Title: Long-Acting Insulin Analogues for Post-Operative Patients with Diabetes: Clinical and Cost Effectiveness

Date: November 28, 2007

Context and policy issues:

The Disease: Diabetes in Canada
Diabetes is a disorder characterized by hyperglycemia due to the inability to produce insulin (Type 1; 10% of the group) or the inability to use insulin effectively (Type 2; 90%). More than 2 million Canadians are believed to have diabetes, and the annual costs for their health care exceed $9 billion. The number of people diagnosed with the disease has increased by over 60% in the past 15 years with the trend expected to continue due to an aging population and rising rates of obesity. Management includes diet modifications, weight control, exercise, glucose monitoring, and often medications including insulin and oral anti-diabetic agents.

The Technology: Long-acting insulin analogues
In the non-diabetic person “basal insulin” is produced continuously, suppressing blood glucose production between meals and overnight. Basal insulin constitutes approximately 50% of daily insulin output with mealtime spikes accounting for the remainder. To mimic the slow, steady basal secretion of insulin provided by the normal pancreas, long-acting insulin analogues were developed using recombinant DNA technology. They provide a relatively constant concentration/time profile over 24 hours with no pronounced peak. Two long-acting insulin analogues are available:


Disclaimer: The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information on available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
The pharmacokinetic profiles of basal insulins like NPH and long-acting insulin analogues vary (Table 1); their prices also differ dramatically (Table 2). These differences among insulin products mean that insulins can be complex to prescribe and are not simply interchangeable from a clinical or cost perspective.

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Onset of Action (hours)</th>
<th>Peak of Action (hours)</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane (NPH, Humulin N, Novolin N)</td>
<td>1-2</td>
<td>5-7</td>
<td>13-18</td>
</tr>
<tr>
<td>Zinc insulin (Lente, Humulin L, Novolin L)</td>
<td>1-3</td>
<td>4-8</td>
<td>13-20</td>
</tr>
<tr>
<td>Extended zinc insulin (Ultralente, Humulin U)</td>
<td>2-4</td>
<td>8-10</td>
<td>18-30</td>
</tr>
<tr>
<td>Long-acting insulin analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine (Lantus)</td>
<td>1-2</td>
<td>None</td>
<td>20-24</td>
</tr>
<tr>
<td>Insulin detemir (Levemir)</td>
<td>1-2</td>
<td>None</td>
<td>10-18</td>
</tr>
</tbody>
</table>

Table from Tran et al. (2007)

### Table 2: Costs of Basal Insulins

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Package size</th>
<th>Price per package (C$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional NPH human insulins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N, vial, 100 units/mL</td>
<td>1 x 10 mL</td>
<td>16.72</td>
</tr>
<tr>
<td>Humulin N, pen, 100 units/mL</td>
<td>5 x 3 mL</td>
<td>47.61</td>
</tr>
<tr>
<td>Humulin L, vial, 100 units/mL</td>
<td>1 x 10 mL</td>
<td>16.72</td>
</tr>
<tr>
<td>Humulin U, vial, 100 units/mL</td>
<td>1 x 10 mL</td>
<td>16.72</td>
</tr>
<tr>
<td>Insulin analogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lantus, penfill cartridge, 100 units/mL</td>
<td>5 x 3 mL</td>
<td>109.87</td>
</tr>
<tr>
<td>Lantus, vial, 100 units/mL</td>
<td>1 x 10 mL</td>
<td>55.07</td>
</tr>
<tr>
<td>Levemir, penfill cartridge, 100 units/mL</td>
<td>5 x 3 mL</td>
<td>109.86</td>
</tr>
</tbody>
</table>

Table from Tran et al. (2007)

**Surgery for patients with diabetes**

Patients with diabetes who are undergoing surgery can present a challenge. Surgery and anaesthesia are known to increase stress response with release of hormones that increase insulin resistance, increase hepatic glucose production, and impair insulin secretion and fat and protein breakdown as well as causing volume depletion and metabolic decompensation; the degree of effect depends on surgical complexity. The proportion of surgical patients with diabetes is 10% to 30% depending on the population and type of surgery – a proportion much higher than the general prevalence of the disease. These patients can suffer an increased rate of adverse outcomes including poor wound healing, wound infections, prolonged hospital length of stay (LOS), and excess mortality, all these factors being associated with increased health care costs.

**Management strategies for patients with diabetes undergoing surgery**

Traditionally, peri-operative management of hyperglycemia has employed sliding scale regular insulin regimens with short-acting insulin given to correct elevations in serum glucose. This practice is now recognized as suboptimal because it is reactive, responding to glucose measurements that reflect control over the previous 6 hours. This tends to promote swings in glucose control and can predispose to diabetic ketoacidosis. Recent literature has therefore urged movement away from the sliding scale approach.

**Long-Acting Insulin Analogues for Post-operative Patients with Diabetes**
Research questions:

Post-operatively, in patients with hyperglycemia/diabetes:
1. What is the clinical effectiveness of long-acting insulin analogues compared to sliding scale insulin regimens?
2. What is the cost effectiveness of long-acting insulin analogues compared to sliding scale insulin regimens?

Methods:

A limited literature search was conducted on key health technology assessment (HTA) resources, including OVID MedLine, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search including the website of the manufacturer of Lantus® (Sanofi-Aventis, US LLC). Results included articles published between 2002 and the present, and were limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, randomized controlled trials (RCTs), economic evaluations and observational studies.

Summary of findings:

Identified were 190 citations in the published literature search from 2002 onward, of which 10 were considered to be potentially relevant and obtained in full text for more detailed review. The grey literature yielded a few promising documents as well. Located in the published and grey literature were three RCTs,\(^3,11,13\) (one available only in abstract form)\(^13\) in addition to several relevant background/review articles.\(^4,8-10,12,14\) No systematic reviews (SRs) or economic evaluations were identified that were directly related to the research questions, although three SRs\(^1,15,16\) supplied some useful information regarding the comparative efficacy and cost of long-acting insulins and alternatives. Two of these included economic evaluations.\(^1,18\) One ongoing clinical trial of perioperative insulin glargine was located.\(^17\)

Randomized controlled trials

Yeldani et al. (2006)\(^11\) studied 94 hyperglycemic patients on the ward after cardiovascular surgery, comparing use of twice-daily NPH/regular insulin (standard care) to once-daily insulin glargine. The study was funded in part by the manufacturer of insulin glargine, although this support was received after the study was completed. Patients were eligible for consideration if their blood glucose was >120 mg/dL (6.7 mmol/L) on post-operative intensive care unit (ICU) admission. Only 32% had been diagnosed as diabetic pre-surgery. Hyperglycemia was treated in ICU with intravenous (IV) insulin infusions.

Those who still required ≥ 1 unit/hour of insulin upon discharge from ICU to the surgical ward (94/165; 57%) were randomized in an unblinded fashion, with patients in the standard therapy arm initially receiving NPH insulin twice daily at eight times the hourly intravenous (IV) infusion rate and regular insulin at four times the hourly IV infusion rate and patients in the study arm receiving insulin glargine once daily at 20 times the hourly IV infusion rate. Dose was adjusted based on blood glucose, aiming for glucose levels of 80-140 mg/dL (4.4-7.8 mmol/L). Patients in the glargine arm received corrective doses of regular insulin only with pre-meal glucose >200 mg/dL (11.1 mmol/L). Adjustments were made twice daily for those on NPH/regular and every 24 hours for those on glargine.
Patients in the two groups were well matched although a higher number in the standard therapy group had been diagnosed as having diabetes pre-surgery (41% versus 23%; not statistically significant) and had received insulin therapy (15% versus 8%; not statistically significant).

Results showed that glycemic control was similar overall in both groups although for patients with a history of diabetes, blood sugar outcomes were significantly better with use of NPH versus insulin glargine (Table 3). The other statistically significant result was incidence of hypoglycemia which was lower for patients on insulin glargine. The authors concluded that although a regimen of NPH/regular insulin produced results that were as good or better than insulin glargine monotherapy, “the simplicity and safety of glargine insulin make it an attractive option for the management of post-operative hyperglycemia.”

### TABLE 3: YELDANI ET AL. POST-OP NPH VERSUS GLARGINE INSULIN

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>NPH/regular insulin</th>
<th>Insulin glargine</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood glucose outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes (32% of patients)</td>
<td>133 mg/dL (range 96-173) (7.4 mmol/L [range 5.3-9.6])</td>
<td>154 mg/dL (range 118-189) (8.6 mmol/L [range 6.6-10.5])</td>
<td>0.016</td>
</tr>
<tr>
<td>No history of diabetes (68% of patients)</td>
<td>118 mg/dL (range 102-135) (6.6 mmol/L [range 5.7-7.5])</td>
<td>124 mg/dL (range 97-161) (6.9 mmol/L [range 5.4-8.9])</td>
<td>0.074</td>
</tr>
<tr>
<td>Overall</td>
<td>124 mg/dL (range 96-173) (6.9 mmol/L [range 5.4-9.6])</td>
<td>131 mg/dL (range 97-180) (7.4 mmol/L [range 5.4-10.0])</td>
<td>0.065</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose 80-140 mg/dL (4.4-7.8 mmol/L)</td>
<td>62.7%</td>
<td>59.8%</td>
<td>0.84</td>
</tr>
<tr>
<td>Blood glucose &gt; 200 mg/dL (11.1 mmol/L)</td>
<td>4.5%</td>
<td>5.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Blood glucose &lt; 60 mg/dL (3.3 mmol/L)</td>
<td>2.0%</td>
<td>0.5%</td>
<td>0.036</td>
</tr>
<tr>
<td>Median hospital LOS (days)</td>
<td>5.0 (SE 0.26, range 2-10)</td>
<td>5.0 (SE 0.52, range 3-23)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

LOS=length of stay; NR=not reported; SE=standard error

Datta et al. (2007) also studied use of insulin glargine post-operatively although this time it was compared with sliding scale regular insulin in patients who underwent bariatric surgery and had blood glucose >144 mg/dL (8 mmol/L) in the recovery room. The authors assert that this trial, published in May/June 2007, was the first to compare once-daily insulin glargine with sliding scale insulin therapy for post-operative patients with hyperglycemia. Partial sponsorship came from the manufacturer after the study was completed with no input as to study planning or execution.

Of the 81 included study patients, 32 had an open procedure and were admitted post-operatively to a surgical ICU for 12 to 24 hours where they were managed with IV insulin drip, while 49 had laparoscopic surgery, went directly to a surgical ward, and did not receive IV insulin. Unblinded randomization occurred when patients were moved to the ward from either the ICU or the recovery room. The sliding scale group (n=39) received regular insulin every 6 hours based on a recent blood glucose level using a pre-determined dosing schedule ranging from no insulin at a blood glucose of 140 mg/dL (7.8 mmol/L) to 12 units at ≥ 221 mg/dL (12.3 mmol/L). The glargine group (n=42) received an initial insulin dose 20 times the last unit per hour IV infusion rate if they had been in ICU or 0.3 units per kilogram of body weight if they were not in the ICU; dosing could be adjusted every 24 hours and a compensatory dose of regular insulin was given for blood glucose > 200 mg/dL (11.1 mmol/L).
Patients in the two groups were well matched with no significant differences between groups. Mean age was 45 years (range, 23 to 69), 84% were female, mean body mass index (BMI) was 54 kg/m² (range, 36 to 91), 64% had been previously diagnosed with diabetes, and 23% had previously been on insulin.

Results showed that glycemic control was statistically less favourable in the group receiving on sliding scale insulin versus those on insulin glargine at the p<0.01 significant level: 154 mg/dL versus 134 mg/dL (8.6 mmol/L versus 7.4 mmol/L). Other outcomes are displayed in Table 4 and reveal superior blood sugar control for the glargine group with very low incidence of hypoglycemia.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Sliding scale regular (n=39)</th>
<th>Insulin glargine (n=42)</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood glucose outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overall mean blood glucose</td>
<td>154 ± 30 mg/dL</td>
<td>134 ± 33 mg/dL</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>8.6 ± 1.7 mmol/L</td>
<td>7.4 ± 1.8 mmol/L</td>
<td></td>
</tr>
<tr>
<td>• Blood glucose ideal at 80-140 mg/dL (4.4-7.8 mmol/L)</td>
<td>45%</td>
<td>60%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>• Blood glucose 141-200 mg/dL (7.8-11.1 mmol/L)</td>
<td>37%</td>
<td>30%</td>
<td>0.03</td>
</tr>
<tr>
<td>• Blood glucose &gt; 200 mg/dL (11.1 mmol/L)</td>
<td>16%</td>
<td>6%</td>
<td>0.04</td>
</tr>
<tr>
<td>• Blood glucose &lt; 60 mg/dL (3.3 mmol/L)</td>
<td>0.01%</td>
<td>0.02%</td>
<td>NR</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean hospital LOS</td>
<td>3.8 ± 1.7 days</td>
<td>3.8 ± 1.7 days</td>
<td>--</td>
</tr>
<tr>
<td>• Surgical wound infections at 30 days*</td>
<td>2 patients</td>
<td>2 patients</td>
<td>--</td>
</tr>
</tbody>
</table>

LOS=length of stay; NR=not reported.
*All 4 patients had undergone a laparoscopic procedure.

Hagelberg et al. (2007) described a small RCT (n=43) in a conference abstract. They compared glycemic control during post-operative days 1 to 4 in patients undergoing elective coronary artery bypass grafting (CABG) who had presented with hyperglycemia on admission. Of these patients, 20% had not been diagnosed with diabetes and a further 35% were deemed to have pre-diabetes (not defined). On admission to hospital, patients were randomized to either glargine or a short acting human insulin marketed in Canada as Novolin R (Novo Nordisk) before surgery, with the glargine group being treated pre-operatively and the sliding scale group being treated in a reactive manner if plasma glucose exceeded 10 mmol/L. The target range for controlled glucose was 4.5 to 7.0 mmol/L pre-prandial and 4.5 to 9.0 mmol/L post-prandial.

Results showed that twice as many glucose values fell within the target range for the glargine group (p<0.001; data not provided). Only 1 of 504 glucose readings fell within the hypoglycemia range. The area under the curve for glucose > 7mmol/L was reduced by 61% by glargine compared to Actrapid (P<0.001). The authors concluded that insulin glargine provided superior post-operative glycemic control as compared with a sliding scale insulin regimen.
Related Systematic Reviews

Three SRs provide some perspective on the efficacy of these drugs and/or clinical situation although they do not address the use of long-acting insulin analogues for post-operative use. They are provided here for background and context.

- Warren et al. (2004): In the United Kingdom, a 2004 HTA report on insulin glargine was conducted by University of Sheffield researchers for the National Health Service R&D HTA Program. The literature search ended early in 2002 and only six full reports were located for analysis. The authors concluded that long-term glycemic control with insulin glargine was not superior to that achieved with NPH insulin although in Type 1 diabetics there was evidence of some benefit in reducing fasting blood glucose and nocturnal hypoglycemic episodes, especially when compared with once-daily NPH insulin. For Type 2 diabetics, both insulin glargine and NPH were effective in the short and long term.

- Meijering et al. (2005): Six anaesthetists/intensivists in The Netherlands performed an SR to assess methods of obtaining tight glycemic control in critically ill patients. Of 24 included studies, nine examined post-operative patients. No studies used long-acting insulin analogues and only three employed sliding scale insulin regimens; the majority used continuous insulin infusion or insulin combined with glucose and potassium. Conclusions were that the best glycemic control in critically ill patients was achieved using continuous insulin infusion constantly adjusted based on frequent glucose measurements. The results of sliding scale insulin regimens were disappointing despite glucose measurements every 1 to 4 hours.

- Tran et al. (2007): A very recent CADTH report provided a meta-analysis of clinical outcomes for long-acting insulin analogues. The literature search and ongoing monitoring up to June 2007 led to inclusion of 34 RCTs, 23 for Type 1 and 11 for Type 2 diabetes. Overall the studies were judged to be of low quality (mean Jadad score of 2.3 out of 5) which can be associated with exaggerated estimates of treatment effect. Adverse events were similar among insulins.

Efficacy results:
- Type 1 diabetes:
  - Insulin glargine: Comparisons with NPH led to a statistical but not a clinical benefit in impact on long-term control as measured by HbA1c values. Pooled estimates showed no statistically significant differences between treatments for hypoglycemia (overall, severe, or nocturnal).
  - Insulin detemir: Comparisons with NPH did not lead to a statistical benefit on HbA1c control. With some regimens detemir performed better than NPH with respect to avoidance of severe or nocturnal hypoglycemia.

- Type 2 diabetes:
  - Insulin glargine: There was no added benefit in control of HbA1c as compared with NPH although the risk of nocturnal hypoglycemia was significantly reduced with insulin glargine.
  - Insulin detemir: No benefits for HbA1c or hypoglycemic episodes were observed.

Cost analyses

No publications directly related to the costs or cost-effectiveness of long-acting insulin analogues for post-operative use. However, pure cost data for various basal insulins was presented in Table 2 of this report, showing the drug cost of long-acting agents to be
considerably higher than NPH insulin. Two economic evaluations of long-acting agents provide some general cost effectiveness information for long-acting insulins overall:1,15

- The 2004 SR described above included an economic analysis of insulin glargine although the authors were limited by a lack of relevant evidence for their review.15 No published economic studies were located therefore evidence was limited to an industry submission comparing insulin glargine to NPH. Because details of this submission were confidential, the models and related material are not available for report readers. The authors concluded that the industry models were poor and hampered by mistakes related to assumptions and calculations. They also stated that estimates of quality-adjusted-life-years (QALYs) in the industry submission (ranged from £792 to £308,105) were often under-estimates. Further economic studies were recommended.

- CADTH very recently assessed the literature on the cost-effectiveness of long-acting insulin analogues.1 Three relevant studies from 2004 and 2005 were analyzed: a cost-effectiveness analysis (CEA) of detemir versus NPH, a cost-and-consequence study of hypoglycemia of glargine versus NPH, and a cost-comparison study of drug costs and costs of care for patients on glargine before and after its introduction in California. The first two studies were industry-sponsored and all three included authors affiliated with the manufacturers. The studies were too heterogeneous to be combined in any way and therefore were assessed individually. All favoured the long-acting insulins:
  
  o The CEA of detemir versus NPH reported an incremental QALY cost of C$44,130 for Type 1 diabetes.
  
  o The cost-and-consequence study of hypoglycemic events for glargine versus NPH calculated a number-needed-to-treat of nine meaning one hypoglycemic event would be avoided for every nine patients treated with glargine versus NPH at a cost of C$664.
  
  o The cost-comparison study reported that switching patients to glargine could save money: diabetes care costs per patient on glargine were C$2865 for the six months pre-glargine and C$1986 for the six months post-glargine introduction because increased drug and outpatient costs with glargine use were offset by decreased emergency department and inpatient costs.

Clinical trials underway
A study on perioperative use of insulin glargine was located in the ClinicalTrials.gov database.17 Commencing in October 2005, as of July 2007 the study was still recruiting adult patients with a planned enrollment of 402. The study sponsors are a Michigan hospital and the manufacturer of glargine. The phase IV, randomized, open-label, dose comparison safety/efficacy trial compares how three different doses of glargine given at home the evening before surgery impact preoperative fasting blood glucose upon arrival at the hospital the morning of surgery. Enrolled patients are required to be self-managed users of insulin glargine; the three doses under review are:

- 80% of the usual glargine dose.
- Glargine dose based on blood glucose (50%, 80% or 100% of the usual dose).
- A regimen determined by the diabetes care physician.

Study completion and estimated date of publication were not provided.
Limitations of the literature
Although three comparative RCTs specific to post-operative use of long-acting insulin analogues were located, all were small and one of them was scantily described in a conference abstract. The study that examined the comparison of most interest, glargine versus sliding scale insulin, enrolled a unique surgical population, this being primarily obese middle-aged women undergoing bariatric surgery, therefore its external validity is very limited.¹

No SRs or meta-analyses have specifically examined use of long-term insulin analogues in post-operative patients. For this report, three SRs contributed related information, one examining insulin regimens (although not long-acting analogues) for critically ill patients, including the peri-operative setting, and two examining long-term insulin analogues (although not in the peri-operative setting).

Economic literature was sparse with an older UK report summarizing literature up to early 2002 and a recent CADTH analysis that was limited in the primary literature available. Neither addressed the use of long-acting insulins in post-operative patients.

Conclusions and implications for decision or policy making:

Patients with diabetes make up a significant proportion of those undergoing surgery and suffer disproportionate complication rates. Management of hyperglycemia and hypoglycemia in the peri-operative period is challenging but for these patients optimal glucose control is worthwhile to decrease adverse effects (and related costs). The literature suggests that management practices and protocols for these patients are constantly evolving and the traditional post-operative sliding scale insulin regimen is suboptimal as it is reactive and can result in poor glucose control.

Inclusion of the recently approved long-acting insulin analogues in post-operative care is becoming an option, although the primary (and secondary) clinical and economic literature in this area is currently sparse. The evidence available does not suggest a significant advantage to use of long-term insulin analogues over NPH, another basal insulin option that costs considerably less.

Prepared by:

Vicki Foerster, MD MSc CCFP
James Murtagh, MHA CHE
Carolyn Spry, BSc MLIS
Health Technology Inquiry Service (HTIS)
E-mail: HTIS@cadth.ca
Toll free phone: 1-866-898-8439
References:


