Drug Class Review

Long-Acting Insulins for Type 1 and Type 2 Diabetes

Original Report

Executive Summary

September 2015

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INTRODUCTION

Type 1 and Type 2 diabetes are prevalent in the United States, with serious long-term consequences including cardiovascular disease, renal disease, and blindness. The Diabetes Control and Complications Trial (DCCT) and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study established the benefits of intensive glycemic control in patients with Type 1 diabetes, and hemoglobin A_{1C} <7% as a treatment target. Endogenous insulin is secreted at a relatively constant basal rate over 24 hours, with increased secretion after meals; long-acting exogenous insulins have been developed to mimic physiologic basal insulin secretion.

Insulin needs fluctuate with daily changes in food intake and physical activity, and excess insulin at any point leads to hypoglycemia. Nocturnal hypoglycemia has received particular attention, because of the concern that patients will be unaware of early adrenergic symptoms before more serious, neurologic consequences occur. Severe hypoglycemia is defined as an event requiring assistance from another person, and has been associated with increased mortality in large trials.

Scope and Key Questions

The goal of this report is to compare the benefits and harms of insulin glargine and insulin detemir, the long-acting formulations currently in use in the United States. In consultation with the Drug Effectiveness Review Project (DERP) participating organizations, The Pacific Northwest Evidence-based Practice Center (EPC) developed the following key questions and inclusion criteria to guide this review:

1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with diabetes mellitus?

2. What is the comparative tolerability and frequency of adverse events with long-acting insulins for children and adults with diabetes mellitus?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions [e.g., obesity]), or other medications (drug-drug interactions) for which long-acting insulins differ in efficacy/effectiveness or frequency of adverse events?

METHODS

Inclusion Criteria

Populations

- Adults or children with Type 1 or Type 2 diabetes mellitus.
- Excluded populations: Individuals with gestational diabetes, pre-diabetes (impaired fasting glucose or impaired glucose tolerance), metabolic syndrome without diabetes, or polycystic ovary syndrome.

Interventions

Table A. Included interventions

Drug	Trade name(s)	Form	FDA Approval
Insulin glargine U100 or U300	Lantus® Toujeo®	Pen or vial	4/20/2000; 2/25/2015
Insulin detemir	Levemir®	Pen or vial	6/16/2005

Comparators

- Included insulin versus another included insulin.
- Insulin in one formulation/device vs. same insulin in another formulation/device.

Outcomes

- Macrovascular disease: cardiovascular events, cardiovascular morbidity (e.g., myocardial infarction and peripheral arterial disease), cardiovascular mortality, stroke/TIA, coronary heart disease, cardiovascular procedures, extremity amputation.
- Microvascular disease: diabetic neuropathy, nephropathy, or retinopathy.
- All-cause mortality.
- Efficacy, including glycemic control measured by morning blood glucose levels or hemoglobin A1c; measured as continuous outcomes or by whether or not patients achieve American Diabetes Association's glycemic goal for adults of <7.0% A_{1C}.
- Harms: including nocturnal hypoglycemia; severe hypoglycemia (requiring assistance from another individual); withdrawals due to adverse events; serious adverse events; malignancy.

Study Designs

- Randomized controlled trials with head-to-head comparisons of included insulins
- For harms, comparative observational studies
- Systematic reviews
- Excluded: Placebo-controlled trials

Setting

- Outpatient

We followed standard DERP methods for literature searching, study selection, data abstraction, validity assessment, data synthesis, and grading the strength of the body of evidence. Detailed methods can be found in the full report. We searched electronic databases through May Week 1 2015. We attempted to identify additional studies through searches of ClinicalTrials.gov and the US Food and Drug Administration's website for medical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from pharmaceutical companies.

We conducted meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough to combine their results. The I^2 statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity in effects between studies. When meta-analysis could not be performed, the data were summarized qualitatively.

RESULTS

Table B: Summary of the evidence by key question for benefits and harms of long-acting insulins in adults

Comparison	Type 1 or Type 2 diabetes	Strength of evidence	Conclusions
Key Question 1: comparative effectiveness			
All comparisons	Type 1 or 2	--	No comparative evidence on long-term health outcomes.
Insulin detemir vs. Insulin glargine 2 RCTs; N=763	Type 1	Low	In patients with mean baseline HbA_{1C} of 8.1% to 8.65%, difference not found in absolute reduction in HbA_{1C} or proportion with HbA_{1C} ≤7.0% without major hypoglycemia at 26 or 52 weeks.
Insulin detemir vs. Insulin glargine 6 RCTs; N=2,750	Type 2	Low	In patients with mean baseline HbA_{1C} of 7.9% to 8.8%, difference not found in absolute reduction in HbA_{1C} or proportion with HbA_{1C} ≤7.0% at 12 to 52 weeks.
Insulin glargine U300 vs. Insulin glargine U100 2 RCTs; N=602	Type 1	Low	Glargine concentration did not affect glycemic control measured by HbA_{1C} at 4 to 6 months.
Insulin glargine U300 vs. U100 3 RCTs; N=2,474	Type 2	Moderate	Glargine concentration did not affect glycemic control at 6 months. HbA_{1C} <7.0%: 36% vs 35%, pooled RR 1.0 (95% CI 0.92 to 1.1; I^2=0%,)
Insulin glargine pen vs. vial	Type 1 or 2	–	No comparative evidence
Key Question 2: comparative harms			
All comparisons	Type 1 or 2	--	No comparative evidence on risk of cancer.
Insulin detemir vs. Insulin glargine 2 RCTs, 2 observational studies; N=15,557	Type 1	Low	Differences were not found in incidence of severe hypoglycemia, serious adverse events or withdrawals due to adverse events over 26 to 52 weeks. Evidence for severe hypoglycemia and withdrawals due to adverse events is imprecise.
		Insufficient	Evidence on nocturnal hypoglycemia was insufficient to draw conclusions due to imprecision and inconsistency.
Insulin detemir vs. Insulin glargine 6 RCTs; N=2,750	Type 2	Low	Differences were not found in incidence of severe hypoglycemia, serious adverse events or nocturnal hypoglycemia (any event or events per patient-year) over 12 to 52 weeks. **Increased risk** of withdrawal due to adverse events with insulin detemir than with insulin glargine.
Insulin glargine U300 vs. Insulin glargine U100 2 RCTs; N=608	Type 1	Low	Rates of severe hypoglycemia, withdrawals due to adverse events, and serious adverse events did not differ between glargine concentrations over 4 to 6 months.
		Moderate	Rates of nocturnal hypoglycemia did not differ between glargine concentrations over 4 to 6 months: 74% vs. 77%, pooled RR 0.97 (95% C 0.88 to 1.1; I^2 24%).
Insulin glargine U300 vs. Insulin glargine U100 3 RCTs; N=2,488	Type 2	Low	Glargine concentration did not affect rates of severe hypoglycemia, withdrawals due to adverse events or serious adverse events over 6 months (3 trials, N=2,488).
		Moderate	Nocturnal hypoglycemia was less likely with insulin glargine U300 than with insulin glargine U100 over 6 months (38% vs. 51%; EPC pooled ***RR 0.75; 95% CI, 0.67 to 0.84***; I^2=0%) (2 trials, N=1,615)
Insulin glargine pen vs. vial	Type 1	–	No comparative evidence
Insulin glargine pen vs. vial 7 observational studies; N=24,564	Type 2	Low	**Rates of severe hypoglycemia were lower** with insulin glargine administered with a pen than insulin glargine via vial and syringe over 12 months

Key Question 3: subgroups			
Insulin detemir vs. Insulin glargine 1 observational study; N = 113	Type 1	Unrated	A single, small, fair-quality observational study (N=113) suggested that neonates of women using insulin detemir were larger at birth and at higher risk of being large for gestational age than those using glargine. This appears to correlate with greater frequency of insulin administration and higher insulin doses. However, this study did not adjust for potential confounding, such that future studies are needed to confirm these findings.
Insulin glargine U300 vs. Insulin glargine U100	Type 1 or 2	–	No comparative evidence
Insulin glargine pen vs. vial	Type 1 or 2	–	No comparative evidence

Limitations of this Report

Methodological limitations of the review within the defined scope included the exclusion of studies comparing one of the long-acting insulins to neutral protamine Hagedorn (NPH) insulin, which may have allowed indirect comparisons of the two long-acting insulins. The main limitation of the included trials is that they were open-label. While the outcomes for glycemic control appear objective, they are directly influenced by the dose frequency, titration and handling of hypoglycemic events, such that knowing which insulin the patient is receiving may influence the results. Additionally, there is limited or no evidence in children, older people, and non-white people, and evidence on long-term use with effectiveness outcomes is missing.

CONCLUSIONS

In adults with Type 1 diabetes, differences in efficacy or harms were not found between insulin detemir and insulin glargine, or insulin glargine U300 and insulin glargine U100. In patients with Type 2 diabetes, no differences were found in efficacy; the few differences found in harms were that insulin glargine may result in fewer patients discontinuing due to adverse events than insulin detemir, nocturnal hypoglycemia may occur in fewer patients with insulin glargine U300 than with insulin glargine U100, and that insulin glargine given via pen may result in lower incidence of severe hypoglycemia than when given by vial and syringe. There was inadequate evidence to assess comparative effects on long-term health outcomes, in subgroups, or the risk of cancer. Current evidence in pregnant women with Type 1 diabetes suggests more research is needed to determine comparative effects of long-acting insulins on the neonate.