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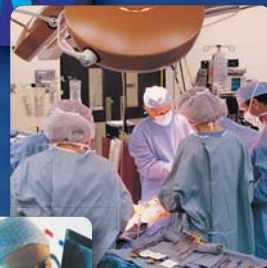


## T E C H N O L O G Y   O V E R V I E W

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Insulin Analogues for Diabetes  
Mellitus: Review of Clinical Efficacy  
and Cost-Effectiveness



*Supporting Informed Decisions*

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# Canadian Agency for Drugs and Technologies in Health

## Insulin Analogues for Diabetes Mellitus: Review of Clinical Efficacy and Cost-Effectiveness

October 2007

We thank Eugenia Palylyk-Colwell for her assistance in creating this overview from two longer reports authored by Banerjee, *et al.*

This overview is based on Technology Reports commissioned by CADTH: Banerjee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, Campbell K, *Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness* [Technology report number 87]; and 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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## Insulin Analogues for Diabetes Mellitus: Review of Clinical Efficacy and Cost-Effectiveness

### Technology and Condition

Short-acting insulin analogues (SAIAs) for the treatment of type 1, type 2, and gestational diabetes mellitus (DM), including insulin lispro (ILis), insulin aspart (IAsp), and insulin glulisine (IGlu). Long-acting insulin analogues (LAIAs) used as basal insulin: insulin glargine (IGlar), and insulin detemir (IDet) for the treatment of type 1 and type 2 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

Separate systematic reviews were undertaken for SAIAs and LAIAs to evaluate the clinical and economic implications of their use in treating DM compared with conventional human insulin (HI) and oral anti-diabetic agents (OADs). For the SAIAs, 86 randomized controlled trials (RCTs) were included: 47 on type 1 DM, 26 on type 2 DM, 10 on types 1 and 2 DM (combined), and three on gestational DM. For the LAIAs, 34 RCTs were eligible for review: 23 on type 1 DM and 11 on type 2 DM. Meta-analyses were performed for certain outcomes. The budget impacts to publicly funded provincial drug plans were examined.

### Implications for Decision Making

- **The impact on blood sugar control was variable.** For patients with type 1 DM, treatment with the SAIAs ILis or IAsp significantly reduced glycated hemoglobin (HbA1c) levels, a widely used marker of blood sugar control, compared to HI. This effect was not seen in those with type 2 DM. The LAIAs have not demonstrated clinically important differences in HbA1c levels in types 1 and 2 DM.
- **Reduced complications from therapy can occur.** The evidence suggests that IGlar can reduce the risk of severe hypoglycemia in type 1 DM patients and the risk of nocturnal hypoglycemia in patients with type 2 DM. IDet reduced the risk of severe and nocturnal hypoglycemia in type 1 DM patients. No reductions in hypoglycemia were observed with the SAIAs or with IDet in type 2 DM patients. For type 1 DM patients, nocturnal hypoglycemia was less frequent with ILis than with HI; and episodes of overall and severe hypoglycemia were similar with the SAIAs and HI.
- **Funding decisions may require more compelling economic evidence.** Publicly funding the insulin analogues will require a 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 two comprehensive health technology assessments available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Banerjee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, Campbell K. *Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness* [Technology Report number 87]; and 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.

# 1 Introduction

Diabetes mellitus (DM) affects more than 2.25 million Canadians, 90% of whom are diagnosed with type 2 (non-insulin-dependent) and 10% with type 1 (insulin-dependent) DM. Gestational DM (GDM) occurs when the body cannot properly use insulin during pregnancy. DM is the seventh leading cause of death in Canada<sup>1</sup> and is associated with morbidity due to microvascular and macrovascular complications, gastroparesis, infections, and skin changes.<sup>2</sup> The treatment of DM and its complications costs more than C\$9 billion annually (including costs that arise from premature death and lost productivity).<sup>1</sup> Expenditures continue to increase because of the increasing incidence of type 2 DM as a result of the aging population and rising obesity rates.

The successful management of DM involves a combination of lifestyle measures (e.g., diet, exercise and weight control), blood-glucose monitoring, oral anti-diabetic drugs (OADs), and insulin. All type 1 DM patients need insulin, whereas type 2 DM patients may manage their disease through lifestyle changes. If still uncontrolled, OADs or insulin are added. In GDM or in patients with DM who become pregnant, treatment with conventional human insulin (HI) is recommended.<sup>3</sup> Insulin is administered by subcutaneous injection via a syringe, pen-like injection device, or pump (also known as continuous subcutaneous insulin infusion or CSII).<sup>3</sup>

The maintenance of near normal glycemic levels has been shown to reduce the risk of microvascular complications in type 1 and type 2 DM.<sup>4-6</sup> The Canadian Diabetes Association's clinical practice guidelines recommend the following glycemic targets for adults:  $\leq 7\%$  for glycated hemoglobin (HbA1c), 4.0 mmol/L to 7.0 mmol/L for preprandial glucose, and 5.0 mmol/L to 10.0 mmol/L for postprandial glucose.<sup>3</sup> In most insulin users, multiple daily injections (MDI) of a short- and intermediate- or long-acting insulin are needed to mimic physiological insulin secretion. Endogenous insulin secretion is a complicated process, with small amounts (basal insulin) secreted throughout the day and larger amounts (bolus insulin) secreted in response to changes in blood glucose (i.e., such as those produced by meals). As a result, patients must coordinate the dosing and timing of their insulin injections with meals and physical activity to avoid hyperglycemia or hypoglycemia.

Insulin analogues (IAs) were developed to more closely mimic the pattern of normal insulin secretion (i.e., rapid increase in levels after eating and basal levels between meals). The short-acting insulin analogues (SAIAs) that are approved in Canada are insulin lispro (ILis) or Humalog<sup>®</sup>, insulin aspart (IAsp) or NovoLog<sup>®</sup>/NovoRapid<sup>®</sup>, and insulin glulisine (IGlu) or Apidra<sup>®</sup>. The approved long-acting insulin analogues (LAIAs) are insulin glargine (IGlar) or Lantus<sup>®</sup> and insulin detemir (IDet) or Levemir<sup>®</sup>. All are available in 100 U/mL strengths. Pre-mixed formulations contain a short-acting and an intermediate-acting insulin analogue (IA) in a fixed ratio. Premixed HI contains neutral protamine Hagedorn (NPH). Premixed IAs contain neutral protamine lispro or aspart as the intermediate-acting insulin (Table 1).

The price – in Canadian dollars – of Humalog<sup>®</sup> varies from \$25.14 (10 mL vial) to \$63.39 (5×3 mL pre-filled pen); that of Humalog<sup>®</sup> Mix25, from \$50.28 (5×3 mL cartridge) to \$63.39 (5×3 mL pre-filled pen); and that of NovoRapid<sup>®</sup>, from \$24.60 (10 mL vial) to \$49.23 (5×3 mL cartridge). The price of conventional HI (e.g., Humulin<sup>®</sup> R) ranges from \$16.72 (10 mL vial) to \$34.67 (3 mL cartridge). The price – in Canadian dollars – of Lantus<sup>®</sup> is \$109.87 (5×3mL cartridge) and that of Levemir<sup>®</sup> is \$109.86 (5×3mL cartridge) compared to that of Humulin<sup>®</sup> N, L or U at \$16.72 (all 10 mL vials).<sup>7,8</sup> Overall, IAs are more expensive than HI.

<b>Table 1: Pharmacokinetic profiles* of insulin and insulin analogues</b>			
<b>Insulin or Insulin Analogue Preparation</b>	<b>Onset of Action (hours)</b>	<b>Peak Action (hours)</b>	<b>Duration of Action (hours)</b>
<b>Conventional short-acting insulin</b>			
HI (Humulin-R, Novolin)	0.5 to 1	2 to 4	5 to 8
premixed HI (Humulin 70/30, 50/50)	0.5 to 1	dual	10 to 16
<b>Short-acting insulin analogues</b>			
ILis or IAsp (Humalog, NovoRapid)	0.1 to 0.25	0.5 to 1.5	5
premixed ILis or IAsp (Humalog Mix 75/25, NovoRapid Mix)	0.1 to 0.25	dual	10 to 16
<b>Conventional long-acting 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 (Ultra lente, Humulin U)	2 to 4	8 to 10	18 to 30
<b>Long-acting insulin analogues</b>			
IGlar (Lantus)	1 to 2	N/A	20 to 24
IDet (Levemir)	1 to 2	N/A	10 to 18

\*Time courses of action represent averages and may differ from person to person and in an individual from one injection to another. HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; NPH=neutral protamine Hagedorn; IGlar=insulin glargine; IDet=insulin detemir; N/A=not applicable.

In light of limited health care resources, decision makers want to know if the use of IAs is justified for all or some populations of DM patients. This information will help determine the listing status of IAs in provincial drug plans.

## 2 Objectives

The aim of the systematic review was to evaluate the clinical efficacy and cost implications of using SAIIAs or LAIIAs in the treatment of DM. This objective was accomplished by addressing the following questions in two separate reviews, one of which examined SAIIAs while the other examined LAIIAs.

- What is the clinical efficacy of IAs compared to conventional HI or OADs in the treatment of type 1 DM, type 2 DM, or GDM?
- What are the benefits and harms from a clinical and patient's perspective?
- Are there subpopulations of DM patients who may benefit from treatment with IAs, in comparison to HIs or OADs?
- What are the benefits and harms of combining IAs with OADs compared to combining conventional HI with OADs in the treatment of type 2 DM, from a clinical and patient's perspective?
- Compared to conventional HI, do IAs produce different clinical effects when used at the onset of the disease versus later, for patients with type 2 DM?
- What is the cost-effectiveness evidence of using IAs in the treatment of type 1 or type 2 DM?

## 3 Clinical Review

### *Methods*

Published literature for SAIAs and LAIAs was obtained by searching the Medline, Biosis Previews, PASCAL and EMBASE databases from 1990 onwards, with no language restrictions. Parallel searches were run on PubMed and the Cochrane databases. The original searches were performed in August 2005. Alerts on MEDLINE, Biosis Previews, and EMBASE databases were regularly reviewed to capture new studies until January 1, 2006 (SAIAs) or February 6, 2006 (LAIAs). Updated searches on the Cochrane databases were done regularly until February 6, 2006. For the LAIAs, relevant reports that were published between February 2006 and June 2007 were noted in the discussion but were not considered in the systematic review. Grey literature was obtained by searching the web sites of regulatory agencies, health technology assessment, near-technology assessment agencies, professional associations (and associated conference sites), and other specialized databases. The Google and Dogpile search engines were used to search the Internet.

Reviewers independently selected trials for inclusion based on the following selection criteria: study design (randomized controlled trial or RCT), population (patients with type 1 DM, type 2 DM, or GDM), intervention [SAIAs (ILis, IAsp or IGlu) or LAIAs (IGlar or IDet)], comparator (conventional HI or OADs), and outcomes [glycemic control by HbA1c level and blood glucose level, hypoglycemic episodes, adverse events (AEs), mortality, quality of life (QoL), and complications from DM]. Reviewers independently extracted data from each trial using a structured form. Any differences between reviewers regarding trial selection or data extraction were resolved by consensus. The quality of the included trials was rated using the Jadad scale,<sup>9</sup> and information on allocation concealment, blinding of assessors, and intention-to-treat analysis was recorded.

When appropriate, data were quantitatively pooled and summary estimates computed using Cochrane Review Manager 4.2.3 software. The fixed-effects or random-effects model was used depending on the statistical heterogeneity between studies. When extensive heterogeneity was present (i.e., Higgin's  $I^2 > 75\%$ ), the data were not pooled. For the analysis of continuous data, when standard deviation (SD) values were not reported, they were calculated from the standard error (SE). If variance was not specified as SD or SE, it was assumed to be one or the other if the values were in the ranges reported in other trials. For HbA1c and hypoglycemia results, negative values for the weighted mean difference (WMD) indicate better results with IAs than with conventional HI or OADs. The WMD is statistically significant if the 95% CI excludes zero. For binary data, a relative risk (RR) of  $< 1$  indicates reduced risk with IAs and is statistically significant if the 95% CI excludes one. The outcome data were analyzed according to the type of DM and IA. For the LAIAs, subgroup analysis was also performed according to the substance used as a bolus.

### *Results*

#### a) Short-acting insulin analogues

A total of 841 citations were identified from the original search. Of these, 761 were excluded, resulting in 80 relevant reports plus nine reports from other sources to yield 89 included reports describing 86 unique RCTs. Reference information for the included RCTs appears in the full report.<sup>7</sup> There were 47 RCTs conducted in type 1 DM (n=10 to 1,184), 27 in type 2 DM (n=21 to 876), 10 in types 1 and 2 DM (n=14 to 892), and three in GDM (n=41 to 65). All studies were conducted in adults except eight RCTs in type 1 DM that involved only pediatric populations. All but eight of the

trials were of low methodological quality (Jadad score  $\leq 2$ ). Because of incomplete data reporting, not all RCTs could be included in all meta-analyses.

**HbA1c:** In type 1 DM, pooled data from 34 RCTs (n=8,435) that compared ILIs with HI revealed that HbA1c levels were lower with ILIs. Subgroup analyses showed that HbA1c levels were statistically significantly lower with ILIs for RCTs longer than three months' duration, in adult patients, and when administered by CSII. Pooled data from eight RCTs (n=2,948) comparing IAsp and HI found that HbA1c levels were lower with IAsp, which was statistically significant for multiple daily injection or CSII. One RCT (n=564) comparing IGlu and HI found no significant differences in HbA1c levels.

For type 2 DM, when data from 10 RCTs (n=2,844) comparing ILIs and HI or six RCTs (n=750) comparing IAsp or biphasic IAsp and HI were pooled, no statistically significant differences were found between treatments. When data from six RCTs (n=1,400) comparing ILIs and sulfonylurea OADs were pooled, a statistically significant reduction in HbA1c with ILIs was found, although there was heterogeneity among trials. The pooled results of two RCTs (n=239) comparing biphasic IAsp and sulfonylureas showed a significant reduction in HbA1c levels with biphasic IAsp. The pooled results of two trials (n=1,768) comparing IGlu and HI did not show a significant reduction.

Five RCTs reported HbA1c data for a combined study population of type 1 and type 2 DM patients. Four of these studies compared ILIs and HI (n=378), and one compared IAsp and HI (n=291). Although the levels of HbA1c were lower, the results were not statistically significant for either SAIA. Two RCTs (n=91) comparing ILIs and HI in GDM patients could be pooled. The HbA1c level was higher with ILIs, but the results were not statistically significant.

**Blood glucose:** For type 1 DM, 27 ILIs and 10 IAsp trials compared eight-point blood-glucose profiles between SAIA and HI. Summary estimates were not calculated, but most RCTs showed that SAIA resulted in lower blood glucose levels after meals compared with HI. Pre-meal blood glucose levels were higher with SAIA in some trials, but unchanged or lower than HI in other trials. Summary estimates were derived for preprandial and postprandial blood-glucose levels in RCTs comparing ILIs (or premixed ILIs) and HI (or premixed HI). In four RCTs (n=233) comparing fasting and three RCTs (n=2014) comparing preprandial levels in type 1 DM, the pooled results showed no statistically significant differences between treatments. Using pooled data from two RCTs (n=2,074) comparing one-hour postprandial blood-glucose levels and six RCTs (n=2,210) comparing two-hour postprandial blood-glucose levels in type 1 DM patients, statistically significant reductions were found with ILIs compared to HI.

In type 2 DM, summary estimates were not calculated for the eight-point glucose profiles but four RCTs showed that patients treated with ILIs had lower blood-glucose profiles post-meals than with OADs, although differences pre-meals, at bedtime, and at night varied among trials. The limited data led to inconclusive comparisons of profiles between ILIs or IAsp and HI. Trials reporting preprandial and postprandial blood-glucose levels showed that ILIs or IAsp controlled postprandial levels better than HI or OADs such as sulfonylureas. There was no conclusive evidence for fasting or preprandial levels.

In combined type 1 and type 2 DM, two RCTs found that eight-point blood-glucose profiles post-breakfast, pre-lunch, post-dinner, and at bedtime were significantly lower with ILIs than HI. Two

RCTs studying preprandial and postprandial levels between ILis and HI had conflicting results. In GDM patients, two RCTs showed lower postprandial levels with ILis.

**Hypoglycemia:** In type 1 DM, most RCTs comparing ILis and HI found no statistically significant differences in the incidence of overall hypoglycemia. Three of 34 trials reporting on hypoglycemia showed a significant reduction with ILis. Because of high heterogeneity, data could not be pooled for several subgroup analyses, i.e., adult patients, >3 months' treatment, parallel trials, MDI. Pooled data from nine of 16 RCTs (n=2,579) reporting rates of severe or major hypoglycemia revealed no statistically significant differences between treatments. Pooled data for nocturnal hypoglycemia from four of eight RCTs (n=1,377) found that rates were statistically significantly lower with ILis. For IAsp versus HI, one of five RCTs showed a significant reduction in overall hypoglycemia, and one of seven RCTs reported a lower rate of severe or major hypoglycemia with IAsp. For nocturnal hypoglycemia, two of three RCTs (n=273) reported a significant reduction with IAsp, but a long-term study over three years (n=753) found no statistically significant differences between IAsp and HI. One trial with IGlu found no significant differences versus HI for symptomatic or nocturnal hypoglycemia, although there was a higher (non-statistically significant) rate of severe hypoglycemia with HI.

In type 2 DM, pooled data from seven RCTs (n=2,762) of ILis versus HI found no significant differences in the rates of overall hypoglycemia. The pooled results of two RCTs (n=1,570) found a significant reduction in nocturnal hypoglycemia with ILis. When data were pooled for two RCTs (n=881) comparing ILis and sulfonylureas, episodes of nocturnal hypoglycemia were significantly reduced with ILis. The calculated relative risk (RR) for comparisons of overall, severe, or nocturnal hypoglycemia between ILis and HI were all non-statistically significant. For IAsp versus HI, the pooled results showed no significant differences in RR between treatments, although RR was significant in one RCT comparing the risk of overall hypoglycemia between IAsp and OADs. The comparisons of IGlu and HI found no significant differences in overall or severe hypoglycemia.

There were no statistically significant differences found for overall hypoglycemia in RCTs of type 1 and type 2 DM patients or of GDM patients.

**Adverse events:** Data on AEs were sparsely reported and if available, were mostly described qualitatively and judged to be unrelated to treatment. Reported AEs included headache, pharyngitis, rhinitis, upper respiratory infection, and injection site reaction. In general, there were no differences between SAIAs and HI.

**Mortality:** For type 1 and type 2 DM, five RCTs for each reported mortality data. There were no differences in the numbers of deaths between SAIAs and HI. The rates were low and inconsistently reported.

**Quality of Life:** Type 1 DM patients preferred ILis over HI because of convenience (i.e., the ability to administer it immediately before a meal). There was limited evidence to support an advantage on the basis of well-being. IAsp was found to be significantly superior to HI for total QoL in three of four RCTs. In type 2 DM, there were no differences in patients' satisfaction or well-being with ILis versus HI, although treatment with biphasic ILis (Mix25) showed higher satisfaction over OADs in some trials, but not in others.

## b) Long-acting insulin analogues

Of the 841 originally identified citations, 817 were excluded, resulting in 24 relevant reports plus 12 reports from other sources to yield 36 included reports describing 34 unique RCTs. Reference information for the included RCTs can be found in the full report.<sup>8</sup> There were 23 RCTs conducted in patients with type 1 DM (n=14 to 749) and 11 with type 2 DM (n=110 to 756). All studies were conducted in adults, except three RCTs in type 1 DM that involved pediatric or young adult populations. Most trials were of limited methodological quality (mean Jadad score of 2.3; seven RCTs in type 1 DM and five RCTs in type 2 DM received a Jadad score of 3). Because of incomplete data reporting, not all RCTs could be included in all meta-analyses.

**HbA1c:** Because of heterogeneity, RCTs in patients with type 1 DM comparing HbA1c levels between IGLar and NPH could not be pooled. The levels were statistically significantly lower in five of 11 RCTs reporting such data; in no case did such differences achieve the minimal clinically important difference of a 1.0 point reduction in HbA1c levels. The pooled estimate from eight RCTs (n=2,937) comparing insulin detemir (IDet) and neutral protamine Hagedorn (NPH) revealed no statistically significant differences between treatments. Subgroup analyses based on bolus type (HI, ILis, or IAsp) resulted in some statistically significant differences with ILis and IAsp given as a bolus for IGLar but not IDet.

In type 2 DM, there were no statistically significant differences in the pooled results from seven RCTs (n=2,967) comparing IGLar and NPH or two RCTs (n=980) comparing IDet and NPH. In these nine RCTs, even when significant differences were detected, the difference was not considered to be clinically significant (i.e., the change was <1% in HbA1c).

**Blood glucose:** In type 1 DM, three RCTs compared IGLar and NPH. Two showed no statistically significant treatment differences in eight-point blood glucose profiles, and one showed significantly lower levels with IGLar at most time points. Eight RCTs compared IDet and NPH, and blood glucose profile results varied between trials. Six RCTs (n=1,682) compared IGLar and NPH on the basis of fasting blood (or plasma) glucose. Pooled estimates showed a significant reduction with IGLar, which was true regardless of bolus type. IDet and NPH were compared in six RCTs (n=2,362), and the pooled estimate for fasting blood (or plasma) glucose was significant in favour of IDet.

In type 2 DM, the comparisons of IGLar or IDet with NPH did not reveal any significant differences in eight-point blood-glucose profiles or fasting-blood (or plasma) glucose between treatments.

**Hypoglycemia:** In type 1 DM, eight RCTs (n=2,996) comparing IGLar and NPH using ILis or HI as bolus insulin provided data for the assessment of hypoglycemia. Pooled estimates, regardless of bolus type, by overall, severe, or nocturnal hypoglycemia resulted in no statistically significant differences between treatments. There was, however, a significant risk reduction in severe hypoglycemia when data from five RCTs (n=2,082) using HI as bolus were pooled. Data pooled from seven RCTs (n=2,437) comparing IDet and NPH using IAsp or HI as bolus insulin showed no significant treatment differences for overall hypoglycemia. There were significant differences in favour of IDet for nocturnal and severe hypoglycemia when data were combined. There were statistically significant risk reductions with IDet when five RCTs (n=1,554) using IAsp as bolus (but not HI) were combined for severe and nocturnal hypoglycemia.

In type 2 DM, the pooled estimates of RCTs comparing IGLar and NPH, regardless of the use of additional anti-diabetic agents, revealed statistically significant risk reductions in overall and

nocturnal hypoglycemia from six RCTs (n=2,211) and five RCTs (n=2,099) respectively, but not severe hypoglycemia. One trial of IDet versus NPH found no statistically significant treatment differences for overall hypoglycemia. There was a significant risk reduction for nocturnal hypoglycemia with IDet.

**Adverse events:** Sixteen of 23 RCTs for type 1 DM and 10 of 11 RCTs for type 2 DM reported AE data. The differences in reporting format precluded data pooling. Overall, AEs did not seem to differ between LAIAs and NPH insulin.

**Mortality:** Three of 23 RCTs for type 1 DM and five of 11 RCTs for type 2 DM reported mortality data. The numbers of deaths were small and seem similar between LAIAs and NPH. None of the reported deaths were considered to be related to treatment.

**Quality of life:** Two RCTs comparing IGLar and NPH or ultra lente (UL) insulin in type 1 DM patients reported QoL data. In the first trial, there was no statistically significant difference in fear of hypoglycemia between treatments. There was a significantly lower worry scale score in IGLar patients, although this was not considered to be clinically significant. In the second trial, IGLar patients had statistically significantly better scores than NPH patients on satisfaction, convenience, flexibility, and willingness-to-continue scores, but not on well-being. No QoL data were available for type 2 DM.

## 4 Economic Review

### *Methods*

Identical literature searches and alerts as those performed for the clinical review were conducted for the economic review, except that an economic filter was used to restrict the results to relevant economic records. Searches were conducted on the Health Economic Evaluations Database (HEED) using a parallel search strategy. Supplementary cost information was obtained by searching formularies.

Reviewers independently selected studies for inclusion based on the following selection criteria: study design [full economic study including cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), or partial economic study including cost analysis, cost comparison, or cost-consequence analysis], study indications (type 1 or type 2 DM, GDM), intervention [SAIAs (ILis, IAsp, IGlu) or LAIAs (IGlar or IDet)], and comparator (conventional HI or OADs). Studies were excluded if only the abstracts were available or if they were published as non-English reports. Reviewers extracted data using a structured form. Any differences between reviewers in study selection or data extraction were resolved by consensus. The quality of the included studies was assessed by reviewers using the 35-item *British Medical Journal (BMJ)* checklist.<sup>10</sup> Any differences were resolved by consensus.

Given the heterogeneity between economic studies, no attempt was made to combine the results into summary estimates. A qualitative systematic review was done to summarize the findings, sources of variation or similarity between studies, and limitations.

## Results

### a) Short-acting insulin analogues

A total of 303 citations were identified from the economic literature search. Of these, 302 were excluded, resulting in one<sup>11</sup> relevant report plus two<sup>12,13</sup> identified from the clinical search and two<sup>14,15</sup> from other sources, to yield five included reports. The quality of the included studies was acceptable according to the *BMJ* checklist, although not all items were applicable. Of the five studies, two<sup>14,15</sup> were cost comparisons over 12 months, one<sup>12</sup> was a willingness-to-pay (WTP) analysis evaluating monthly costs, and two<sup>11,13</sup> were WTP-based CBAs that presented patients' preferences for one-month treatment extrapolated to annual estimations. Three<sup>11,14,15</sup> studies compared ILis and HI, and two<sup>12,13</sup> compared Mix25 with pre-mixed HI (30/70). All studies were industry-sponsored. No studies were identified for IAsp.

In the two<sup>14,15</sup> cost-comparison studies (which included type 1 and type 2 DM patients), no significant differences in total health care costs were found between ILis and HI users. The higher pharmacy costs that were incurred with ILis seemed to be offset by lower in-patient hospitalization costs. In the WTP analysis<sup>12</sup> (which included only type 2 DM patients), it was found that patients preferred Mix25 over HI 30/70, and regarding WTP, patients would pay an extra C\$179 per month for Mix25. In the first WTP-based CBA<sup>11</sup> conducted in Australia, the net annual benefit of replacing HI with ILis was C\$352.90 (drug costs only). The second WTP-based CBA<sup>13</sup> was a survey of Canadian taxpayers, of which 6.2% had DM, although the proportion using insulin was not provided. The net benefit of replacing HI 30/70 with Mix25 was C\$255.36 per year. Caution is warranted in interpreting this result because the population does not represent the target population of SAIA users. Sensitivity analyses were conducted in the WTP and WTP-based CBA studies, details of which are provided in the full report with a discussion of the limitations of the included studies.<sup>7</sup> Despite the heterogeneity between studies, the two cost comparisons concluded that ILis and HI were similar, and the three WTP-based studies concluded that ILis or Mix25 were more favourable than HI or HI 30/70.

### b) Long-acting insulin analogues

From the originally identified 303 citations, 302 were excluded, resulting in one<sup>16</sup> relevant report plus one<sup>17</sup> identified from the clinical search and one<sup>18</sup> from other sources, to yield three included reports. The quality of the included studies was acceptable, although not all items on the *BMJ* checklist were applicable. Of the three studies, one<sup>16</sup> was a CEA comparing IDet- and NPH-based basal or bolus therapies in type 1 DM using a lifetime horizon, one<sup>17</sup> was a cost-and-consequence study comparing IGLar and NPH in type 1 and type 2 DM combined, and one<sup>18</sup> was a cost-comparison study (type of DM unspecified) using claims data to compare patients treated with IGLar versus those who were untreated, over six-month periods. Two<sup>16,17</sup> of the three studies were industry-sponsored.

In the CEA,<sup>16</sup> it was reported that the IDet-based regimen would result in an incremental cost equivalent to C\$51,427 per life-year gained and an incremental cost of C\$44,130 per quality-adjusted life-year (QALY) gained in 2003 dollars for one type 1 DM patient over a lifetime. In the two<sup>17,18</sup> studies that compared IGLar and NPH, the benefit gained from patients avoiding severe hypoglycemic events with IGLar offsets the higher drug cost, resulting in net cost savings with IGLar. Sensitivity analyses were conducted in two<sup>16,17</sup> studies, details of which are available in the full report with a discussion of the limitations of these studies.<sup>8</sup>

## 5 Limitations

There are several limitations in the clinical review and meta-analyses. Not all included RCTs reported data of interest for the outcomes, and this may have introduced bias and prevented all RCTs from being included in the meta-analyses. The comparability of treatment arms was made difficult because of variation in treatments and insulin dosage adjustments according to patients' needs. There was heterogeneity among the RCTs, which precluded pooling of the data in some instances. Other issues included multiple publications of the same RCTs, failure to describe the method of allocation concealment, variations in the definition and characterization of hypoglycemia, and restrictive inclusion criteria, which may not make it possible to generalize results to all patients with DM. Most RCTs were  $\leq 6$  months in duration, and data on AEs, mortality, and QoL were limited. No RCTs investigating LAIAs in GDM were found.

There are also several limitations in the economic review. Overall, the number of included studies was small. No economic studies comparing IAsp with HI could be identified. For SAIAs, the results are based on one agent (i.e., ILis or Mix25). Most studies did not differentiate between type 1 and 2 DM, and the methods and sources of clinical data in some may have introduced bias. Most studies were industry-sponsored or affiliated and were based on a maximum one-year time horizon. One study<sup>16</sup> used a lifetime horizon, but the clinical data were based on a meta-analysis for which the maximum length of follow-up in RCTs was 24 weeks.

## 6 Health System Implications

The number of Canadians affected by DM is increasing. From 1998 to 1999, 865,908 Canadians were diagnosed with DM. The number increased to 1,063,698 in 2000 to 2001 and to 1,222,882 in 2003.<sup>19-21</sup> Assuming that all type 1 DM and 10% of type 2 DM<sup>22</sup> patients use insulin, the corresponding numbers of insulin users during this time were 164,523 (1998 to 1999), 202,103 (2000 to 2001), and 232,348 (2003). This estimate is based on a ratio of 1:9 for type 1:type 2 DM. The proportion of DM also varies according to age.

Budget impact analyses were undertaken to estimate the financial implications of "open listing" SAIAs and LAIAs in provincial drug plans. Because of limited data and time constraints, the results are intended to provide a general indication of how this would affect future budgets. For precise estimates, decision makers should conduct a budget estimation with adequate and specific data.

For each province, the budget was estimated over three years (2006 to 2008) for a scenario where the status quo was maintained (i.e., IAs were not listed or the current listing status stayed the same). Then, in another scenario, the budget was forecasted where IAs were open-listed. By subtracting the former from the latter, the potential impact of changing the formulary listing of IAs was estimated. Details about the method are available in the full reports.<sup>7,8</sup> The estimated budget impact depended on the switching rate (10% to 100%) between conventional insulin to IAs and on the individual province. For SAIAs, the estimated three-year budget impact (2006 to 2008) varied from C\$217,335 to C\$12,300,339 if 10% of patients switched to SAIAs and from C\$1,565,574 to C\$52,882,768 if 100% of patients switched to SAIAs, depending on the province. For LAIAs, the estimated three-year budget impact varied from C\$605,708 to C\$13,921,951 if 10% of patients switched to LAIAs and from C\$3,534,906 to C\$79,115,423 if 100% of patients switched to LAIAs, depending on the province. Not all provinces were analyzed, and several assumptions were made that could limit the

analysis. In terms of psychosocial outcomes such as social acceptability and ease of use, there is no evidence that IAs are disadvantageous. They may have a positive influence because of convenience of use.

## 7 Conclusions

### *Short-acting insulin analogues*

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

In type 2 DM patients, HbA1c levels, occurrences of hypoglycemia, and QoL were similar between those using HI and those using SAIAs. Compared to OADs, HbA1c levels and patient satisfaction were improved among those treated with SAIAs.

Uncertainty remains about the use of SAIAs in GDM patients and pregnant women with DM. Two studies show that postprandial glucose levels are significantly reduced in GDM patients who are treated with ILis, compared to those treated with HI.

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

### *Long-acting insulin analogues*

In type 1 DM patients, IGLar but not IDet resulted in greater reductions in HbA1c levels than NPH insulin, but the magnitude of the difference did not reach the minimal clinically important level. IGLar reduced the risks of severe hypoglycemia in patients on HI, and IDet reduced the risks of severe and nocturnal hypoglycemia in patients on IAsp.

In type 2 DM patients, the HbA1c levels were similar when treated with NPH, IGLar, or IDet. In addition, IGLar reduced the risk of nocturnal but not severe hypoglycemia.

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

The number of Canadians with DM and the number of insulin users are increasing, resulting in increased expenditures. If conventional insulin users switch to the more expensive LAIAs, there will be further demands on drug plans. Because long-term data on LAIAs are unavailable, the impact on health care resources is difficult to predict.

Overall, the available evidence suggests that SAIAs and LAIAs are not justified for all individuals with DM. High-quality, long-term studies are needed to determine the benefits and harms of IAs

compared to conventional insulins. Data on patients' mortality and QoL are lacking. The impact on health care costs beyond 12 months is unknown.

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