Canadian Agency for Drugs and Technologies in Health

COMPUS Optimal Therapy Newsletter: Insulin Analogues

In this issue:

The Canadian Agency for Drugs and Technologies in Health recognizes the importance of this information to physicians and the COMPUS Expert Review Committee has carefully reviewed the evidence to offer some practical guidance to the prescribing and use of insulin analogues.

COMPUS: Canadian Optimal Medication Prescribing and Utilization Service

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Decision Support for Insulin Analogues

What are insulin analogues and how do they compare?

The Rapid Acting Insulin Analogues, Insulin Lispro (Humalog®) and Insulin Aspart (Novorapid®), have molecular modifications from human insulin that enhance their subcutaneous absorption.[1,2] This rapid absorption allows rapid-acting insulin analogues to be given at the time of meals, theoretically providing enhanced flexibility for patients on basal/bolus regimens and for patients using continuous subcutaneous insulin infusion (CSII). These agents represent alternatives to regular human insulin (Humulin® R, Novolin® GE Toronto).

The Long Acting Insulin Analogues, Insulin Glargine (Lantus®) and Insulin Detemir (Levemir®), have molecular modifications from human insulin that decrease solubility or enhance protein binding to delay their absorption and extend their activity.[1,3,4] These modifications allow long-acting insulin analogues to produce a relatively steady release of insulin to provide basal requirements. These agents represent alternatives to NPH (Neutral Protamine Hagedorn) insulin (Humulin® N, Novolin® GE N).

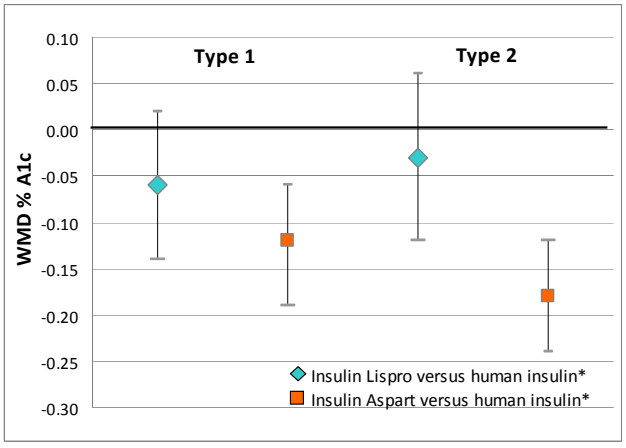
Assessing the value of insulin analogues

The Canadian Agency for Drugs and Technologies in Health (CADTH) has conducted a systematic review of the literature regarding insulin analogues.[5,6] Meta-analysis of statistical results and an expert review committee were used to develop optimal therapy recommendations.[7] This comparative review also included an economic evaluation of insulin analogues in the adult population.[8] The review of the efficacy (glycemic control), side effects (hypoglycemia, weight gain), quality of life and cost of insulin analogues allowed for an assessment of their relative value. This assessment may help guide physicians and patients when making decisions around insulin choice.

Hemoglobin A1C (A1C)

A1C represents the primary surrogate for glycemic control in most clinical studies. Head-to-head comparisons of insulin analogues and regular human/ NPH insulin allows for an unbiased evaluation of the clinical impact of the pharmacokinetic advantages of insulin analogues. Overall, the impact on A1C is very modest and not always statistically significant. The difference in A1C that may be considered clinically significant is uncertain, although a threshold of 1% has been suggested.[9] As shown in Figures 1 and 2, differences in A1C vary across the agents and patient populations, but none of the insulin analogues demonstrated a difference that approached clinical significance as compared to human insulins.[7] In limited studies with children and adolescents, no significant reduction in A1C was shown with insulin analogues relative to human insulins.[5,6]

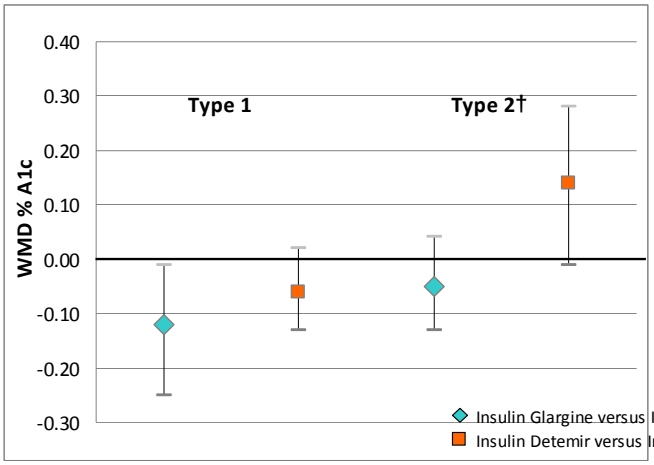
Figure 1. The impact of rapid-acting insulin analogues given by multiple daily injections on A1C (adults)



* For type 2 diabetes, studies include comparison of Insulin Lispro Mix and Insulin Aspart Mix versus human insulin Mix products

WMD—weighted mean difference

Figure 2. The impact of long-acting insulin analogues on A1C (adults)



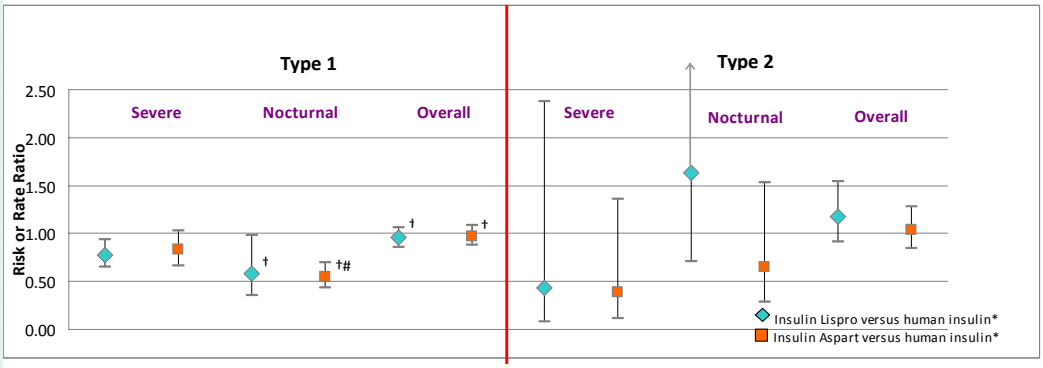
† For type 2 diabetes patients who were taking oral antidiabetes drugs

Hypoglycemia

Although A1C is an important measure of long term glycemic control, the avoidance of hypoglycemia can be of more immediate relevance in the day-to-day life of people with diabetes. With the rapid onset of meal-time rapid-acting insulin analogues and the consistent basal levels of the long-acting insulin analogues, these agents have the potential to limit this important adverse event. In clinical trials, hypoglycemia is usually evaluated as a risk (proportion of patients that experience one or more events in each study arm) or a rate (number of events experienced per person). Comparisons of insulin analogues and regular human/NPH insulins utilize risk ratios and rate ratios to quantify differences between treatments.

In seven of the eight comparisons for overall and severe hypoglycemia, rapid-acting insulin analogues did not produce a statistically significant reduction in the risk of hypoglycemia in adults with type 1 or type 2 diabetes (Figure 3).[7] However, rate ratios for nocturnal hypoglycemia in patients with type 1 diabetes were statistically significant in favour of the insulin analogues. Adolescent and pre-adolescents have been less studied. One study of adolescents comparing insulin lispro with human insulin showed a significant reduction in nocturnal hypoglycemia (Rate ratio 0.61: 95% CI 0.57 to 0.64) and overall hypoglycemia (Rate ratio 0.90: 95% CI 0.88 to 0.93).[10]

Figure 3. Rapid-acting insulin analogues given by multiple daily injections and hypoglycemia (adults)



† Rate Ratio; all other effect estimates are Risk Ratios

Nocturnal hypoglycemia rate ratio for delivery by continuous subcutaneous infusion, no MDI data available

* For type 2 diabetes, studies comparing Insulin Lispro Mix or Insulin Aspart Mix versus premixed human insulin mix were included in the meta-analysis

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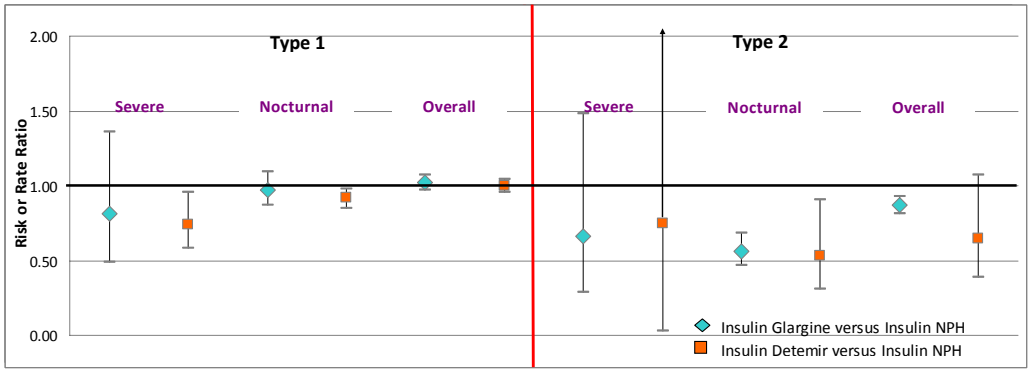
Figure 4. Long-acting insulin analogues and hypoglycemia (adults)



The majority of measures of hypoglycemia do not indicate a significant advantage for long-acting insulin analogues (Figure 4).[7] In the adolescent/pre-adolescent population there was no significant advantage with the use of insulin glargine; whereas, evidence from one study in children showed a modest reduction in the risk and frequency of nocturnal hypoglycemia and a small reduction in the rate of overall hypoglycemia with the use of insulin detemir.[6] Overall, the lower level of hypoglycemia seen in adults with insulin analogues was statistically significant for only eight of the 24 comparisons. Even when statistically significant, differences between insulin analogues and conventional insulins in terms of hypoglycemia risks and rates were generally modest. Furthermore, there were challenges in interpreting the hypoglycemia data due to inconsistencies in enrolment criteria, and hypoglycemia definitions.[5,6]

Patient Satisfaction/Lifestyle/Quality of Life

Although the clinical benefits of insulin analogues are generally modest, it is possible that they enhance patient satisfaction and quality of life due to improved convenience and other benefits resulting from their pharmacokinetic characteristics. Unfortunately, this aspect of insulin analogues has not been well studied. The limited data that are available are difficult to interpret due to the variety of scales used to measure these outcomes. In type 1 diabetes, a total of six RCTs have demonstrated superiority of rapid-acting insulin analogues in terms of overall satisfaction with treatment, while other studies have reported no significant differences between treatments. Some studies have also reported statistically significant differences in favour of rapid-acting insulin analogues in terms of flexibility, convenience, and willingness-to-continue. There is limited evidence for quality of life (QoL) and patient satisfaction in the pre-adolescent population which suggests that rapid-acting analogues were preferred because of improved convenience.[5] This may be an important consideration for many families for justifying the increased cost of rapid-acting insulin analogues to deal with children and adolescents with unpredictable dietary patterns and physical activity. Overall, well-being scores have generally not shown significant differences between rapid-acting analogues and regular human insulin. Rapid-acting insulin analogues have failed to show significant differences in treatment satisfaction or willingness-to-continue in patients with type 2 diabetes; the evidence is limited to two RCTs.[5] Only one study has assessed QoL associated with long-acting insulin analogues in type 1 diabetes. It showed no difference in well-being scores for insulin glargine over insulin NPH, although patient satisfaction was higher in the insulin glargine arm. QoL with long-acting insulin analogues has not been compared to insulin NPH in type 2 diabetes. Overall, the evidence regarding advantages of insulin analogues over conventional insulins in terms of patient satisfaction and quality of life is weak, and there is a need for further research.

Price Comparisons

Insulin analogues are more expensive than human insulin and insulin NPH. Figure 5 presents the price per millilitre of the various insulins.

Cost-effectiveness

The COMPUS economic analysis[8] compared alternative insulin agents, with respect to onset of diabetes-related complications and expected medical costs over the lifetime of an average adult patient, with type 1 or type 2 diabetes.

For patients with type 1 diabetes, use of rapid-acting insulin analogues, when compared with regular human insulin, was associated with cost-effectiveness estimates that are below widely-cited cost-effectiveness thresholds.

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The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

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Results for rapid-acting insulin analogues in patients with type 2 diabetes, or for long-acting insulin analogues in patients with type 1 diabetes, were less clear. In some instances, cost-effectiveness estimates were below widely cited thresholds; however, in others, they exceeded these cost-effectiveness thresholds.

Findings for long-acting insulin analogues in patients with type 2 diabetes were more consistent. In all cases cost-effectiveness estimates exceeded widely cited cost-effectiveness thresholds.

Thus, with the exception of rapid-acting insulin analogues in patients with type 1 diabetes, routine use of insulin analogues, especially long-acting insulin analogues in adults with type 2 diabetes, is unlikely to represent an efficient use of finite health-care resources.

Decision Guidance: Choosing an Insulin Product

This brief review of the evidence surrounding insulin analogues can be used to help support decision around insulin choice. There is no one correct answer for all patients but it may be possible to make some general guidance statements. As always, the needs of the individual patient must be considered in the selection of an insulin product that best fits their circumstances.

Bolus Insulin Therapy[13]

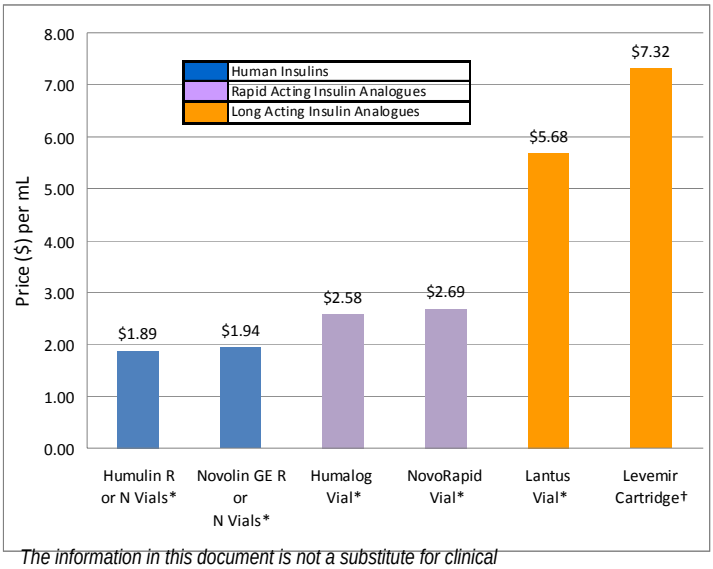
Type 1 Diabetes – either regular human insulin or rapid-acting insulin analogues can be considered as first line therapy (except in adolescent patients). In adolescent patients, rapid-acting insulin analogues may be considered as first-line.

Type 2 Diabetes – for patients requiring bolus therapy, **regular human insulin may be considered first**. Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking human insulin may benefit from the rapid-acting insulin analogues.

Basal Insulin Therapy[13]

In patients with type 1 or type 2 diabetes requiring basal insulin, **insulin NPH should be considered first**. Although the evidence is limited and inconsistent, patients experiencing significant hypoglycemia while using insulin NPH, may benefit from the long-acting insulin analogues.

Figure 5. Price of human insulin, insulin NPH and insulin analogues



* Ontario Drug Benefits Formulary/Comparative Drug Index- December 3, 2008

† NovoNordisk Canada, Mississauga, ON- December 9, 2008

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