Summary

✓ Insulin glargine is a biosynthetic human insulin analogue that controls blood glucose levels over 24 hours without a pronounced peak.

✓ In most studies in patients with type 2 diabetes mellitus (DM), insulin glargine did not significantly reduce fasting blood glucose, fasting plasma glucose or hemoglobin A1c compared to NPH insulin.

✓ Most trials showed a statistically significant decrease in the incidence of nocturnal and symptomatic hypoglycemia. This may not be as much of a concern in most patients with type 2 DM compared to type 1 DM.

✓ Current evidence suggests that patients who are adequately controlled with NPH insulin will not gain additional benefit from insulin glargine.

The Technology

Insulin glargine is a biosynthetic, long-acting, clear human insulin analogue with an acidic pH. Upon subcutaneous injection, insulin glargine is neutralized and forms microprecipitates that release insulin in a constant profile over 24 hours.

Regulatory Status

Insulin glargine (Lantus™) is indicated for once daily subcutaneous administration in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus (DM) who require basal (long-acting) insulin for the control of hyperglycemia. It is available in many countries. Health Canada granted a notice of compliance to Aventis Pharma Inc. on April 3, 2002, but the product has not yet been launched.

Patient Group

Type 2 DM is a progressive disorder caused by defects in insulin secretion from pancreatic beta cells, tissue resistance to insulin and increased hepatic glucose output. In Canada, two million people have diabetes. About 90% have type 2 DM.

Patients with type 2 DM are at a significantly increased risk for long-term complications such as retinopathy, nephropathy and neuropathy. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated, however, that intensive blood glucose control with sulfonylureas or insulin significantly decreases microvascular complications and reduces the risk of myocardial infarction with borderline significance.

Current Practice

Canadian guidelines recommend that the treatment of patients with type 2 DM be tailored to the individual, aiming for glycemic targets as close to normal as possible; and in most people, as early as possible. If glycemic targets are not achieved with lifestyle management within two to three months, oral hypoglycemic agents should be used. Multiple oral hypoglycemic agents or insulin with oral hypoglycemic agents may be used if treatment goals are still not reached. Insulin monotherapy is generally used
when diet, exercise, lifestyle and oral hypoglycemic agents are ineffective or contraindicated. It may be used as initial therapy in the presence of marked hyperglycemia (A1c >9.0%). With intensive glycemic control, there is a risk of hypoglycemia, but this risk is lower in people with type 2 DM than in those with type 1 DM.9

Oral hypoglycemic agents include sulfonylureas, alpha-glucosidase inhibitors, biguanides, thiazolidinediones and meglitinides.4 Intermediate and long-acting insulin preparations are used to provide a baseline insulin level.

The Evidence

Eight randomized trials (three reported in abstracts) investigated the use of insulin glargine in patients with type 2 DM (Table 1). Trials were open-label because of differences in the appearance of the insulin formulations (NPH insulin is cloudy, while insulin glargine is clear). Insulin glargine was studied with short-acting insulin formulations10-12 or oral hypoglycemic agents.13-17 Primary end points included fasting plasma glucose (FPG), fasting blood glucose (FBG) and hemoglobin A1c (A1c), but not morbidity or mortality.

All the studies compared once daily insulin glargine to once or twice daily NPH insulin. Four studies involved insulin-naive patients receiving oral hypoglycemic agents including sulfonylureas, metformin, pioglitazone, rosiglitazone or acarbose;13-16 and four studies involved patients previously treated with insulin.10-12,17 In most studies, insulin glargine did not significantly reduce FPG, FBG or A1c compared to NPH insulin.

Adverse Effects

Most trials showed significant decreases in reported nocturnal10,13-17 and symptomatic11,13-15 hypoglycemia with insulin glargine (Table 2). One trial reported a significant difference in severe hypoglycemia.10,19 However, hypoglycemia is less common in people with insulin-treated type 2 DM compared with type 1 DM.20

Two meta-analyses were reviewed, both looking at rates of hypoglycemia. One calculated a relative risk reduction (RRR) of 11% (p=0.0006) in all symptomatic hypoglycemia and a RRR of 26% (p<0.0001) in all symptomatic nocturnal hypoglycemia.21 The other reported a significantly lower incidence of severe hypoglycemia (RRR=50%, p=0.0237) and severe nocturnal episodes (RRR=61.1%, p=0.0159).22

Injection site pain was more frequent with insulin glargine than with NPH, but these were mild and resolved in a few days or weeks.18

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### Table 1: Randomized trials comparing efficacy of insulin glargine with NPH insulin in patients with type 2 DM

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Mean Change from Baseline</th>
<th>FPG in mmol/L (p value)</th>
<th>A1c in % (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yki-Jarvinen et al.13,18,19</td>
<td>IG qhs NPH qhs</td>
<td>NR NR (NR)</td>
<td>-0.76</td>
<td>-0.66 (NR)</td>
</tr>
<tr>
<td>Riddle et al.14</td>
<td>IG qhs NPH qhs</td>
<td>-4.5 -4.1 (NS)</td>
<td>-1.65</td>
<td>-1.59 (NS)</td>
</tr>
<tr>
<td>Fritsche et al.15,18</td>
<td>IG qam NPH qhs</td>
<td>-5.1 -5.2 -5.3 (NR)</td>
<td>-1.24 -0.96 -0.84</td>
<td></td>
</tr>
<tr>
<td>Eliaschewitz et al.16</td>
<td>IG qhs NPH qhs</td>
<td>NR NR (NR)</td>
<td>-1.4</td>
<td>-1.5 (NR)</td>
</tr>
<tr>
<td>Rosenstock et al.10,18,19</td>
<td>IG qhs NPH qhs or bid</td>
<td>NR NR (NR)</td>
<td>-0.41</td>
<td>-0.59 (&lt;0.01)</td>
</tr>
<tr>
<td>Massi Benedetti et al.17,18</td>
<td>IG qhs NPH qhs</td>
<td>-2.8 -2.7 (0.65)</td>
<td>-0.46</td>
<td>-0.38 (0.4)</td>
</tr>
<tr>
<td>Fonseca et al.11,18,19</td>
<td>IG qhs NPH qhs</td>
<td>-1.0 -1.1 (NR)</td>
<td>-0.35</td>
<td>-0.44 (NR)</td>
</tr>
<tr>
<td>Siegmund et al.12,18</td>
<td>IG od NPH bid</td>
<td>NR NR (NR)</td>
<td>-0.40</td>
<td>-0.20 (NR)</td>
</tr>
</tbody>
</table>

FPG=fasting plasma glucose, A1c=hemoglobin A1c, n=number of patients randomized, IG=insulin glargine, NPH neutral protamine Hagedorn insulin, qam=every morning, qhs=every bedtime, od=once daily, bid= twice daily, NR=not reported, NS=not significant, *plus oral glimepiride once daily, †fasting blood glucose, ‡0.0002 versus NPH, §>0.2 versus NPH.
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)

### Administration and Cost

Insulin glargine (Lantus™) is supplied as 100 IU/mL in 10 mL vials and 3 mL cartridges. It must not be diluted or mixed with any other insulin or solution, as this can alter its pharmacokinetics and cause precipitation.

The Canadian price for insulin glargine is expected to be greater than that of NPH insulin. In the US, insulin glargine is US$58.42 per 10 mL vial compared with about US$30.00 for NPH.

### Concurrent Developments

Two trials in the AT.LANTUS study are evaluating the most effective way to initiate glargine safely in insulin-naive patients with type 1 or type 2 DM.

### Rate of Technology Diffusion

Patients who have adequate glycemic control and minimal hypoglycemic events with NPH insulin will likely not derive additional benefit from insulin glargine. They may, however, find once daily dosing more convenient compared with multiple doses of NPH insulin.

The UK’s National Institute for Clinical Excellence (NICE) projected the yearly incremental cost-effective ratios for insulin glargine versus NPH insulin to be between £32,500 to £72,000 per quality adjusted life-year in type 2 DM. NICE does not recommend insulin glargine for routine use in people with type 2 DM who require insulin therapy, unless they require assistance from a caregiver or health care professional to administer their insulin injections, if they experience recurrent symptomatic hypoglycemic episodes that interfere with their lifestyle or if they would otherwise need twice daily basal insulin injections in combination with oral hypoglycemic agents.

### Implementation Issues

The long-term safety and lower cost of NPH insulin compared with insulin glargine could limit its implementation. Insufficient supply was an issue during the European and US launches of insulin glargine and may be an issue in Canada.

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**Table 2: Randomized trials comparing safety of insulin glargine with NPH insulin in patients with type 2 DM**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Patients Reporting at Least One Episode of Hypoglycemia</th>
<th>All Symptomatic (p value)</th>
<th>Nocturnal (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yki-Jarvinen et al.</td>
<td>IG qhs NPH qhs</td>
<td>33% (p=0.04) 10%</td>
<td>24% (p=0.001)</td>
<td></td>
</tr>
<tr>
<td>Riddle et al.</td>
<td>IG qhs NPH qhs</td>
<td>13.9% 4.0% (p=0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fritsche et al.</td>
<td>IG qam NPH qhs</td>
<td>56% 17% (p=0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliaschewitz et al.</td>
<td>IG qhs NPH qhs</td>
<td>NR 15.6% (p=0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenstock et al.</td>
<td>IG od NPH qhs or bid</td>
<td>61.4% 40.2% (p=0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massi Benedetti et al.</td>
<td>IG qhs NPH qhs</td>
<td>35% 12% (p=0.0002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fonseca et al.</td>
<td>IG qhs NPH qhs</td>
<td>17.3% 15.4% (p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siegmund et al.</td>
<td>IG od NPH bid</td>
<td>NR NR (NR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=number of patients randomized, IG=insulin glargine, NPH=neutral protamine Hagedorn insulin, qhs=every bedtime, qam=every morning, od=once daily, bid=twice daily, NR=not reported, NS=not significant, *events per patient year, †estimated from graph, §confirmed nocturnal symptomatic hypoglycemia (blood glucose <4 mmol/L), ¶confirmed nocturnal symptomatic hypoglycemia (blood glucose <2.8 mmol/L).
References


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