *Eight-point blood glucose profiles*

**IGlar versus NPH:** Three trials<sup>30,37,42</sup> compared the effects of IGLar versus NPH on eight-point blood glucose profiles in type 1 DM patients. No significant differences were shown in two trials where the bolus was HI<sup>30</sup> or ILis.<sup>37</sup>

One trial<sup>42</sup> with ILis as the bolus, showed that the blood glucose levels of the IGLar group were significantly lower than the NPH group at most times except pre-dinner and bedtime, and significantly higher at nighttime. These differences were statistically significant.

**IDet versus NPH:** Eight RCTs compared the effects of IDet versus NPH on the eight-point blood glucose profiles of type 1 DM patients. Of these, five<sup>25,31,33,36,40</sup> used IAsp as the bolus, and three<sup>28,43,45</sup> used HI. Of the trials that used IAsp as the bolus, three<sup>25,31,40</sup> showed no significant difference in blood glucose profiles at any times compared with the NPH trials. The RCT of Kølendorf *et al.*<sup>33</sup> showed that blood glucose levels were lower before breakfast and lunch, and higher pre-dinner in the IDet group. The Pieber *et al.*<sup>36</sup> RCT showed that blood glucose levels at bedtime and nighttime were significantly lower in patients treated with IDet twice daily (morning and bedtime) compared with those treated with NPH at the same two times.

For the three RCTs using HI as a bolus, one trial<sup>28</sup> showed no significant differences in the blood glucose profiles between treatments, one trial<sup>43</sup> showed a significantly lower blood glucose in the IDet group pre-breakfast, and one trial<sup>45</sup> showed a significantly lower blood glucose in the IDet group post-lunch and post-dinner.

Thus, it remains uncertain whether the effect of long-acting insulin analogues on the eight-point blood glucose profiles is robust, compared with NPH.

##### *Fasting blood glucose*

**IGlar versus NPH:** Six RCTs compared the effects of IGLar versus NPH on fasting blood (or plasma) glucose in type 1 DM patients (Table 9). Of these, two<sup>26,38</sup> used bolus ILis, and four<sup>27,35,39,41</sup> used bolus HI. Pooled estimates showed a significant reduction in fasting blood (or plasma) glucose in the IGLar group compared with the NPH group, regardless of bolus type. The WMD (95% CI) were -0.92

(-1.21, -0.63), -1.02 (-1.37, -0.67), and -0.86 (-1.37, -0.35) for both bolus types, for bolus ILis, and for bolus HI respectively. The extent of heterogeneity among trials is shown in Table 9.

**IDet versus NPH:** Six RCTs compared the effects of IDet versus NPH on fasting blood (or plasma) glucose in type 1 DM patients (Table 9). Of these, two<sup>43,45</sup> used bolus HI and four<sup>31,36,40,46</sup> used bolus IAsp. The pooled estimate showed a significant reduction in fasting blood (or plasma) glucose in the IDet group. The WMD (95% CI) was -0.87 (-1.27, -0.46). When a subgroup analysis was performed, the reduction in fasting blood (or plasma) glucose was significant for the subgroup using IAsp as the bolus but not the subgroup using HI as the bolus. The WMD (95% CI) were -0.50 (-1.59, 0.60) and -1.01 (-1.58, -0.43) respectively. Overall, type 1 DM patients receiving IGlAr or IDet as basal insulin had lower fasting blood (or plasma) glucose compared with NPH.

Comparison	Category	Number of Trials	Number of Patients	Random Effects Model	
				WMD (95% CI)	Heterogeneity I <sup>2</sup>
IGlar versus NPH	bolus=all	6	1,682	-0.92 (-1.21, -0.63)	18.9%
	bolus=ILis	2	744	-1.02 (-1.37, -0.67)	0%
	bolus=HI	4	938	-0.86 (-1.37, -0.35)	44.1%
IDet versus NPH	bolus=all	6	2,362	-0.87 (-1.27, -0.46)	49.1%
	bolus=HI	2	1,036	-0.50 (-1.59, 0.60)	65.9%
	bolus=IAsp	4	1,326	-1.01 (-1.58, -0.43)	55.5%

CI=confidence interval; IAsp=insulin aspart; HI=conventional human insulin; IDet=insulin detemir; IGlAr=insulin glargine; ILis=insulin lispro; NPH=neutral protamine Hagedorn; WMD=weighted mean difference.

## Type 2 DM

### *Eight-point blood glucose profiles*

**IGlar versus NPH:** For IGlAr versus NPH, there was no evidence of statistically significant differences between treatments in eight-point blood glucose profiles, although there is an indication that IGlAr might have lowered pre-dinner blood glucose<sup>58,59</sup> and post-dinner blood glucose.<sup>58</sup>

**IDet versus NPH:** For IDet versus NPH, eight-point blood glucose profiles were similar in both treatments when IAsp<sup>50</sup> was used as the bolus or treatment was supplemented with an OAD.<sup>51</sup>

### *Fasting blood glucose*

There were no significant differences between IGlAr and NPH treatments or between IDet and NPH treatments for fasting blood (or plasma) glucose. The Rosenstock *et al.*<sup>57</sup> RCT showed that the fasting plasma glucose levels of patients treated with IGlAr at bedtime were significantly lower than those of patients treated with rosiglitazone (Ros) in addition to sulfonylurea (Sfu; max dose) and metformin (Metf).

### **c) Hypoglycemia**

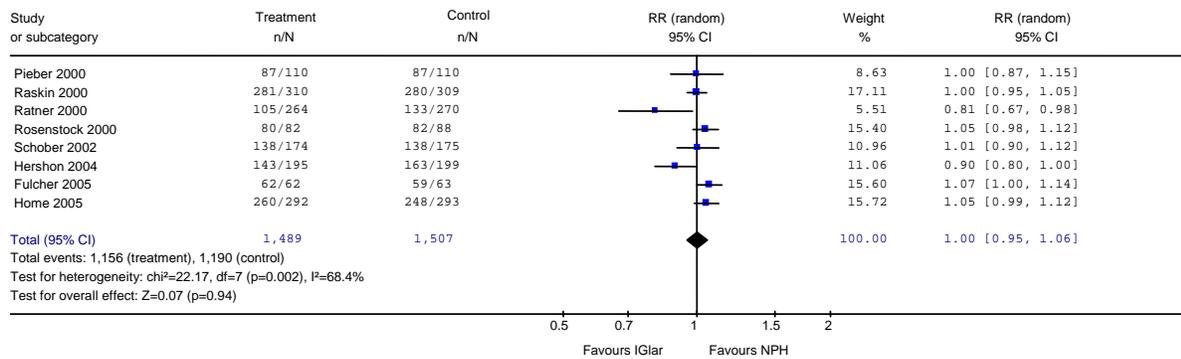
Hypoglycemia is the most common adverse effect of insulin therapy (Appendices 10a and 10b). Some investigators categorized hypoglycemia as overall, severe or major, and nocturnal, whereas others did not. The definition of hypoglycemia varied between trials (Appendices 11a and 11b). We categorized hypoglycemia as it had been defined by the authors of each report. The relative risk (RR) and risk difference (RD) of hypoglycemia were determined using the number of patients who had the

condition, for each treatment arm. We grouped the RCTs according to the type of bolus insulin or OAD used and performed subgroup analyses accordingly.

### Type 1 DM

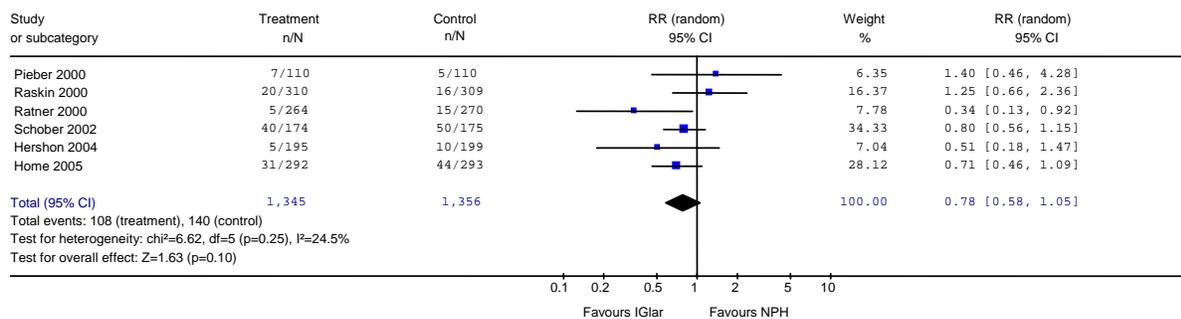
**IGlar versus NPH:** Of eight RCTs examining the effect of IGlar versus NPH on hypoglycemia in type 1 DM patients, eight,<sup>26,29,30,35,38,39,41,44</sup> six,<sup>29,30,35,38,39,44</sup> and seven<sup>26,29,30,35,38,39,44</sup> reported the number of patients experiencing overall, severe, and nocturnal hypoglycemia respectively. The bolus insulin used in each trial was ILis or HI. The pooled estimates of all trials, regardless of bolus insulin type, showed no statistically significant differences between treatments for overall, severe, and nocturnal hypoglycemia. The RR (95% CI) were 1.00 (0.95, 1.06), 0.78 (0.58, 1.05), and 0.92 (0.81, 1.04) respectively (Figures 6 to 8). Two RCTs<sup>26,41</sup> with 381 patients did not report on severe hypoglycemia, and one RCT<sup>41</sup> with 256 patients did not report on nocturnal hypoglycemia.

**Figure 6: RR of hypoglycemia (overall) in type 1 DM patients (IGlar versus NPH)**



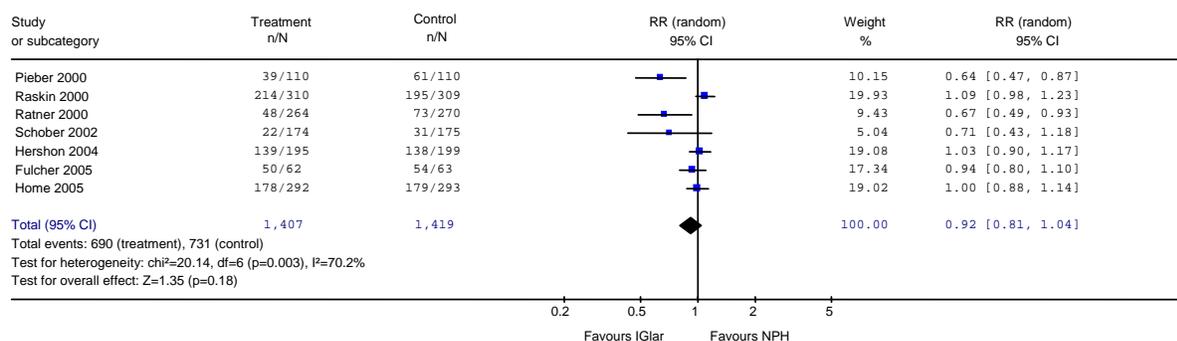
CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RR=relative risk.

**Figure 7: RR of hypoglycemia (severe) in type 1 DM patients (IGlar versus NPH)**



CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RR=relative risk.

**Figure 8: RR of hypoglycemia (nocturnal) in type 1 DM patients (IGlar versus NPH)**



CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RR=relative risk.

For overall hypoglycemia, no statistically significant differences between treatments were observed among trials using ILis<sup>26,38</sup> or HI<sup>29,30,35,39,41,44</sup> as bolus insulin (Table 10). The extent of heterogeneity among trials was 68.4% for all bolus types, 71.6% for bolus ILis, and 65.3% for bolus HI.

For severe hypoglycemia, a statistically significant risk reduction was observed with IGlar treatment compared with NPH treatment in five RCTs<sup>29,30,35,39,44</sup> using HI as the bolus [RR (95% CI): 0.73 (0.55, 0.95)] (Table 10). There was little heterogeneity among these trials ( $I^2=7.4\%$ ). The number needed to treat (NNT) and the corresponding 95% CI obtained by pooling these RCTs was 33 (20, 100), which means that 33 patients (with a 95% CI of 20 to 100 patients) would need to be treated with IGlar to avoid one severe hypoglycemic event. On pooling all RCTs using HI or ILis as the bolus, the NNT (95% CI) was 50 (25,  $\infty$ ). One trial, using IGlar plus ILis<sup>38</sup> as the bolus, showed no significant difference in the number of patients having severe hypoglycemia compared with the NPH plus ILis group (Table 10).

For nocturnal hypoglycemia, no statistically significant differences between treatments were observed among RCTs using ILis<sup>26,38</sup> or HI<sup>29,30,35,39,44</sup> as the bolus insulin (Table 10). The extent of heterogeneity among trials were 70.2%, 74.7%, and 59.9% when considering all bolus types, bolus HI, and bolus ILis respectively.

Overall, there were no statistically significant differences between IGlar and NPH treatments for overall, nocturnal, and severe hypoglycemia, when the data of trials with different bolus types were combined. There were no statistically significant differences between treatments for overall and nocturnal hypoglycemia in trials whether ILis or HI were used as the bolus. There was a statistically significant reduction in risk for severe hypoglycemia in trials using HI as the bolus.

**Table 10: RR and RD of hypoglycemia in type 1 DM patients (IGlar versus NPH)**

				Random Effects Model			
Hypo-glycemia Type	Category	Number of Trials	Number of Patients	RR (95% CI)	Heterogeneity $I^2$	RD (95% CI)	NNT (95% CI)*
overall	bolus=all	8	2,996	1.00 (0.95, 1.06)	68.4%	0.00 (-0.04, 0.04)	NC
	bolus=HI	6	2,252	0.98 (0.91, 1.06)	71.6%	-0.01 (-0.07, 0.04)	NC

**Table 10: RR and RD of hypoglycemia in type 1 DM patients (IGlar versus NPH)**

				Random Effects Model			
Hypo-glycemia Type	Category	Number of Trials	Number of Patients	RR (95% CI)	Heterogeneity I <sup>2</sup>	RD (95% CI)	NNT (95% CI)*
	bolus=ILis	2	744	1.03 (0.96, 1.10)	65.3%	0.03 (-0.04, 0.09)	NC
severe	bolus=all	6	2,701	0.78 (0.58, 1.05)	24.5%	-0.02 (-0.04, 0.00)	50 (25, ∞)
	bolus=HI	5	2,082	0.73 (0.55, 0.95)	7.4%	-0.03 (-0.05, -0.01)	33 (20, 100)
	bolus=ILis	1	619	1.25 (0.66, 2.36)	NA	0.01 (-0.02, 0.05)	NC
nocturnal	bolus=all	7	2,826	0.92 (0.81, 1.04)	70.2%	-0.04 (-0.09, 0.02)	NC
	bolus=HI	5	2,082	0.84 (0.69, 1.02)	74.7%	-0.06 (-0.12, 0.01)	NC
	bolus=ILis	2	744	1.02 (0.88, 1.19)	59.9%	0.02 (-0.09, 0.12)	NC

CI=confidence interval; HI=conventional human insulin; ILis=insulin lispro; NA=not applicable; NC=not calculated; NNT=number needed to treat; RD=risk difference; RR=relative risk. \*NNT (=1/RD) not calculated if 95% CI for RD included both positive and negative values. If 95% CI for RD extends from negative to positive values, then 95% CI for NNT will range between number needed to treat to benefit one [NNT(benefit)] to number needed to treat to harm one [(NNT(harm))].

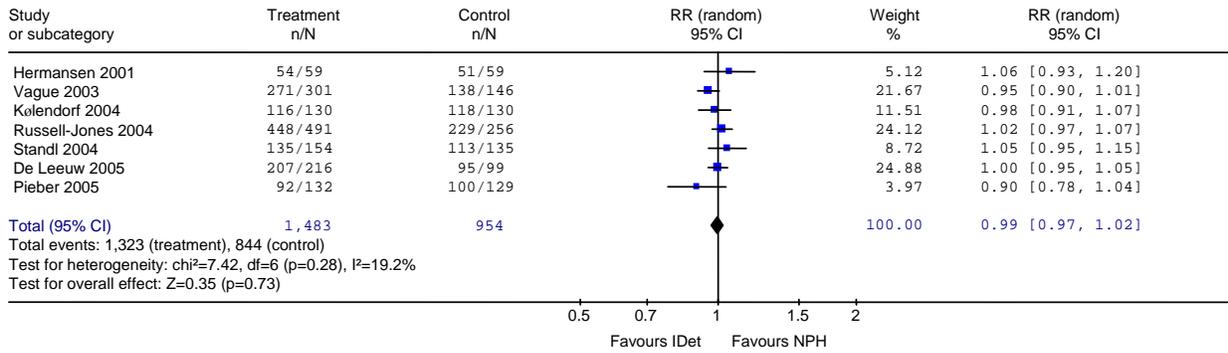
**IDet versus NPH:** Of eight trials examining the effect of IDet versus NPH on hypoglycemia in type 1 DM patients, seven,<sup>25,28,33,36,43,45,46</sup> eight,<sup>25,28,31,33,36,43,45,46</sup> and seven<sup>25,31,33,36,43,45,46</sup> reported overall, severe, and nocturnal hypoglycemia respectively. The bolus insulin in each trial was IAsp or HI.

The pooled estimates of all trials, regardless of bolus insulin type, showed no statistically significant differences between treatments for overall hypoglycemia [RR (95% CI): 0.99 (0.97, 1.02)], and a statistically significant risk reduction in the IDet group for nocturnal hypoglycemia [RR (95% CI): 0.89 (0.82, 0.97)] and severe hypoglycemia [RR (95% CI): 0.75 (0.59, 0.95)] compared with the NPH group (Figures 9 to 11). For overall hypoglycemia, no statistically significant differences between treatments were observed among trials using IAsp<sup>25,33,36,46</sup> or HI<sup>28,43,45</sup> as bolus insulin (Table 11). There was little or no heterogeneity among trials (I<sup>2</sup>=19.2% for all bolus types, I<sup>2</sup>=17.4% for bolus IAsp, and I<sup>2</sup>=0% for bolus HI).

For severe hypoglycemia, a statistically significant reduction in RR was observed with IDet treatment compared to NPH treatment in RCTs<sup>25,31,33,36,46</sup> using IAsp as the bolus [RR (95% CI): 0.70 (0.52, 0.95)] (Table 11). The RD was not statistically significant (Table 11). When HI<sup>28,43,45</sup> was used as the bolus, no statistically significant differences between IDet and NPH treatments were observed [RR (95% CI): 0.83 (0.56, 1.22)]. There was no heterogeneity among trials (I<sup>2</sup>=0%).

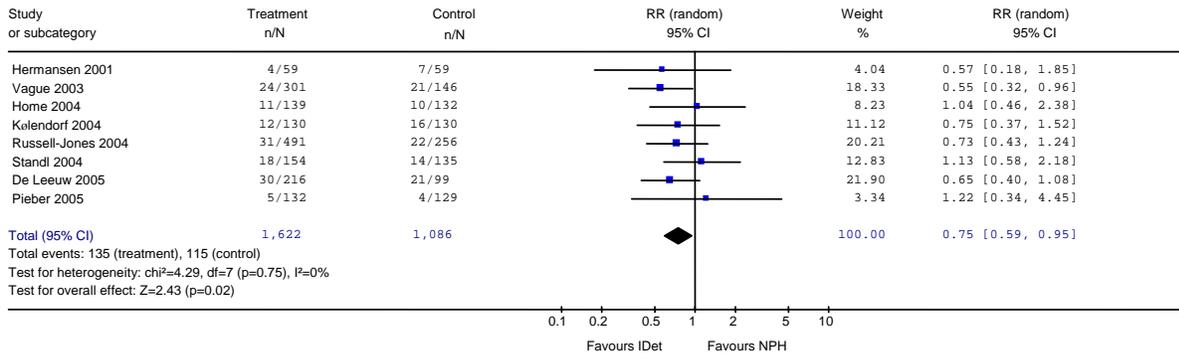
For nocturnal hypoglycemia, a statistically significant reduction in RR was observed with IDet treatment compared with NPH treatment in RCTs<sup>25,31,33,36,46</sup> using IAsp as the bolus [RR (95% CI): 0.84 (0.73, 0.95)] (Table 11). The NNT (95% CI) was 10 (7, 16). When HI<sup>43,45</sup> was used as the bolus, no statistically significant differences between treatments were observed [RR (95% CI): 0.97 (0.89, 1.06)]. The extent of heterogeneity among the trials was 62.1% for bolus IAsp and 0% for bolus HI.

**Figure 9: RR of hypoglycemia (overall) in type 1 DM patients (IDet with NPH)**



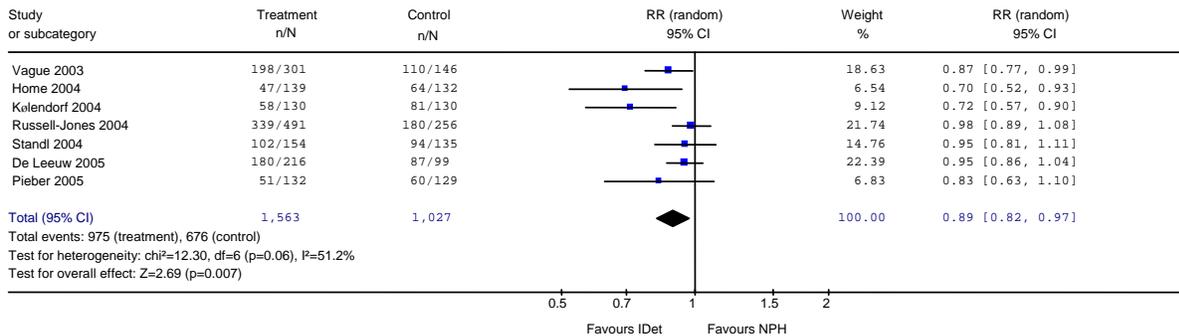
CI=confidence interval; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RR=relative risk.

**Figure 10: RR of hypoglycemia (severe) in type 1 DM patients (IDet with NPH)**



CI=confidence interval; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RR=relative risk

**Figure 11: RR of hypoglycemia (nocturnal) in type 1 DM patients (IDet with NPH)**



CI=confidence interval; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RR=relative risk

**Table 11: RR and RD of hypoglycemia in type 1 DM patients (IDet versus NPH)**

Hypoglycemia Type	Category	Number of Trials	Number of Patients	Random Effects Model			NNT (95% CI)*
				RR (95% CI)	Heterogeneity I <sup>2</sup>	RD (95% CI)	
overall	bolus=all	7	2,437	0.99 (0.97, 1.02)	19.2%	-0.01 (-0.03, 0.02)	NC
	bolus=IAs p	4	1,283	0.97 (0.94, 1.01)	17.4%	-0.03 (-0.06, 0.01)	NC
	bolus=HI	3	1,154	1.03 (0.99, 1.07)	0%	0.02 (-0.01, 0.06)	NC
severe	bolus=all	8	2,708	0.75 (0.59, 0.95)	0%	-0.02 (-0.04, 0.00)	50 (25, 100)
	bolus=IAs p	5	1,554	0.70 (0.52, 0.95)	0%	-0.02 (-0.06, 0.01)	NC
	bolus=HI	3	1,154	0.83 (0.56, 1.22)	0%	-0.02 (-0.05, 0.02)	NC
nocturnal	bolus=all	7	2,590	0.89 (0.82, 0.97)	51.2%	-0.07 (-0.12, -0.03)	14 (8, 33)
	bolus=IAs p	5	1,554	0.84 (0.73, 0.95)	62.1%	-0.10 (-0.14, -0.05)	10 (7, 16)
	bolus=HI	2	1,036	0.97 (0.89, 1.06)	0%	-0.02 (-0.08, 0.04)	NC

CI=confidence interval; HI=conventional human insulin; IAsp=insulin aspart; NC=not calculated; NNT=number needed to treat; RD=risk difference; RR=relative risk; \*NNT (=1/RD) was not calculated if the 95% CI for RD included both positive and negative values. If the 95% CI for RD extends from negative to positive values, then the 95% CI for NNT will range between number needed to treat to benefit one [NNT(benefit)] to number needed to treat to harm one [(NNT(harm))].

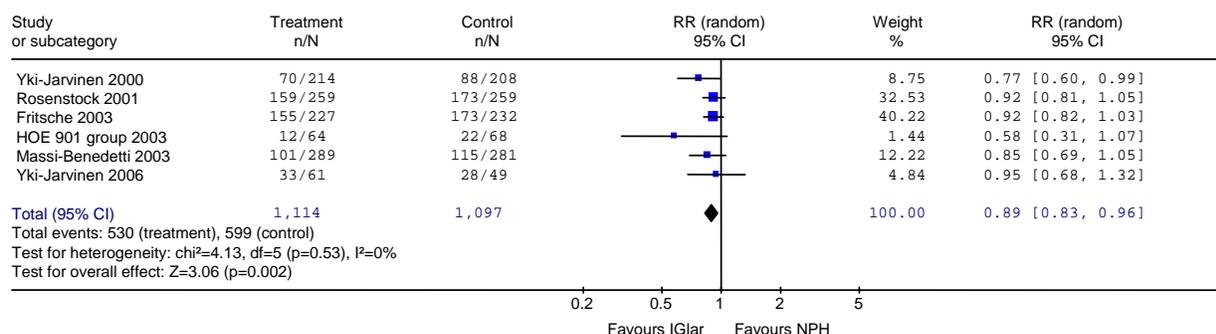
In summary, there were no statistically significant differences between IDet and NPH treatments for overall hypoglycemia, but there was a statistically significant risk reduction in nocturnal and severe hypoglycemia for the IDet group when data of trials with different bolus types were combined. There were no statistically significant differences between treatments for overall hypoglycemia in trials using IAsp or HI as the bolus, but there was a statistically significantly reduced risk for nocturnal hypoglycemia in the IDet group when IAsp was used as the bolus. This was not the case when HI was used as the bolus.

## Type 2 DM

**IGlar versus NPH:** Of six trials examining the effect of IGlar versus NPH on hypoglycemia in type 2 diabetic patients, six,<sup>49,53,56,58-60</sup> five,<sup>49,53,56,58,60</sup> and four<sup>48,49,53,55</sup> reported overall, nocturnal, and severe hypoglycemia respectively. An additional anti-diabetic agent in each trial was OAD or HI.

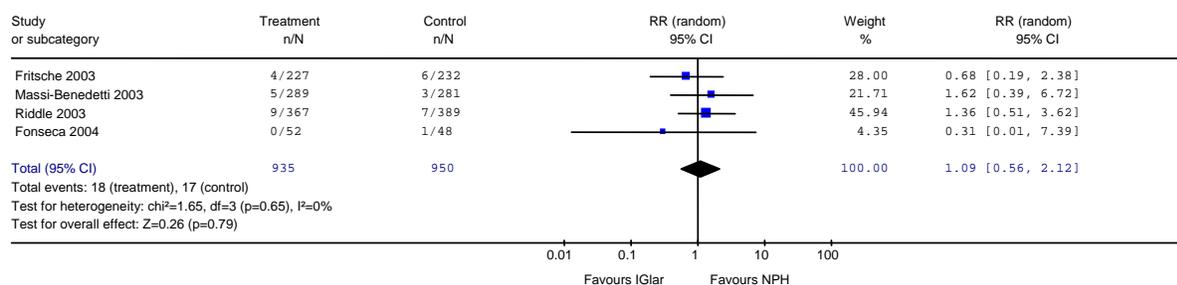
The pooled estimates of all trials regardless of additional anti-diabetic agents showed statistically significant risk reduction with IGlar treatment for overall and nocturnal, but not severe hypoglycemia. The RR (95% CI) were 0.89 (0.83, 0.96), 0.57 (0.44, 0.74), and 1.09 (0.56, 2.12) respectively (Figures 12 to 14).

**Figure 12: RR of hypoglycemia (overall) in type 2 DM patients (IGlar versus NPH)**



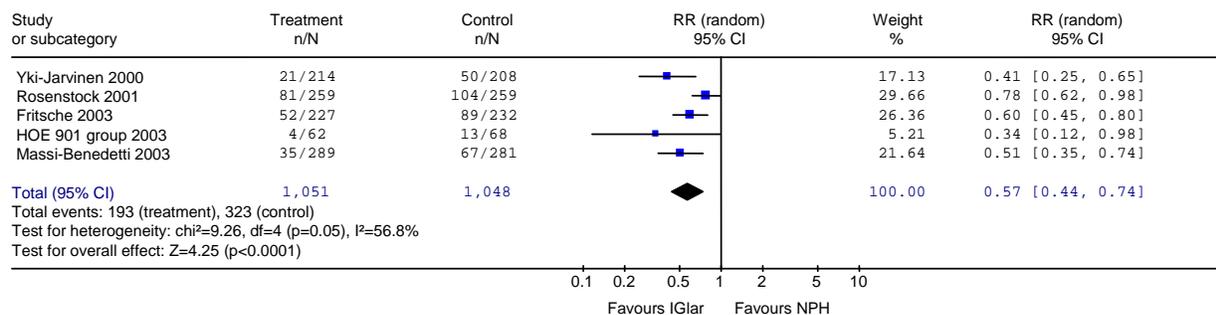
CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RR=relative risk

**Figure 13: RR of hypoglycemia (severe) in type 2 DM patients (IGlar with NPH)**



CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RR=relative risk

**Figure 14: RR of hypoglycemia (nocturnal) in type 2 DM patients (IGlar with NPH)**



CI=confidence interval; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RR=relative risk

For overall hypoglycemia, there was a statistically significant risk reduction in treatment with IGlar plus an OAD compared with NPH plus an OAD.<sup>49,53,58-60</sup> The RR (95% CI) was 0.87 (0.80, 0.95). There was no heterogeneity among trials ( $I^2=0\%$ ) (Table 12). The NNT (95% CI) was 13 (8, 33). One trial<sup>56</sup> reported no statistically significant difference for overall hypoglycemia between IGlar and NPH treatments in addition to HI.

**Table 12: RR and RD of hypoglycemia in type 2 DM patients (IGlar versus NPH)**

Hypoglycemia Type	Category	Number of Trials	Number of Patients	Random Effects Model			NNT (95% CI)*
				RR (95% CI)	Heterogeneity I <sup>2</sup>	RD (95% CI)	
overall	all	6	2,211	0.89 (0.83, 0.96)	0%	-0.07 (-0.11, -0.03)	14 (9, 33)
	HI	1	518	0.92 (0.81, 1.05)	NA	-0.05 (-0.14, 0.03)	NC
	OAD	5	1,693	0.87 (0.80, 0.95)	0%	-0.08 (-0.12, -0.03)	13 (8, 33)
severe	all	4	1,885	1.09 (0.56, 2.12)	0%	0.00 (-0.01, 0.01)	NC
	OAD	3	1,785	1.16 (0.59, 2.28)	0%	0.00 (-0.01, 0.02)	NC
	HI	1	100	0.31 (0.01, 7.39)	NA	-0.02 (-0.08, 0.03)	NC
nocturnal	all	5	2,099	0.57 (0.44, 0.74)	56.8%	-0.12 (-0.16, -0.09)	8 (6, 11)
	HI	1	518	0.78 (0.62, 0.98)	NA	-0.09 (-0.17, -0.01)	11 (6, 100)
	OAD	4	1,581	0.52 (0.43, 0.64)	0%	-0.13 (-0.16, -0.09)	8 (6, 11)

CI=confidence interval; HI=conventional human insulin; NA=not applicable; NC=not calculated; NNT=number needed to treat; OAD=oral anti-diabetic agent; RD=risk difference; RR=relative risk. \*NNT (=1/RD) not calculated if 95% CI for RD included positive and negative values. If 95% CI for RD extends from negative to positive values, then 95% CI for NNT will range between number needed to treat to benefit one [NNT(benefit)] to number needed to treat to harm one [(NNT(harm))].

For severe hypoglycemia, there were no statistically significant differences between IGlar and NPH treatments. The RR (95% CI) were 1.09 (0.56, 2.12) and 1.16 (0.59, 2.28) for all RCTs using an additional OAD or HI and for those using an additional OAD respectively (Table 12). There was no heterogeneity among trials ( $I^2=0\%$ ). One trial<sup>48</sup> using HI as the bolus also showed no statistically significant differences between treatments.

For nocturnal hypoglycemia, a statistically significant risk reduction was observed with IGlar compared with NPH among RCTs also using an OAD.<sup>49,53,58,60</sup> The RR (95% CI) was 0.52 (0.43, 0.64). There was no heterogeneity among trials ( $I^2=0\%$ ) (Table 12). The NNT (95% CI) was 8 (6, 11). When IGlar was given in addition to HI,<sup>56</sup> there was a statistically significant risk reduction in nocturnal hypoglycemia [RR (95% CI): 0.78 (0.62, 0.98)]. The NNT (95% CI) was 11 (6, 100).

Two trials compared the treatment effects of IGlar versus pioglitazone (Pio)<sup>54</sup> or rosiglitazone (Ros)<sup>57</sup> in type 2 DM patients. More patients had overall and severe hypoglycemia when treated with IGlar compared with Pio. More patients had overall and nocturnal hypoglycemia when treated with IGlar compared with Ros. Fewer patients had severe hypoglycemia when treated with IGlar compared to Ros. But the differences were statistically significant only for overall hypoglycemia in the case of IGlar versus Pio and for nocturnal hypoglycemia in the case of IGlar versus Ros.

Statistically significant risk reductions were seen with IGlar treatment for overall and nocturnal, but not severe hypoglycemia, compared with NPH; particularly when IGlar was used in addition to an OAD.

**IDet versus NPH:** One trial<sup>50</sup> reported the number of patients experiencing overall hypoglycemia while being treated with IDet or NPH in addition to IAsp. No statistically significant difference between treatments was observed [RR (95% CI): 0.91 (0.75, 1.11)], but there was statistically a significant risk reduction for nocturnal hypoglycemia in the IDet group [RR (95% CI): 0.66 (0.45, 0.96)]. The NNT (95% CI) was 13 (7, ∞).

**d) Adverse events (excluding hypoglycemia)**

Of the 23 RCTs on type 1 DM patients, 16<sup>25,26,28-31,35,36,38-41,43-46</sup> reported adverse events to varying degrees. Of the 11 RCTs on type 2 DM patients, 10<sup>48-50,53,54,56-60</sup> did so.

Trial investigators used various types and formats to report adverse events in the RCTs. As a result, the data could not be pooled. Adverse events did not seem to be different with the long-acting insulin analogues compared with NPH. Adverse events that were commonly reported with the long-acting insulin analogues were injection site reaction,<sup>25,26,29,30,35,36,38,39,41,44-46,48,53,56,60</sup> upper respiratory tract infection,<sup>26,44,46,48,53</sup> gastrointestinal disorders,<sup>26,44,50,57,59</sup> neuropathy,<sup>48</sup> edema,<sup>25,48,54,60</sup> rhinitis,<sup>26,44,46</sup> headache,<sup>25,26,38,46</sup> and weight gain.<sup>29,38,48-50,53,54,57,59,60</sup> Adverse events that were commonly reported with NPH were injection site reaction,<sup>25,29,30,35,36,38,39,41,45,46,48,53,56,60</sup> upper respiratory tract infection,<sup>26,44,46,48,53</sup> gastrointestinal disorders,<sup>26,44,50,59</sup> neuropathy,<sup>48</sup> edema,<sup>48,54,57</sup> rhinitis,<sup>26,44,46</sup> headache,<sup>26,38,54,60</sup> and weight gain.<sup>29,38,48-50,53,54,57,59,60</sup> Details appear in Appendices 12a and 12b.

**e) Mortality**

**Type 1 DM**

Of the 23 RCTs on type 1 DM patients, three reported mortality data (Appendix 13a). Ratner *et al.*<sup>39</sup> reported no deaths in the IGlAr treatment arm and one death in the NPH treatment arm. The cause of death was considered to be unrelated to the study medication. Pieber *et al.*<sup>36</sup> reported no deaths in the NPH treatment arm and one death in the IDet treatment arm. The cause of death was unknown. Raskin *et al.*<sup>38</sup> reported no deaths in IGlAr or NPH treatment arms.

**Type 2 DM**

Of the 11 RCTs on type 2 DM patients, five reported mortality data (Appendix 13b). Fritsche *et al.*<sup>49</sup> noted two (0.9%) deaths in the IGlAr treatment arm and one (0.4%) death in the NPH treatment arm. Conversely, Massi-Benedetti *et al.*<sup>53</sup> reported one (0.3%) death in the IGlAr treatment arm and six (2.1%) deaths in the NPH treatment arm. Meneghini *et al.*<sup>54</sup> reported one death in the IGlAr treatment arm and none in the OAD (pioglitazone) treatment arm. Haak *et al.*<sup>50</sup> reported one death (0.3%) in the IDet treatment arm and none in the NPH treatment arm. None of the deaths was related to the study medication. The HOE901 Study group<sup>60</sup> reported that there were no deaths in the IGlAr or NPH treatment arms.

**f) QoL**

Two RCTs<sup>34,47</sup> comparing the effects of IGlAr with conventional intermediate- or long-acting insulin [NPH or ultra lente (UL)] in type 1 DM patients reported QoL data. The Kudva *et al.*<sup>34</sup> RCT reported that patients being treated with IGlAr showed no statistically significant difference in fear of hypoglycemia compared with NPH patients (mean±SD: 1.8±0.13 versus 1.7±0.13, p=0.44 in the behaviour scale score), but they did have a statistically significantly lower worry scale score (mean±SD: 1.2±0.12 versus 1.4±0.11, p=0.04). This difference is not considered to be clinically important on a scale that can exceed a score of 25 points for greater fear and worry.<sup>62-64</sup> The Whitthaus *et al.*<sup>47</sup> RCT reported that the scores on all items (satisfaction, convenience, flexibility, and willingness to continue) in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were statistically significantly better with IGlAr than with NPH. In the Well-Being Questionnaire (WBQ),

there was no statistically significant difference between the two treatments in 80% of the items (i.e., depression, anxiety, energy, and positive well-being) (Appendix 14). None of the identified RCTs on type 2 DM patients reported QoL data.

### 4.3 Discussion

Of the 34 RCTs that were included in our review, 23 were on type 1 DM and 11 were on type 2 DM patients. For type 1 DM, 13 RCTs<sup>26,27,29,30,32,35,37-39,41,42,44,47</sup> compared IGlAr with NPH; one<sup>34</sup> compared IGlAr with UL; and nine<sup>25,28,31,33,36,40,43,45,46</sup> compared IDet with NPH. For type 2 DM, seven RCTs<sup>48,49,53,55,56,58-60</sup> were on IGlAr versus NPH, two<sup>54,57</sup> were on IGlAr versus OAD, and two<sup>50-52</sup> were on IDet versus NPH.

In type 1 DM patients, the HbA1c levels were significantly lowered in the IGlAr group compared with the NPH group in one trial,<sup>32</sup> in which IAsp was used as the bolus insulin. The pooled estimate of RCTs where HI was used as the bolus insulin, showed no significant difference between IGlAr and NPH. There were no significant differences observed in HbA1c levels between the IDet and NPH groups, regardless of whether the bolus insulin was IAsp or HI. Type 1 DM patients receiving IGlAr or IDet as basal insulin had significantly lower fasting blood (or plasma) glucose compared with NPH.

For type 1 DM patients, no significant differences were seen between IGlAr and NPH treatments for overall, nocturnal, or severe hypoglycemia when the data from trials with different bolus types were combined. There was a significant risk reduction for severe hypoglycemia in trials using HI as the bolus. There were no significant differences between IDet and NPH treatments for overall hypoglycemia, but there was a significant reduction in relative risk in nocturnal and severe hypoglycemia for the IDet group when data from trials with different bolus types were combined. The RR for nocturnal and severe hypoglycemia was significantly reduced in the IDet group compared with the NPH group when IAsp was used as the bolus. This was not the case when HI was used.

Of the 23 RCTs on type 1 DM patients, two<sup>34,47</sup> reported on QoL, and the results were variable.

In type 2 DM patients, there were no significant differences with respect to HbA1c levels between treatment with long-acting insulin analogues (i.e., IDet or IGlAr) or NPH. There were also no significant differences between IGlAr and NPH treatment for fasting blood (or plasma) glucose. There were significant reductions in RR with IGlAr treatment for overall and nocturnal, but not severe hypoglycemia. One RCT<sup>50</sup> reported the number of patients experiencing overall and nocturnal hypoglycemia while being treated with IDet or NPH in addition to IAsp. No significant difference between treatments was observed for overall hypoglycemia, but there was significant risk reduction for nocturnal hypoglycemia in the IDet group. No QoL data were available in the included RCTs on type 2 DM patients.

As none of the trials was blinded, there is potential for bias. Patients on IGlAr may report less nocturnal hypoglycemia if they were led to believe that the frequency should decrease. Given that nocturnal hypoglycemia is an event that patients often miss, there may be ascertainment bias in that the patients on NPH may be looking for it more.

A decrease in nocturnal hypoglycemia can be important as this is when undetected hypoglycemia may progress to dangerous levels without the patient being able to take appropriate action.<sup>65</sup> Compared with NPH, there seemed to be a decrease in nocturnal hypoglycemia in type 1 DM

patients treated with IDet and in type 2 DM patients treated with IGLar or IDet. Not all RCTs, however, could be pooled because of incomplete data reporting.

Intensive therapy to reduce HbA1c can result in an increased number of hypoglycemic events. Efforts need to be made to control this. Consideration needs to be given to different approaches for the prevention of hypoglycemia. For example, changes in timing of bedtime snacks for type 1 DM patients could be effective in reducing the risk of nocturnal hypoglycemia, regardless of the type of insulin that they may be on. Such prevention strategies would be more attractive economically than choosing a more expensive long-acting insulin analogue over NPH.

Two landmark studies<sup>7,8</sup> reported 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,<sup>8</sup> 1,441 type 1 DM patients were randomly assigned to intensive insulin therapy or conventional insulin therapy and followed for a mean of 6.5 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 United Kingdom Prospective Diabetes Study (UKPDS)<sup>7</sup> randomly assigned 3,867 type 2 DM patients to intensive glucose-control treatment policy or conventional treatment policy. UKPDS<sup>7</sup> showed that an intensive treatment to maintain an 11% lower HbA1c – median 7.0% over the first 10 years after diagnosis of DM – reduces the frequency of microvascular complications but not DM-related mortality or myocardial infarction. The lower the glycemia means a lower risk of microvascular complications. In our review, although lower HbA1c levels were achieved with IGLar than with NPH in type 1 DM in some trials, the magnitude of the difference is not considered to be clinically important. Long-term data on these analogues are unavailable to confirm if this small change translates into fewer complications.

This systematic review and meta-analysis have some limitations. Not all RCT reports documented data on all the outcomes of interest. This can introduce bias, because it has been shown that significant results are more likely to be reported than non-significant results.<sup>66</sup> Also, because of incomplete reporting of data, not all RCTs could be included in the meta-analyses of all outcomes, thereby reducing the statistical power to detect small differences. The comparability of the treatment arms was difficult to determine because of variations in treatments and dose adjustments according to patients' needs. Therefore, when selecting RCTs with comparable treatment arms, we used broad inclusion criteria.

During the selection of relevant trials, it was discovered that there were multiple publications of the same trials. This arose when we compared investigators of the trials and trial characteristics. Duplicate reporting can lead to biased results. For example, it has been reported that the inclusion of duplicated data in Tramer *et al.*'s meta-analysis of ondansetron led to a 23% overestimation of its anti-emetic efficacy.<sup>67</sup> As far as possible, we have excluded duplicate publications of the same trial. It would be useful if trials were identified so that duplicate publications could be easily determined. Efforts are being initiated to encourage trial registration<sup>68</sup> by the investigators, and we hope that this will make trial identification easier.

The adequacy of allocation concealment could not be determined in most trials. This can also introduce bias. Low-quality trials can contribute to overall increased estimates of benefit.<sup>21,22</sup> Most trials were of limited quality, so the results should be viewed cautiously.

It is acknowledged that there is no validated threshold value for Higgin's  $I^2$ . Different investigators have used different threshold values for determining when meta-analysis is inappropriate. For this systematic review, the decision that data would not be pooled if  $I^2 > 75\%$  was made a priori.

Although QoL is an issue in the treatment of DM patients, only two of the 34 included RCTs addressed this issue. Because they assessed QoL using different scales, it was difficult to compare results between trials.

The details about adverse events were not always reported in the RCTs. Because the RCTs were of short duration, it is unknown what adverse events could occur in the long term. Rare adverse events are often not seen in small, short-term trials. The inclusion of observational studies may provide additional data on harms, but this was beyond the scope of this review.

There were some variations in the way that investigators defined hypoglycemia and the way that they characterized the different types of hypoglycemia. In trials where hypoglycemia type was unspecified, it was assumed to be overall hypoglycemia. For analyses, overall and symptomatic hypoglycemia were considered to be in the same group.

We could not address one of our objectives (i.e., to determine if there are differences in the clinical effects of long-acting insulin analogues compared with conventional intermediate- or long-acting insulins when used at the onset versus later in the course of the disease) because of lack of data. With the available evidence, we were unable to identify specific groups of DM patients who may substantially benefit from treatment with long-acting insulin analogues. We also did not identify any RCTs comparing long-acting insulin analogues to conventional intermediate- or long-acting insulins in GDM.

The patient selection criteria for the trials were restrictive, so the results may not be generalizable to all DM patients. Patients with diabetic complications were excluded in most trials. None of the RCTs reported on the effects of conventional intermediate- or long-acting insulins or long-acting insulin analogues in complications of diabetes.

Warren *et al.*<sup>69</sup> published a systematic review in which they concluded that IGLar was not any more effective than NPH in reducing HbA1c levels or controlling symptomatic or severe hypoglycemia. For controlling nocturnal hypoglycemia, they showed that IGLar was superior to once-daily NPH, but not to twice-daily NPH. Our systematic review showed that IGLar treatment resulted in a reduced risk of severe hypoglycemia in type 1 DM with HI as the bolus (though not with ILis as the bolus) compared with NPH. Severe hypoglycemia was not significantly different with IGLar or NPH in type 2 DM. Our systematic review had different inclusion criteria compared to those of Warren *et al.*<sup>69</sup> Their systematic review included 13 trials of which nine were RCTs. Our systematic review included 23 RCTs on IGLar, including RCTs<sup>26,29,30,32,34,37,54,57,59</sup> that have been published since Warren *et al.*'s review.

## 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 with an economic filter, to restrict 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 March 2006 and updated searches on the Cochrane databases regularly. The last Cochrane updates for this report were performed in February 2006. Relevant results found between February 2006 and June 2007 have been noted in the conclusion but are excluded from the economic review. A search was run on HEED: Health Economic Evaluations Database using a parallel search strategy. We obtained supplementary cost information by searching formularies.

#### 5.1.2 Selection criteria and method

##### a) *Selection criteria*

A study was included in the review only if it met the following criteria:

- Study design: full economic study including cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, or cost-benefit analysis; or partial economic study including cost analysis, cost comparison, and cost-consequence analysis
- Study subjects had type 1 DM, type 2 DM, or GDM
- Intervention: long-acting insulin analogues
- Comparator: intermediate- or long-acting conventional insulin or oral anti-diabetic agents.

##### b) *Selection method*

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

#### 5.1.3 Data extraction strategy

After selecting relevant studies, one reviewer (HL) extracted data from each study using a structured form, and another reviewer (SB) checked the data. Differences were resolved by consensus.

#### 5.1.4 Strategy for quality assessment

We used the 35-item BMJ checklist (Appendix 16) to assess the quality of included economic studies. Two reviewers (SB and HL) independently assessed each included economic study and resolved differences by consensus.

### 5.1.5 Data analysis methods

Given the heterogeneity among the economic studies, no attempt was made to combine the results into summary estimates. Instead, we did a qualitative systematic review, summarizing the findings and limitations of the included economic studies.

## 5.2 Results

### 5.2.1 Study identification

A flowchart (based on the QUOROM statement)<sup>70</sup> showing the study selection appears in Figure 15. We identified a total of 303 citations from the economic literature search, after citations that were identified in the previous clinical search were removed. From these, three potentially relevant reports were selected for scrutiny. Of these three, one<sup>71</sup> was selected for inclusion. One economic study<sup>72</sup> was identified from the clinical search, and one<sup>73</sup> was identified from alerts that were established after the original literature search was completed. Thus, a total of three studies were included.

### 5.2.2 Quality assessment results

The quality assessment results appear in Appendix 16.

All three studies<sup>71-73</sup> presented a clear statement of the study question, indicating the form of the economic evaluation and the analysis perspectives. The study by Zhang *et al.*<sup>73</sup> did not state the rationale for choosing the comparator, and the other two studies<sup>71,72</sup> did not mention the economic importance of the research question.

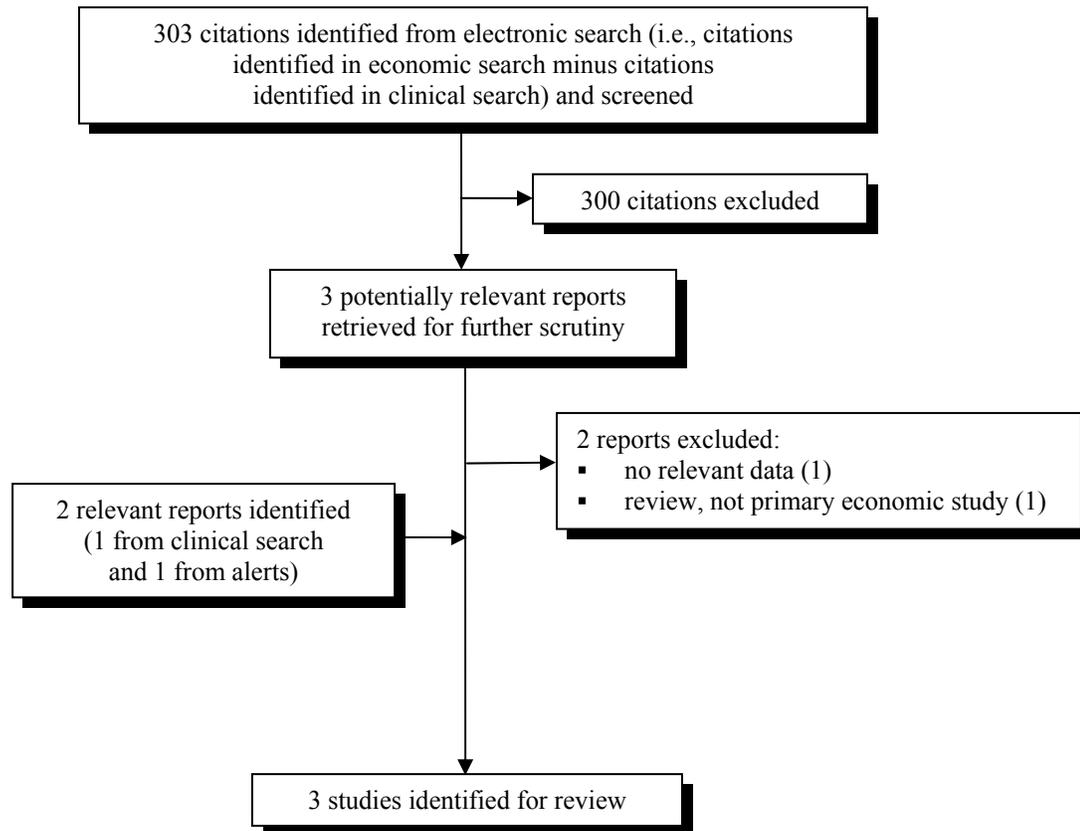
Not all items on the BMJ checklist were applicable for these studies: 89%, 80%, and 63% of the items were applicable for the studies by Palmer *et al.*,<sup>71</sup> Bullano *et al.*,<sup>72</sup> and Zhang *et al.*<sup>73</sup> respectively. When only the applicable items were considered, the percentages of items satisfied for each study were 87%, 68%, and 50% respectively for Palmer *et al.*,<sup>71</sup> Bullano *et al.*,<sup>72</sup> and Zhang *et al.*<sup>73</sup>

### 5.2.3 Study characteristics

Of the three included studies, one was a cost-effectiveness analysis,<sup>71</sup> one a cost-and-consequence study,<sup>72</sup> and one a cost-comparison study.<sup>73</sup> The study characteristics are summarized in Appendix 17.

The cost-effectiveness analysis by Palmer *et al.*<sup>71</sup> adopted a validated, well-known diabetes model, where a series of interdependent Markov sub-models were used to simulate the complications of diabetes. They compared IDet-based therapy with NPH-based basal-bolus therapy for type 1 DM patients in the UK. Their study was from the perspective of National Health Services (NHS) reimbursement, and they used a lifetime horizon.

**Figure 15: Selection of economic studies**



The retrospective study by Bullano *et al.*<sup>72</sup> compared the rates of hypoglycemia and the associated cost consequence in patients who started on IGLar or NPH. The authors obtained pharmacy and medical claims data for individual from a managed care plan in southeastern US. They identified a total of 1,434 DM patients, among whom 310 were in the IGLar group and 1,124 in the NPH group. The authors did not give the number of patients with type 1 DM or type 2 DM. The hypoglycemia event rates were determined with a negative binomial regression model based on a subgroup of patients who had available post-index (after treatment began) HbA1c values. The covariates included the pre-index count of hypoglycemic events, age, gender, best (lowest) post-index HbA1c level, use of insulin, and use of oral hypoglycemic agents.

The study by Zhang *et al.*<sup>73</sup> was similar to the study by Bullano *et al.*<sup>72</sup> in terms of design and data extraction procedure. The diabetes type was not described. Zhang *et al.*<sup>73</sup> used claims data from a state reimbursement program in California. They compared patients having continuous enrolment at least six months before and six months after the IGLar index date with a reference group (i.e., patients not treated with IGLar during those periods). For each group, they determined the costs for diabetes-related care for both six-month periods. They not only considered pharmacy costs, but also costs for emergency department, outpatient, and inpatient care.

The first two studies<sup>71,72</sup> were supported by grants from pharmaceutical companies. Some of the authors of the three included studies were employed by Aventis Pharmaceuticals or Novo Nordisk.

## 5.2.4 Study Results

Because of the heterogeneity that stemmed from study designs, insulin regimens, and study settings, the three reviewed studies<sup>71-73</sup> were not fully comparable. The study by Palmer *et al.*<sup>71</sup> favoured IDet-based therapy over NPH-based therapy. Bullano *et al.*<sup>72</sup> favoured IGlaxar-based therapy over NPH-based therapy. Zhang *et al.*<sup>73</sup> suggested that IGlaxar use was associated with a proportional reduction of hypoglycemia-related inpatient claims (Appendix 18).

### a) **Baseline results**

Palmer *et al.*<sup>71</sup> used the CORE Diabetes model<sup>74</sup> to generate cost-effectiveness results. In their model, they used hypoglycemic events, body mass index, and HbA1c values from a meta-analysis of four RCTs (three<sup>31,43,75</sup> published and one unpublished) comparing IDet-based basal-bolus treatment with NPH-based basal-bolus treatment. They reported that the IDet-based treatment would result in an incremental cost of £22,474 (C\$51,427) per life-year gained and an incremental cost of £19,285 (C\$44,130) per quality-adjusted life-year (QALY) gained, for one type 1 DM patient over a lifetime. They showed that there was a 58% probability that IDet-based basal-bolus treatment would be cost-effective compared to NPH-based basal-bolus treatment, if the willingness to pay for one more life-year was not lower than £30,000 (C\$68,649). The currency exchange rate used for conversion was that for 2003 (i.e., the year when the study was conducted).

Bullano *et al.*<sup>72</sup> showed that at the HbA1c level of 7%, the absolute risk difference in hypoglycemic events per patient per year between treatment with IGlaxar and NPH was 0.11. This corresponds to a NNT of nine for IGlaxar versus NPH, which means that one hypoglycemic event would be avoided for every nine patients treated with IGlaxar instead of NPH. The additional cost incurred in treating nine patients with IGlaxar instead of NPH was US\$423 (C\$664). The mean cost per hypoglycemic event in the outpatient setting was US\$472 (C\$741), and the mean attributable total cost per hypoglycemic event was US\$1,087 (C\$1,707). The currency exchange rate used for conversion was that for 2002, (i.e., the year when the study was conducted). In this population, treatment with IGlaxar resulted in cost savings.

In the study by Zhang *et al.*,<sup>73</sup> the diabetes care costs per patient in the IGlaxar group were US\$1,824.35 (C\$2,865) and US\$1,639.17 (C\$1,986.02) for six months before and after the index date respectively. This resulted in a cost savings of US\$185.17 (C\$291) in the post-index period. The corresponding values for the reference group were US\$680.08 (C\$1,068) and US\$608.08 (C\$955) for before and after index dates and a savings in the post-index period of US\$71.53 (C\$117). Compared to the reference group, the absolute cost reduction for each IGlaxar user was US\$113.64 (C\$178). Taking into consideration the higher baseline treatment cost in the IGlaxar group compared with the reference group, the authors found that the relative cost savings was US\$68.99 (C\$108). The currency exchange rate used for conversion was that for 2002, (i.e., the year when the study was conducted). In the IGlaxar group, the increased pharmacy and outpatient care costs were offset by the reduced emergency-department and inpatient care costs.

### b) **Sensitivity analysis results**

Palmer *et al.*<sup>71</sup> showed that the differences in HbA1c had the greatest impact on the incremental cost-effectiveness ratio (ICER). When hypoglycemic events and body mass index were not considered and only the differences in HbA1c were considered (0.37% reduction with IDet versus 0.22% reduction with NPH), the costs per QALY gained increased from £19,285 (C\$44,130) to £20,910 (C\$47,848). Varying the cost of a major hypoglycemic event between £0 (C\$0) and £382 (C\$874) had a small effect on the ICER [£19,968 per QALY (C\$45,693 per QALY) and £18,787 per QALY (C\$42,990 per QALY)] respectively. For shorter time horizons of five years and 15 years, the

ICERs were £36,885 per QALY (C\$84,403) and £22,766 per QALY (C\$52,095) respectively. If the characteristics of the simulated cohort in this study were similar to the sample in the Diabetes Control and Complications Trial,<sup>8</sup> the IDet-based combination would be more efficient based on the estimated ICER value [(£16,293 per/QALY (C\$37,283 per QALY)].

Bullano *et al.*<sup>72</sup> performed sensitivity analyses showing that when the mean or last HbA1c value was substituted for the best HbA1c value in the negative binomial regression model, the calculated hypoglycemic event rate changed by <1%. This resulted in a NNT of nine patients to avoid one hypoglycemic event. With target HbA1c values of 8% and 9%, the NNT was between nine and 10. For an NNT of 10, treatment with IGlAr was associated with cost savings compared with NPH.

Zhang *et al.*<sup>73</sup> did not perform sensitivity or statistical analysis for their baseline results. Instead, they did a separate analysis on a subset of patients to assess the cost implications of switching from thiazolidinedione or NPH insulin to IGlAr. The daily cost of treatment per patient was reduced by US\$1.81 (C\$2.84) by switching from thiazolidinedione to IGlAr and increased by US\$0.46 (C\$0.72) by switching from NPH to IGlAr. The authors did not examine the impacts of these switchings on medical claims (other than pharmacy claims) in this sample.

## 5.3 Discussion

Of the three included economic studies, two compared IGlAr with NPH, and one compared IDet with NPH. Two studies<sup>71,72</sup> were sponsored by industry, and all three studies had at least one investigator affiliated with the company that developed the long-acting insulin analogue. Both studies<sup>72,73</sup> on IGlAr versus NPH suggested that the avoidance of hypoglycemic events with IGlAr offsets the increased drug cost and resulted in cost savings. Palmer *et al.*<sup>71</sup> concluded that for type 1 DM patients, within a plausible range of assumptions, IDet-based basal-bolus therapy is likely to be considered good value for money [£19,285 (C\$44,129) per QALY] when compared with NPH-based basal-bolus therapy in the UK. These studies have some limitations.

Palmer *et al.*<sup>71</sup> based their analysis on differences in HbA1c value of -0.15 with IDet compared with NPH and assumed that this difference was maintained over a lifetime. Our meta-analysis of eight RCTs<sup>25,31,33,36,40,43,45,46</sup> comparing IDet with NPH in type 1 DM patients, showed that there were no significant differences in HbA1c levels between the two treatments. From this perspective, the results of Palmer *et al.*<sup>71</sup> are not generalizable and need to be viewed in context.

Palmer *et al.*<sup>71</sup> used the results of a meta-analysis of four RCTs (three<sup>31,43,75</sup> published and one unpublished), for which the maximum length of follow-up was 24 weeks. This is short compared with the lifetime horizon used in their economic evaluation. As a result, their projection for long-term effectiveness is unsubstantiated.

In the Bullano *et al.* study,<sup>72</sup> the IGlAr group and the NPH group were significantly different in several demographic and clinical characteristics including mean age, duration of follow-up, percentage of people with different co-morbidities, and payer type. They reported for hypoglycemia a NNT value of nine in DM patients achieving an HbA1c level of 7%. Our meta-analysis showed that in type 1 DM patients, for severe hypoglycemia, the risk difference between IGlAr and NPH corresponded to the NNT (95% CI) of 50 (25 to ∞). In type 2 DM patients, the risk difference between IGlAr and NPH was not significant. The results of Bullano *et al.*<sup>72</sup> pertain to the population that they studied and cannot be generalized.

Zhang *et al.*<sup>73</sup> showed that the inpatient and emergency department claims between pre- and post-index periods changed by a greater degree in the IGLar-treated group than in the reference group. In their study, the characteristics of the two groups, including diabetic complications and co-morbid conditions, were apparently not equivalent. The IGLar group was likely sicker than the reference group and probably benefited more when treated. Therefore, it is uncertain if the study results were due to the better efficacy of IGLar treatment compared with treatment in the reference group or due to different characteristics in the two groups.

We did not identify any long-term economic studies on IGLar treatment or economic studies specifically on type 2 DM patients. Of the three studies, two<sup>72,73</sup> were non-specific (i.e., involved DM patients) so they may have had a proportion of type 2 DM patients in their study samples. Both these studies were based on a one-year horizon.

Warren *et al.*<sup>69</sup> reviewed the economic analysis for IGLar submitted to NICE by Aventis. They found that the models in the submission were generally of poor quality, and that the cost per QALY of IGLar over the comparator was underestimated. Because details of the industry submission were confidential, they were not presented in the published HTA report. Warren *et al.* did not identify any other economic reviews when they prepared their report. Our review included three recent economic studies, including one full economic evaluation on IDet versus NPH. The other two on IGLar versus NPH were not full economic evaluations, so the results could not be compared with Warren *et al.*'s evaluation.

## 6 HEALTH SERVICES IMPACT

### 6.1 Population Impact

The number of people with diabetes in Canada for 1998 to 1999, 2000 to 2001, and 2003 were 865,908; 1,063,698; and 1,222,882 respectively.<sup>76-78</sup> The prevalence of diabetes varied depending on province, age, sex, and year.<sup>79</sup> There was a gradual increase over the years (Table 13).

Insulin is indicated for all type 1 DM and for those type 2 DM patients who cannot achieve adequate glycemic control by other measures. Of all diagnosed DM cases, 90% are type 2 and 10% are type 1.<sup>80</sup> As a result, 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 assuming that 10% of type 2 DM patients would be on insulin therapy – based on a report by Boucher *et al.*<sup>81</sup> – the estimated number of insulin users in Canada for these years were 164,523, 202,103, and 232,348 respectively.

As with the prevalence of DM, there seems to be an increase in the number of insulin users. This estimation is subject to the reliability of the ratio of 1:9 between type 1 DM and type 2 DM. The proportion of types of DM among total DM patients varies according to the age range considered. Type 1 DM most commonly develops before the age of 30 years, and type 2 DM typically develops with increasing age.<sup>5</sup> Thus, the numbers are likely to be overestimates of the number of type 2 DM patients and underestimates of the number of type 1 DM patients in the younger age group, with the opposite in the older age group. The impact of these biases on the estimate of total insulin users is difficult to determine because of the lack of specific data.

**Table 13: Prevalence of diabetes in Canada**

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
Quebec	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			2.9	3.5	3.7	3.7
Northwest Territories			1.6	3.9	3.5	3.5
Nunavut			F	F	F	F

Data obtained from Statistics Canada,<sup>76-78</sup> data with coefficient of variation >33.3% suppressed (F) because of extreme sampling variability.

## 6.2 Budget Impact

### 6.2.1 Objective

This budget impact analysis was undertaken from the perspective of provincial drug plans to estimate based on limited data the financial implications of giving long-acting insulin analogues open listing. For precise values, drug planners need to conduct their budget estimation with specific and sufficient data.

### 6.2.2 Method

In Canada, there is no national guideline for doing a budget impact analysis. The governments of Alberta, Manitoba, and Ontario give templates to manufacturers for budget impact information, requiring different levels of detail.<sup>82</sup> In this analysis, we used a claim-based approach, given the available data.

We estimated each province's budget in future years under the scenario where no long-acting insulin analogues are listed in the formulary, and the present status for other relevant insulin continues. Then, we forecasted the budget under the scenario where long-acting insulin analogues have open listing. Finally, by subtracting the former from the latter, we evaluated the potential financial impact of listing long-acting insulin analogues on provincial drug plans.

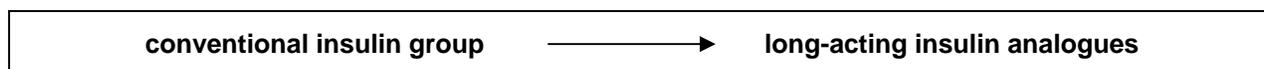
In the first scenario, the total budget was the sum of expenditures on all included insulin products. For each insulin product, the total cost was the sum of the number of potential users and the cost per person per year for that product. The number of potential users was estimated by linear regression based on the available drug utilization data. Some products showed declining use with time, but we did not allow for negative values. In those cases, we adjusted the values to zero, to be realistic.

In the second scenario, where long-acting insulin analogues have open listing, we estimated the number of potential users for each type of insulin product and then calculated the expenditures. The regression analysis in the first scenario generated increasing or decreasing numbers of potential users for each type of insulin over the years. We took these year-by-year changes into subsequent calculations to incorporate the growth or reduction in the pool of conventional insulin users over time for reasons other than the listing of long-acting insulin analogues.

We calculated the budget for future years by assuming that a proportion of conventional insulin users switched to the insulin analogues, but that no reverse switching (from insulin analogue to conventional insulin) occurred. We also assumed that patients who were starting to take insulin, would first be treated with conventional insulin. As a result, the number of insulin analogues users in the first future year equalled the number of patients leaving the conventional insulin pool. In the following years, the number of insulin analogue users would continue to increase with additional conventional insulin users switching to insulin analogues.

Estimating the number of conventional insulin users was more complex. In the first future year, the number of conventional insulin users equalled the number of conventional insulin users from the previous year (obtained from drug utilization data) minus the number switching to insulin analogues (based on an assumed switching rate) plus the number due to annual growth (estimated from linear regression analysis). For subsequent future years, we calculated the number of conventional insulin users similarly, except that we estimated the number for the corresponding previous year from linear regression. We programmed the calculations using Excel and checked the validity by testing to see if the budget impact was negligible when no patients switched to insulin analogues.

As the yearly switching rate is unknown, we conducted our analyses assuming different values: 10%, 25%, 50%, 75%, and 100%. For instance, if the switching rate is 10% yearly, then 10% of conventional insulin users in one year would switch to long-acting insulin analogues the following year. The switching scenario in our analysis is:



Because our analysis was done from a provincial drug plan perspective, it tends to reflect all costs to the drug plan, and may include part of pharmacy markups and dispensing fees, depending on the province.

The drug utilization data included total annual expenditures, number of patients, unit price of each insulin product, and number of dosage form units reimbursed.

The unit cost information for conventional insulin came from two sources: the published provincial drug benefit formularies and if that was unavailable, the provincial drug benefit databases. For the long-acting insulin analogues, no province listed IGLar or IDet (as of March 2006), so for IGLar, we used the price (C\$55.07) provided by the Patented Medicine Prices Review Board PMPRB.<sup>83</sup>

Because the price of IDet is under review by PMPRB (as of March 31, 2006), we used the current wholesale purchase price provided by the manufacturer (Novo Nordisk Canada Inc.). We used the WHO-defined daily dose for insulin products.<sup>84</sup>

We did a yearly budget analysis from 2006 to 2008. Then, we summed the yearly results for a three-year budget impact estimation. We used an inflation rate of 3%. We obtained the formulary status of the insulin products from the Canadian Institute for Health Information (Table 14).

Table 14: Formulary status												
Description	DIN PDIN	BRAND NAME	BC	AB	SK	MB	ON	NB	NS	PE	NL	YT
INSULIN(HUMAN)	00984299	GE NPH PENFILL VIAL ONLY									B	
INSULIN(HUMAN)	00908991	HUMLIN NPH VIAL ONLY									B	
INSULIN(HUMAN)	00646148	HUMULIN LENTE INJ MEDIUM 100U/mL susp ER	B	B	B	B	B	B	B	B	B	B
INSULIN(HUMAN)	02241310	HUMULIN N 100U/mL sol	B									
INSULIN(HUMAN)	01959239	HUMULIN N 100U/mL susp	B	B	B	B		B	B	B	B	B
INSULIN(HUMAN)	09853804	HUMULIN N 100U/mL susp 3mL Cartridge					B					
INSULIN(HUMAN)	00587737	HUMULIN N INJ 100U/mL sol	B	B	B	B	B	B	B	B	B	B
INSULIN(HUMAN)	00977675	INSULIN NOVOLIN GE NPH									B	
INSULIN(HUMAN)	02024241	NOVOLIN GE LENTE INJ SC 100U/mL susp			B	B					B	
INSULIN(HUMAN)	02024225	NOVOLIN GE NPH INJ 100U/mL susp	B	B	B	B	B	B	B	B	B	B
INSULIN(HUMAN)	02024268	NOVOLIN GE NPH PENFILL INJ 100U/mL susp	B	B	B	B	B	B	B	B	B	B
INSULIN(HUMAN)	09853782	NOVOLIN GE NPH PENFILL INJ 100U/mL susp - 3mL					B					
INSULIN(PORK)	00514535	LENTE PURIFIED PORK INSULIN INJ 100U/mL susp ER			B	B		B			B	
INSULIN(PORK)	00514551	NPH PURIFIED PORK INSULIN INJ 100U/mL sol	B	B	B	B	B	B	B		B	B
INSULIN(HUMAN)	00733075	HUMULIN ULTRALENTE INJ 100U/mL susp ER	B	B	B	B	B	B	B	B	B	B
INSULINGLARGINE	02245689	LANTUS 100 U/mL										

Source: National Prescription Drug Utilization Information System (NPDUIS), Canadian Institute for Health Information (CIHI), 2005  
 Formulary data as of September 2005 were used except where noted for British Columbia, Alberta (October 1, 2005), Saskatchewan, Manitoba (products available through Part III of the Manitoba Formulary that have not been announced are excluded), Ontario, Newfoundland and Labrador, Nova Scotia, New Brunswick, First Nations and Inuit Health Branch, Yukon (November 2004). Information does not differentiate between different plans and programs available in each jurisdiction.  
 For product with "B" status, no justification required for reimbursement.  
 B = benefit.

The insulin products used in our analyses were long-acting insulin analogues and alternative conventional insulins (Table 11). The products that were selected for the analysis were determined by considering four situations: whether it is listed in the current provincial drug benefit formulary, whether the Health Canada Drug Product Database showed “active product” status for it, whether its utilization data for the latest year are available, and whether the forecasted expenditure by simple linear regression is positive.

<b>Table 15: Included insulin products by province</b>									
	<b>DIN</b>	<b>BC</b>	<b>SK</b>	<b>MB</b>	<b>AB</b>	<b>ON</b>	<b>NL</b>	<b>NS</b>	<b>NB</b>
<b>Long-Acting Insulin Analogues</b>									
LANTUS (IGLAR)		✓	✓	✓	✓	✓	✓	✓	✓
LEVEMIR (IDET)		✓	✓	✓	✓	✓	✓	✓	✓
<b>Conventional Insulin Group</b>									
<b>(NPH)</b>									
NOVOLIN GE NPH INJ	2024225	✓	✓	✓	✓	✓	✓	✓	✓
NOVOLIN GE NPH PENFILL INJ	2024268	✓	✓	✓	✓	✓	✓	✓	✓
NOVOLIN NPH INJ	612197	✓							
NPH PURIFIED PORK INSULIN (ILETIN II NPH)	514551	✓	✓	✓	✓	✓	✓	✓	✓
NOVOLIN GE NPH INJ	1934066	✓							
HUMULIN N INJ	587737		✓	✓	✓	✓	✓	✓	✓
HUMULIN N	1959239		✓	✓	✓		✓	✓	✓
HUMULIN N	9853804					✓			
<b>(Lente)</b>									
HUMULIN L LENTE INJ	646148	✓	✓	✓	✓	✓	✓	✓	✓
<b>(Ultra Lente)</b>									
HUMULIN ULTRA LENTE	733075	✓	✓	✓	✓	✓	✓	✓	✓

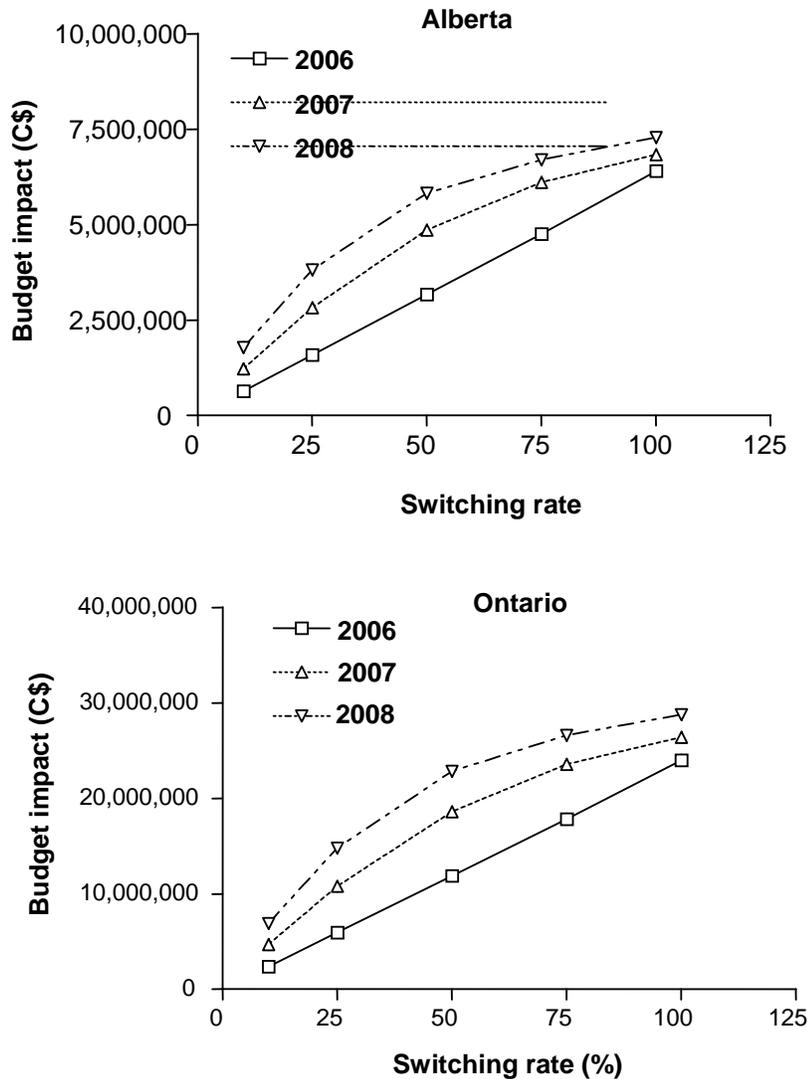
### 6.2.3 Results

The total budget required by drug plans for insulin products increases when long-acting insulin analogues are listed (Table 16), because of the higher cost of the analogues. The budget impact increased linearly with the switching rate for the first future year (i.e., 2006) but tended to level off in subsequent years (i.e., 2007 and 2008) (Figure 16).

**Table 16: Budget impact estimation results by province by year**

Province	Switching Rate	Budget Impact by Year			Budget Impact for 3 Years
		2006	2007	2008	
BC	10%	466,590	908,739	1,330,739	2,706,068
	25%	1,167,683	2,098,579	2,855,365	6,121,627
	50%	2,335,300	3,613,092	4,385,853	10,334,245
	75%	3,502,701	4,560,278	5,067,273	13,130,252
	100%	4,691,192	5,005,755	5,382,238	15,079,186
AB	10%	634,122	1,223,855	1,779,998	3,637,975
	25%	1,585,552	2,823,559	3,815,055	8,224,166
	50%	3,169,117	4,854,045	5,821,770	13,844,932
	75%	4,754,601	6,101,090	6,697,749	17,553,440
	100%	6,404,588	6,827,957	7,279,280	20,511,826
SK	10%	482,490	928,268	1,338,078	2,748,837
	25%	1,208,183	2,140,864	2,863,397	6,212,444
	50%	2,415,783	3,678,208	4,355,118	10,449,109
	75%	3,624,649	4,628,876	5,038,140	13,291,665
	100%	4,886,276	5,204,383	5,529,335	15,619,993
MB	10%	461,815	896,887	1,311,673	2,670,375
	25%	1,153,275	2,068,901	2,810,703	6,032,880
	50%	2,304,301	3,560,616	4,304,946	10,169,863
	75%	3,457,461	4,487,141	4,955,026	12,899,628
	100%	4,635,530	4,940,421	5,274,353	14,850,304
ON	10%	2,377,252	4,666,685	6,878,014	13,921,951
	25%	5,942,919	10,776,014	14,777,260	31,496,192
	50%	11,885,755	18,581,754	22,804,383	53,271,893
	75%	17,828,593	23,542,932	26,584,306	67,955,830
	100%	23,984,274	26,371,808	28,759,342	79,115,423
NB	10%	142,486	276,519	403,408	822,413
	25%	356,169	639,223	867,563	1,862,955
	50%	710,614	1,098,614	1,333,836	3,143,064
	75%	1,066,658	1,392,279	1,559,196	4,018,133
	100%	1,440,517	1,569,321	1,698,124	4,707,962
NS	10%	251,992	494,329	729,148	1,475,469
	25%	627,261	1,139,351	1,563,532	3,330,144
	50%	1,254,525	1,965,857	2,414,906	5,635,288
	75%	1,882,049	2,488,994	2,796,872	7,167,914
	100%	2,525,248	2,752,335	2,973,617	8,251,200
NL	10%	108,859	205,153	291,696	605,708
	25%	270,910	472,313	621,472	1,364,695
	50%	541,826	810,133	951,283	2,303,242
	75%	812,400	1,023,262	1,115,925	2,951,586
	100%	1,105,673	1,178,480	1,250,753	3,534,906

**Figure 16:** Trend in budget impact over three years



## 6.2.4 Discussion

Our analysis quantitatively shows that as increasing numbers of patients switch to long-acting insulin analogues, provincial drug plans will need to increase their budgets accordingly. Because the analysis was based on several assumptions, the results should be viewed with these limitations in mind.

In real-life situations, insulin regimens must be adapted to each patient's treatment goals, health, and behaviour. This includes using specific insulin doses. Our budget impact analysis did not consider these variations. Using the WHO's defined daily dose for each insulin product and assuming that patients did not change their insulin regimens over the time horizon of our analysis, we would have overestimated the cost of insulin products to government drug plans. It is likely that people switch between insulin types in the period that we considered in our analysis or they may not use the same dose for the entire period. Because the budgets would have been overestimated for both future

scenarios, our estimation is likely reliable. Also, when the switching rate was zero, our analysis model generated a zero or negligible result, confirming the model's validity.

Another variable in our analysis is the unit cost of each type of insulin. In Canada, drug beneficiaries' reimbursements vary and may include dispensing fees or require a patient's co-payment, depending on the provincial drug plan and patients' specific situations. Also, the prices for IGLar and IDet used in our analysis may not be the same when they are eventually listed in the drug plans. Given these variables, our forecasted budget impact must be interpreted in the context of each province's drug plan. If the prices are adjusted, the budget impact evaluation would change accordingly.

Switching between the insulin products is a complex issue in terms of its direction and degree. To simplify it, 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. Given the available data, it seemed impossible to capture this complex situation for our analysis. Our assumptions about patients' switching patterns may have resulted in overestimating the number of insulin analogue users and underestimating the number of conventional insulin users in the second scenario. Given the higher unit cost of insulin analogues, our budget impact is likely to be overestimated.

Alberta, New Brunswick, Nova Scotia, Ontario, and Newfoundland provided fiscal year data. British Columbia, Manitoba, and Saskatchewan gave calendar year data. Thus, the corresponding estimations for each province were fiscal-year or calendar-year results, depending on the province.

Because our estimation for future years was based on provincial reimbursement data, and products and prices specific to each province, our budget forecasts are specific to each province. In computing the budget impact, the rate of patients switching from conventional-insulin to long-acting insulin analogues was varied over a wide range (10% to 100%) to adequately capture the possible scenarios. Our budget impact analysis provides insight into how the provincial drug plans would be affected if long-acting insulin analogues were open-listed.

## **6.3 Ethical-Equity and Psychosocial Issues**

### **6.3.1 Ethical issues**

Universal access to care is the foundation of the Canadian health care system. This relates mainly to services covered by each provincial insurance plan (e.g., access to physicians and hospital care) and less so to access to ambulatory treatments, which are not covered equally by all provincial health care plans. In discussing access to newer or more expensive medications, universality is an essential component, because potentially beneficial medications should be equally accessible to all individuals independent of private drug insurance plans.

Two principles that underlie the ethical medical treatment of patients – justice and respect for persons – presuppose reasonable access to all available medications that have demonstrated efficacy for a disease. Two other principles (beneficence and non-maleficence) also factor into this discussion. In this context, beneficence implies the demonstrated efficacy of a medication, and non-maleficence is the lack of incremental risk of minor or serious adverse events due to a medication.

The potential (theoretical) advantage of long-acting insulin analogues (i.e., IGLar and IDet) include a lower risk of hypoglycemia, reported in some, but not all comparisons, and specifically in terms of risk of severe hypoglycemic episodes and nocturnal hypoglycemia. No specific deleterious effects of the long-acting insulin analogues have been determined, although the duration of their widespread use is too short to determine long-term effects, such as mitogenicity (ability to affect cell division).

Another ethical issue to be considered is that of informed consent. Health care professionals should make their patients aware of the available treatment options and their reasons for choosing a specific approach for the patient. Informed consent is not required for insulin analogues in jurisdictions where they are approved for use. Where approval for the use of an agent has not been granted for a particular indication (e.g., pregnancy or very young children), the off-label use of such an agent requires informed consent from the patient or a surrogate.

### 6.3.2 Psychosocial issues

DM is a psychologically and behaviourally demanding disease, and psychosocial factors play a pivotal role in almost all aspects of its management.<sup>4,85</sup> Individuals with DM face a series of challenges that affect all aspects of their daily lives. They often feel so overwhelmed by the daily challenges of managing their disease and so burdened by the self-care demands that they undergo “diabetes burn-out” (the inability to meet the ongoing demands for excellent self-care).<sup>86</sup>

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 more often present in diabetic ketoacidosis at disease onset, have more episodes of this condition during the course of DM, attend clinics less frequently, and are less likely to achieve and maintain good DM control.<sup>87</sup> Nearly half of all teens with type 1 DM have a period of “pervasive non-compliance” with their routines such as insulin injections, monitoring, and nutritional planning. These teens are more likely to show significant psychopathology, particularly depression, as young adults.<sup>88</sup> Others have reported an increased prevalence of depression in adults with type 1 DM compared with the general population.<sup>5,89-91</sup> Depression is associated with poor control and health complications in type 1 DM and type 2 DM.<sup>92</sup>

Emotional stress may provoke behavioural changes that result in a lack of adherence to dietary, exercise, or therapeutic regimens, with significant negative consequences. For example, fear of hypoglycemia may interfere with an individual’s ability to achieve normoglycemia. This may be based on previous episodes of severe hypoglycemia, or it may be part of anxiety about DM.<sup>93</sup> Fear of hypoglycemia influences patients’ health outcomes such as blood glucose, management awareness and control, self-treatment modifications, and post-episode lifestyle changes.<sup>94</sup>

Nearly a quarter of teenage and young adult females with type 1 DM have a full-blown or sub-threshold eating disorder at some stage.<sup>95</sup> Eating disorders are often associated with insulin omission to control weight through induced glycosuria, poor glycemic control, and earlier onset of DM-related complications.<sup>96</sup>

Any consideration of the benefits or risks of long-acting insulin analogues must take into account the psychosocial issues, such as convenience of use and personal preference of these agents over traditional treatment approaches, in addition to clinical and economic issues.

Long-acting insulin analogues are dispensed in vials (IGlar) and cartridges (IGlar, IDet) for use with syringes and insulin pens respectively, in the same way as other insulin preparations. There have been insufficient studies to be able to reach conclusions on the impact of long-acting insulin analogues on the quality of life of people with type 1 DM or type 2 DM. More studies are warranted, specifically on the relationship between long-acting analogue use and hypoglycemia, because there may be a potential for reducing fear of hypoglycemia in some individuals.

The increased cost of long-acting analogues may deter some individuals without drug insurance coverage from using them. Insulin, however, constitutes a relatively small expense in comparison to the cost of other diabetes supplies, especially that of glucose strips.

Overall, the demonstrated and theoretical psychosocial outcomes provide no evidence of disadvantage with long-acting insulin analogues for people requiring insulin.

## 7 CONCLUSIONS

The evidence suggests that the use of long-acting insulin analogues does not result in the attainment of clinically important outcomes for all individuals with DM. In patients with type 1 DM, IGlar resulted in statistically significantly greater reduction in HbA1c levels compared with NPH, in some trials. The magnitude of the reduction, however, was not clinically important. Among patients with type 2 DM, HbA1c levels were similar when treated with NPH, IGlar, or IDet. IGlar reduced the risks of severe hypoglycemia in type 1 DM patients on bolus HI, and IDet reduced the risks of severe and nocturnal hypoglycemia in type 1 DM patients on bolus IAsp. For patients with type 2 DM, pooled analyses suggest that IGlar reduced the risk of overall and nocturnal but not severe hypoglycemia, while one RCT suggested that IDet can significantly reduce the incidence of nocturnal hypoglycemia. RCTs investigating QoL were sparse. Long-term studies of good quality are needed to determine the benefit and harm of long-acting insulin analogues compared with conventional insulins.

Three economic studies, which were sponsored by industry or had industry affiliation, showed results in favour of long-acting insulin analogues compared with NPH. These findings are limited to the study settings. Future studies should be conducted with a longer time horizon, and be based on updated and more reliable clinical data.

The prevalence of diabetes is increasing among Canadians and, along with it, the number of insulin users. This will result in increased expenditures for insulin products. If conventional insulin users switch to the more expensive insulin analogues, there will be further demands on drug plans. As long-term data on insulin analogues are unavailable, the impact on health care resources is difficult to predict.

Nine RCTs<sup>97-105</sup> and four economic studies<sup>106-109</sup> published after the completion of our report were identified from alerts (February 2006 to June 2007). Of these nine published RCTs, information on three<sup>98,99,102</sup> were available from posters<sup>33,40,51</sup> and were already included in our assessment.

Of the nine RCTs, three<sup>97-99</sup> were on type 1 DM, and six<sup>100-105</sup> were on type 2 DM (Appendix 19 and 20). Of the three RCTs on type 1 DM, one<sup>97</sup> compared IGlar with NPH, and two compared IDet with NPH.<sup>98,99</sup> Of the six RCTs on type 2 DM patients, two<sup>101,105</sup> compared IGlar with OAD, two<sup>100,104</sup>

compared IGlár with NPH, and two<sup>102,103</sup> compared IDet with NPH. The overall results of these RCTs are similar to those of RCTs included in our report and are unlikely to affect its conclusions.

All four economic studies<sup>106-109</sup> published in 2007 are model-based full economic evaluations that lead to the same conclusions as the three studies included in our assessment. The recent four studies suffer from the same limitations as the three studies included in our assessment, including weak evidence supporting the assumptions of clinical outcomes, the impact of hypoglycemia on health-related quality of life outcomes, and the potential influence by pharmaceutical industry sponsorship as reflected by employees serving as authors. Four economic studies comparing IGlár with NPH were sponsored by Sanofi-Aventis (the manufacturer of IGlár).

A Cochrane review by Horvath *et al.*,<sup>110</sup> comparing long-acting insulin analogues with NPH in type 2 DM patients, was published after the completion of our assessment. Their findings were similar to ours: metabolic control, measured by HbA1c, and adverse effects did not differ in a clinically relevant way between treatment groups. There was no statistically significant difference in severe hypoglycemia between treatment groups. Overall and nocturnal hypoglycemia were statistically significantly lower in patients treated with IGlár or IDet than with NPH. Hovarth *et al.* suggested a cautious approach to therapy with IGlár or IDet until long-term efficacy and safety data are available.

The formulary status of the conventional insulins and long-acting insulins has been updated since the completion of our assessment (Appendix 22). The change in the formulary status is unlikely to significantly change the results of our budget impact analysis (BIA).

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