Long-Acting Insulins for
Type 1 and Type 2 Diabetes

Final Update #1 Report

May 2017

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.
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TABLE OF CONTENTS

INTRODUCTION ....................................................................................................................... 4
Scope and Key Questions .................................................................................................................. 5

METHODS SUMMARY .............................................................................................................. 5
Inclusion Criteria ............................................................................................................................. 5
Review Procedures .......................................................................................................................... 6

RESULTS .................................................................................................................................. 6
Overview ....................................................................................................................................................... 7
Summary of Findings by Drug Comparison .......................................................................................... 8
A. Insulin versus Insulin ................................................................................................................... 8
B. Within Insulin Comparisons .......................................................................................................... 10
C. Fixed-dose Combination Products ................................................................................................ 11
Detailed Assessments for Key Questions 1, 2, and 3 by Drug Comparison .............................................. 12
A. Insulin versus Insulin ................................................................................................................... 12
B. Within Insulin Comparisons .......................................................................................................... 29
C. Fixed-dose Combination Products ................................................................................................ 37

APPLICABILITY OF THE EVIDENCE ...................................................................................... 40

LIMITATIONS OF THE EVIDENCE .......................................................................................... 40

TABLES
Table 1. Included interventions ........................................................................................................ 5
Table 2. Definitions of strength of evidence ratings ........................................................................... 6
Table 3. Degludec compared with glargine in adults with Type 1 diabetes: study characteristics ............. 13
Table 4. Degludec compared with glargine in adults with Type 2 diabetes: study characteristics .......... 15
Table 5. Studies of insulin detemir compared with glargine on hemoglobin A1C in patients with type 1 diabetes ....................................................................................................................................................... 22
Table 6. Newer studies of insulin detemir compared with glargine on hemoglobin A1C in patients with type 2 diabetes ....................................................................................................................................................... 23
Table 7. Effects of insulin detemir compared with glargine on hypoglycemia in adult patients with type 1 diabetes ....................................................................................................................................................... 26
Table 8. Insulin glargine U300 versus U100 in adults with Type 1 diabetes .............................................. 32
Table 9. Insulin glargine U300 compared with glargine U100 in adults with type 2 diabetes ..................... 34

FIGURES
Figure 1. Results of literature searches ............................................................................................ 7
Figure 2. Adults with Type 2 diabetes achieving hemoglobin A1C ≤7% with degludec compared with glargine ....................................................................................................................................................... 17
Figure 3. Rates of nocturnal hypoglycemia in adult patients with Type 1 diabetes treated with degludec compared with glargine ....................................................................................................................................................... 18
Figure 4. Rates of nocturnal hypoglycemia in adult patients with Type 2 diabetes treated with daily degludec compared with glargine ....................................................................................................................................................... 20
Figure 5. Patients achieving hemoglobin A1C ≤7% with insulin detemir compared with glargine ............ 24
Figure 6. Withdrawals from study due to adverse events: insulin detemir versus glargine ..................... 28

APPENDIXES AND EVIDENCE TABLES
Published in a separate document.
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. Insulin treatment can reduce the risk of these complications, but also increases the risk of hypoglycemia, which can cause injury, seizures, and increased overall mortality. Patients with Type 1 diabetes require exogenous insulin therapy.1,2 For Type 2 diabetes, therapy may begin with lifestyle modifications, followed by oral hypoglycemic drugs like metformin, but exogenous insulin is generally necessary as endogenous production declines.1,3

Endogenous insulin is secreted at a relatively constant basal rate over 24 hours, with increased secretion after meals.4 Both long- and short-acting exogenous insulins have been developed to mimic this physiologic insulin secretion. Ideally, exogenous basal insulin would be long-acting to reduce the number of daily injections needed, and have a flat pharmacodynamic profile without a peak that could cause fasting hypoglycemia.4 Insulin glargine at doses of 0.4 units/kg to 0.5 units/kg has a duration of action of about 20 hours to 24 hours without a peak, and is approved for use once daily.1,5-8 In 2015, the first “follow-on” biosimilar insulin product was approved by the US Food and Drug Administration; noted in this report as “F-O glargine”. Insulin detemir has a duration of action of 7.6 to 24 hours according to its product label; it has no pharmacodynamic peak at a dose of 0.2 units/kg, though some peak at 0.4 units/kg. Insulin detemir is approved for use once or twice daily.1,8,9 Insulin degludec has a longer duration of action, more than 42 hours, with a flat pharmacodynamic profile at doses from 0.4 to 0.8 units/kg. It is approved for use once daily.10-12

With persistent hyperglycemia, glucose attaches irreversibly to proteins including hemoglobin, at a rate dependent on plasma glucose concentration. Glycated hemoglobin, or hemoglobin A1C, is used clinically as a measure of glycemic control. The percent of total hemoglobin that is glycated reflects the mean blood glucose level over the 3-month lifespan of the red blood cell, best predicting levels over the previous 2 to 3 months.13 Based on the results of the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study in Type 1 patients and the ACCORD trial in patients with Type 2 diabetes, the American Diabetes Association’s 2015 Standards of Medical Care in Diabetes suggests that “a reasonable hemoglobin A1C goal for many nonpregnant adults is <7%.”14

The primary adverse event concerns with long-acting insulins are severe hypoglycemia, nocturnal hypoglycemia, and increased risk of cancer. Insulin needs fluctuate with daily changes in food intake and physical activity, and excess insulin at any point leads to hypoglycemia. Severe hypoglycemia is defined as “an event requiring assistance from another person,” and has been associated with increased mortality in large trials.14 Nocturnal hypoglycemia has received particular attention, also because of the concern that patients will be unaware of early symptoms before more serious consequences occur.

Changes in structure that increase the duration of action in long-acting insulins may change other properties as well. For example, affinity for the insulin-like growth factor receptor may differ between analogs and human insulin, which could in theory affect mitogenic activity and cancer risk.1,15-17
Scope and Key Questions

The goal of this report is to compare the benefits and harms of long-acting insulins that are available in the U.S. Representatives of the organizations participating in the Drug Effectiveness Review Project to guide this review approved the following key questions:

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 SUMMARY

Inclusion Criteria (PICOTS)

Populations, Study Designs, and Setting

• Randomized controlled trials of 12 weeks duration or longer in adults or children with Type 1 or Type 2 diabetes mellitus in the outpatient setting

Interventions

Table 1. Included interventions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name(s)</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin glargine U100 or U300</td>
<td>Basaglar® (U100)</td>
<td>Pen</td>
</tr>
<tr>
<td></td>
<td>Lantus® (U100)</td>
<td>Vial or pen</td>
</tr>
<tr>
<td></td>
<td>Follow-on (F-O) glargine (U100)</td>
<td>Vial</td>
</tr>
<tr>
<td></td>
<td>Toujeo® (U300)</td>
<td>Pen</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>Tresiba®</td>
<td>Pen</td>
</tr>
<tr>
<td>Insulin degludec/insulin aspart</td>
<td>Ryzodeg® 70/30</td>
<td>Pen</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>Levemir®</td>
<td>Pen or vial</td>
</tr>
</tbody>
</table>

*a = In the text references to glargine U100 refer to Lantus, except where “pen” is specified, where pen U100 is Basaglar, and pen U300 is Toujeo. “F-O glargine” refers to the follow-on product while “glargine” refers to the originator product (i.e. Lantus®)

Comparators

• Included insulin versus another included insulin, including formulations/devices.

Outcomes

• Macrovascular disease, microvascular disease, and all-cause mortality.
• Efficacy: glycemic control measured by fasting blood glucose levels or hemoglobin A1C;
• Harms: nocturnal hypoglycemia; severe hypoglycemia; withdrawals due to adverse events; malignancy.

Review Procedures

We followed systematic review methodology and procedures developed specifically for DERP\textsuperscript{18} and that are in accordance with current guidance, for example, using dual review for study inclusion, quality assessments and data abstraction.\textsuperscript{19}

**Literature Search.** Literature searches, including Medline and the Cochrane Library databases, were conducted with dates through November 2016.

**Data Synthesis.** In addition to tables summarizing study characteristics and findings, and narrative synthesis of the evidence, quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. Specific methods used can be found in our DERP Methods Manual.\textsuperscript{18} The $I^2$ statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity in effects between studies.\textsuperscript{20,21}

**Grading the Strength of Evidence.** We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (Table 2).\textsuperscript{22} Grades do not refer to the general efficacy or effectiveness.

**Table 2. Definitions of strength of evidence ratings**

<table>
<thead>
<tr>
<th>Strength Rating</th>
<th>Definition</th>
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<tbody>
<tr>
<td>High</td>
<td>We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.</td>
</tr>
<tr>
<td>Low</td>
<td>We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.</td>
</tr>
</tbody>
</table>

**Peer Review and Public Comment.** We received peer review comments from 2 content experts and public comments from 3 pharmaceutical manufacturers. Comments were reviewed and the appropriate changes to the report were made where possible.
RESULTS

Overview

Through comprehensive searching, a total of 2,217 records were identified and screened for inclusion in the review. Cumulatively, we have received dossiers from 3 pharmaceutical manufacturers: Eli Lilly (Basaglar®; Insulin Glargine), Novo Nordisk (Levemir®; Insulin Degludec), and Sanofi (Lantus®; Toujeo®, Insulin Glargine U300). By applying the eligibility and exclusion criteria to these, we ultimately included 61 studies (in 69 publications), including 42 head-to-head trials23-63 (in 50 publications),23-72 16 observational studies,73-88 2 pooled analyses,89,90 and 1 systematic review.91 Figure 1 shows the flow of studies through the selection process. A list of studies excluded after full-text review and reasons for exclusion is provided in Appendix D. We found very little comparative evidence of the efficacy/effectiveness or harms of long-acting insulins in children with diabetes.

Figure 1. Results of literature searches

![Diagram of study selection process]

Note: Studies in parentheses are those that were identified in the current report update. All other study counts are cumulative.
Summary of Findings by Drug Comparison

A. Insulin versus Insulin

**Insulin Degludec vs. Insulin Detemir**

**Type 1 Diabetes**

- Two fair-quality trials provided low-strength evidence that glycemic control measured by hemoglobin A1C did not differ between degludec and detemir in either children and adolescents (N=350) or adults (N=456) with Type 1 diabetes.
- Evidence on episodes of nocturnal hypoglycemia, severe hypoglycemia or withdrew due to adverse events was insufficient to compare these outcomes in patients receiving degludec and detemir.

**Insulin Degludec vs. Insulin Glargine**

**Type 1 Diabetes**

- Three good- or fair-quality trials provided low-strength evidence that glycemic control measured by hemoglobin A1C did not differ between degludec and glargine with treatment duration between 16 and 52 weeks (evidence analyzed for 1,076 adult patients).
- Three good- or fair-quality randomized controlled trials including 1,072 patients provided low-strength evidence that patients treated with daily degludec had lower rates of nocturnal hypoglycemia than those treated with daily glargine (pooled rate ratio 0.61, 95% CI 0.46 to 0.82; I^2=55%).
- Few patients with Type 1 diabetes receiving degludec and glargine had episodes of severe hypoglycemia or withdrew due to adverse events, and evidence was insufficient to compare these outcomes.

**Type 2 Diabetes**

- Moderate-strength evidence from 4,434 patients in 6 good- or fair-quality trials showed no difference in glycemic control between patients given daily degludec and daily glargine for 16 to 52 weeks. Two efficacy measures showed the same result; patients achieving hemoglobin A1C less than 7% (pooled RR 0.96; 95% CI 0.90 to 1.03; I^2=0%; 6 RCTs), and patients achieving the same goal with no episodes of confirmed hypoglycemia (pooled RR 1.0, 95% CI 0.88 to 1.1; I^2=17%; 3 RCTs).
- Two good-quality trials (in 1 publication) provided low-strength evidence that degludec given 3 times weekly for 26 weeks has lower efficacy than glargine given daily. Evidence from 926 patients showed lower proportions achieving hemoglobin A1C less than 7% with degludec 3 times weekly (47% vs. 56%, pooled RR 0.84, 95% CI 0.74 to 0.95; I^2=0%). The FDA has approved daily rather than 3 times weekly dosing.
- Low-strength evidence from 3,927 patients in 6 good- or fair-quality trials did not show a difference in the proportion of patients experiencing severe hypoglycemia between daily degludec and daily glargine.
- Patients treated with daily degludec had fewer episodes of nocturnal hypoglycemia than those treated with daily glargine, according to moderate-strength evidence from
4,612 patients in 7 randomized controlled trials\textsuperscript{44,45,53-55,62,63} (pooled rate ratio 0.71, 95% CI 0.59 to 0.85; $I^2=0\%$).

- Low-strength evidence from 456 patients in 1 good-quality trial\textsuperscript{61} showed more episodes of nocturnal hypoglycemia for patients given degludec 3 times weekly before breakfast, compared with those given daily glargine (rate ratio 2.1, 95% CI 1.1 to 4.2). The FDA has approved daily rather than 3 times weekly dosing.

- Low-strength evidence from 7 trials\textsuperscript{44,45,53-55,62,63} showed no difference in withdrawals due to adverse events in 4,612 patients with Type 2 diabetes given daily degludec and daily glargine.

- Evidence was insufficient to compare severe hypoglycemia or withdrawals between patients treated 3 times weekly with degludec and those given daily glargine, or rates of nocturnal hypoglycemia for those given degludec 3 times weekly in the evening and those given daily glargine.

- There were no statistically significant differences between patients in Japan and in larger populations in Asia and worldwide in the effects of degludec compared with glargine on glycemic efficacy or nocturnal hypoglycemia.

**Insulin Detemir vs. Insulin Glargine**

**Type 1 Diabetes**

- There was low-strength evidence, based on 2 fair-quality open-label trials (N=763),\textsuperscript{25,28} that there was no difference between detemir and glargine in glycemic control measured by achieving hemoglobin A\textsubscript{1C} goals or mean plasma glucose levels at 26 or 52 weeks.

- Low-strength evidence from these 2 trials and 2 observational studies suggested no difference in the risk of severe hypoglycemic events or withdrawal due to adverse events between detemir and glargine.\textsuperscript{25,28,73,78,81} Evidence on nocturnal hypoglycemia was insufficient.

- Evidence on the risk of perinatal mortality, adverse neonatal birth weight, and neonatal hypoglycemia with use of detemir or glargine throughout pregnancy was insufficient due to inconsistency in findings and methodological limitations of 2 small observational studies (N=203).\textsuperscript{73,81}

**Type 2 Diabetes**

- There was low-strength evidence based on a good-quality systematic review of 4 trials and 2 more recent fair quality trials (total N=2,750) that there was no difference between detemir and glargine in glycemic control measured by achieving hemoglobin A\textsubscript{1C} goals and the reduction in hemoglobin A\textsubscript{1C} at 12 to 52 weeks.\textsuperscript{24,26,27,29,31,34}

- There was low-strength evidence of no difference between detemir and glargine in the risk for any cancer in the short-term (4 cohort studies; N=115,858; hazard or odds ratios 0.97 to 1.02 for glargine and 0.96 to 1.14 for detemir compared with no insulin exposure).\textsuperscript{82,83,85,87}

- Low-strength evidence based on 6 randomized controlled trials and 6 observational studies suggested that there was no difference between detemir and glargine in the incidence of severe or nocturnal hypoglycemia.\textsuperscript{24,27,75,78-80,86,88,91}
Moderate-strength evidence based on meta-analysis of 6 trials indicates that withdrawals due to adverse events occurred significantly more frequently for patients assigned to detemir compared with glargine over 12 to 52 weeks (pooled RR 2.1; 95% CI, 1.4 to 3.3; $I^2=0\%$).24,26,27,29,31,34

B. Within Insulin Comparisons

**Insulin Degludec U200 vs. Insulin Degludec U100**

**Type 2 Diabetes**
- Evidence from a single study was insufficient to compare differences in glycemic control measured by hemoglobin A1C, nocturnal hypoglycemia, severe hypoglycemia or withdrawals due to adverse events between degludec U200 and degludec U100 in adult patients with Type 2 diabetes.39

**F-O Glargine vs. Glargine**

**Type 1 Diabetes**
- One fair-quality trial provided low-strength evidence that glycemic control measured by hemoglobin A1C did not differ between F-O glargine and glargine in adults with Type 1 diabetes (N=535).38
- Evidence on episodes of nocturnal hypoglycemia, severe hypoglycemia or withdrew due to adverse events was insufficient to compare these outcomes in patients receiving F-O glargine and glargine.38

**Type 2 Diabetes**
- One fair-quality trial provided low-strength evidence that glycemic control measured by hemoglobin A1C did not differ between F-O glargine and glargine adults with Type 2 diabetes (N=756).57
- Few patients had episodes of nocturnal or severe hypoglycemia or withdrew due to adverse events, and evidence was insufficient to compare these outcomes in patients receiving F-O glargine and glargine.57

**Insulin Glargine U300 vs. Insulin Glargine U100**

**Type 1 Diabetes**
- Low-strength evidence from 4 fair-quality trials (N=871)36,48,49,52 found that glycemic control measured by hemoglobin A1C did not differ between patients given glargine U300 and glargine U100 for 2 to 6 months.
- These 4 trials36,48,49,52 provide low-strength evidence of no difference between glargine U300 and glargine U100 in severe hypoglycemia and withdrawals due to adverse events and moderate strength evidence of no difference in nocturnal hypoglycemia after 2 to 6 months’ treatment (pooled RR 0.91, 95% CI 0.80 to 1.05; $I^2=39.1\%$).
**Type 2 Diabetes**

- There is moderate-strength evidence from 4 fair-quality trials\(^{23,30,35,59}\) (N = 2,718) that glycemic control measured by hemoglobin A\(_{1C}\) did not differ between patients treated for 6 months with glargine U300 and glargine U100. These trials also provide low-strength evidence of no differences in rates of severe hypoglycemia or withdrawals due to adverse events.
- Three fair-quality trials\(^{30,35,59}\) (N = 1,856) provided moderate-strength evidence that rates of nocturnal hypoglycemia were lower with glargine U300 than with glargine U100 (37% vs. 50%; pooled RR 0.74, 95% CI 0.66 to 0.82; \(I^2=0\%\)).

**Insulin Glargine U100 Pen vs. Insulin Glargine U100 Vial**

- No randomized controlled trials comparing glargine delivered via pen versus vial met inclusion criteria.

**Type 2 Diabetes**

- Seven observational studies\(^{77,90}\) of 24,564 patients with Type 2 diabetes provided low-strength evidence that rates of severe hypoglycemia were lower with glargine via pen than with glargine via vial and syringe (pooled RR 0.72; 95% CI, 0.65 to 0.79; \(I^2=0\%\)).

**C. Fixed-dose Combination Products**

**Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Degludec**

**Type 2 Diabetes**

- Evidence was insufficient to compare differences in glycemic control measured by hemoglobin A\(_{1C}\), nocturnal hypoglycemia, severe hypoglycemia or withdrawals due to adverse events between FDCP degludec/aspart, and degludec in adult patients with Type 2 diabetes.\(^{56}\)

**Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Detemir**

**Type 1 Diabetes**

- One fair-quality trial\(^{47}\) provided low-strength evidence that glycemic control measured by hemoglobin A\(_{1C}\) did not differ between FDCP degludec/aspart and detemir (N=548).
- Evidence on episodes of nocturnal hypoglycemia, severe hypoglycemia or withdrew due to adverse events was insufficient to compare these outcomes in patients receiving FDCP degludec/aspart and detemir.\(^{47}\)
Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Glargine

Type 2 Diabetes

- One fair-quality trial\textsuperscript{50} provided low-strength evidence that glycemic control measured by hemoglobin A\textsubscript{1C} did not differ between FDCP degludec/aspart, and glargine (N=530).
- Evidence on episodes of nocturnal hypoglycemia, severe hypoglycemia or withdrew due to adverse events was insufficient to compare these outcomes in patients receiving FDCP degludec/aspart and glargine.

Detailed Assessments for Key Questions 1, 2, and 3 by Drug Comparison

A. Insulin versus Insulin

Insulin Degludec vs. Insulin Detemir

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

Type 1 Diabetes

We included 2 fair-quality randomized controlled trials comparing degludec and detemir in patients with Type 1 diabetes.\textsuperscript{42,60} Both were 26-week, multinational trials. One was conducted in children and adolescents (N=350; 1 to 17 years).\textsuperscript{60} In this study, degludec 100 U/mL was given once daily and detemir 100 U/mL was given once-or twice-daily, both given via insulin pen. Prandial insulin aspart was given in both treatment arms. The total daily insulin dose was calculated to achieve a basal:bolus ratio of between 50:50 and 30:70 with no basal dose reduction. The other trial was conducted in adults (N=456).\textsuperscript{42} Degludec 100 U/mL and detemir 100 U/mL were both given once per day, with aspart 100 U/mL given at mealtimes in both treatment arms. Patients in both treatment arms were titrated individually once a week to a plasma glucose of 3.9 to 4.9 mmol/L.

Both trials provided low-strength evidence that glycemic control did not differ between degludec and detemir. In children and adolescents with Type 1 diabetes the estimated treatment difference in mean hemoglobin A\textsubscript{1C} percent change from baseline after 26 weeks was 0.15% (95% CI -0.03 to 0.32). In adults, the estimated treatment difference was -0.09% mean hemoglobin A\textsubscript{1C} reduction (95% CI -0.23 to 0.05). The proportion of adults achieving hemoglobin A\textsubscript{1C} <7% was 41.1% for degludec compared with 37.3% for detemir (OR 1.27, 95% CI 0.77 to 2.0).

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

Type 1 Diabetes

Two fair-quality randomized controlled trials comparing degludec and detemir in patients with Type 1 diabetes,\textsuperscript{42,60} as described in Key Question 1 above, were included.
Hypoglycemia
There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in pediatric patients given degludec and detemir (RR 1.30, 95% CI 0.80 to 2.11). Evidence was also insufficient to compare rates of nocturnal hypoglycemia in pediatric patients (RR 1.07, 95% CI 0.94 to 1.27). Evidence of differences in rates of hypoglycemia was also insufficient in adult patients given degludec and detemir. The episodes/patient/year of severe hypoglycemia was 0.31 for degludec vs. 0.39 for detemir (Rate ratio 0.92, 95% CI 0.46 to 1.81). The episodes/patient/year of nocturnal hypoglycemia was 4.14 for degludec vs. 5.93 for detemir (Rate ratio 0.66, 95% CI 0.49 to 0.88).

Withdrawals due to Adverse Events
Few patients withdrew due to adverse events, and evidence was insufficient to compare rates in pediatric patients given degludec and detemir (RR 0.14, 95% CI 0.01 to 1.52), and in adults (RR 1.51, 95% CI 0.22 to 10.54).

Insulin Degludec vs. Insulin Glargine
Key Question 1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with diabetes mellitus?

Type 1 Diabetes
Glycemic control
We included 3 open-label randomized controlled trials comparing degludec to glargine in adult patients with Type 1 diabetes and mean age 43 years. Two trials were rated fair-quality, and 1 (BEGIN Basal-Bolus Type 1, N=629) was rated good-quality for objective outcomes less affected by the open-label design. One trial compared glargine with 2 molar concentrations of degludec, which in terms of insulin units were both equivalent to 100 U/mL. The FDA has approved 2 unit concentrations of degludec, 100 U/mL and 200 U/mL, with molar concentrations of 600 nmol/mL and 1200 nmol/mL, respectively. Data on these are reported here.

The BEGIN Flex T1 trial compared degludec administered at a fixed time daily to “forced flexible” timing where the interval between doses ranged from 8 to 40 hours. Together the 3 trials included a total of 1,300 patients, and treatment duration ranged from 16 to 52 weeks (Table 3).

Table 3. Degludec compared with glargine in adults with Type 1 diabetes: study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Trial Name</th>
<th>Sample Size</th>
<th>Study Duration</th>
<th>Age Range Included</th>
<th>Insulin Dosing</th>
<th>Additional Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkeland, 2011</td>
<td>37</td>
<td>N=178</td>
<td>16 weeks</td>
<td>18 to 75 years</td>
<td>Starting dose: degludec 600 µmol/L 29 U degludec 900 µmol/L 28 U, glargine 23 U (all 100 U/mL) Timing: once daily, evening Titration target: FPG 4.0 to 6.0 mmol/L</td>
<td>Mealtime insulin aspart</td>
</tr>
<tr>
<td>Home, 2012</td>
<td>269</td>
<td>16 weeks</td>
<td>18 to 75 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Sample Size</td>
<td>Study Duration</td>
<td>Age Range Included</td>
<td>Insulin Dosing</td>
<td>Additional Therapies</td>
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</tr>
<tr>
<td>Heller, 2012</td>
<td>46</td>
<td>N=629</td>
<td>≥18 years</td>
<td>Starting dose: degludec 29U, glargine 28 U(^a) (both 100 U/mL)</td>
<td>Mealtime insulin aspart</td>
<td></td>
</tr>
<tr>
<td>Mathieu, 2013</td>
<td>51</td>
<td>N=493</td>
<td>≥18 years</td>
<td>Starting dose: degludec Forced-Flex 29 U, degludec fixed 27 U, glargine 28 U (all 100 U/mL)</td>
<td>Mealtime insulin aspart</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** FPG, fasting plasma glucose; N, number of patients randomized; NR, not reported; U, international units (units) of insulin

\(^a\)Estimated from reported doses in U/kg and mean patient body weights in each trial arm.

The 3 trials provided low-strength evidence that glycemic control did not differ between degludec and glargine in adults with Type 1 diabetes. Across the 3 trials, the decrease in HbA\(_{1C}\) (percent glycated hemoglobin) from baseline to the end of treatment was slightly less in patients given degludec than in those given glargine, but the difference was not statistically significant (weighted mean difference in percent HbA\(_{1C}\) change of 0.07%, 95% CI -0.05% to 0.19%; \(I^2=27\%\)). This pooled analysis includes 1 of 2 degludec arms in Mathieu 2013 (with fixed daily timing) and in Birkeland 2011 (600 µmol/L, the FDA-approved formulation of 100 U/mL degludec). One trial\(^46\) also reported the percent of patients reaching the goal of HbA\(_{1C}\) less than 7%, which did not differ between those treated with degludec and glargine (RR 0.93, 95% CI 0.76 to 1.2).

Two trials included an extension study where patients continued on the insulin assigned during the trial.\(^46,51,72\) Neither trial re-randomized participants, and in both 75% of patients randomized in the main trial continued into the extension. Treatment was extended to 2 years in 1 study\(^46,72\) and 1 year in the other.\(^51\) In both studies, efficacy in the extension period was similar to that in the main trial, with no statistically significant differences in hemoglobin A\(_{1C}\) between degludec and glargine in either time period.

**Type 2 Diabetes**

Nine good- or fair-quality trials compared treatment with degludec and glargine in a total of 5,623 adult patients with Type 2 diabetes (Table 4; 9 trials in 8 primary publications).\(^44,45,53-55,61-63\) Most trials had an insulin titration target for fasting plasma glucose of about 4 to 5 mmol/L.
though for 1 trial\textsuperscript{62} it was 4 to 6 mmol/L; targets did not differ between patients treated with degludec and glargine. Three trials (in 2 publications)\textsuperscript{61,62} compared patients treated 3 times a week with degludec to those treated daily with glargine; in the other 6 trials all patients received daily insulin. Using meta-analysis, we analysed comparisons of daily degludec to daily glargine together, but conducted separate analyses of trial arms comparing 3 times weekly degludec to daily glargine. (The FDA has approved daily rather than 3 times weekly degludec; we include information on both dosing frequencies in this report because both were explored in drug development, given that degludec has a longer duration of action than other insulins. However, we will exclude 3 times weekly degludec in any update reports.) Two trials were included in 1 primary publication, Zinman 2013, and treated a total of 462 patients 3 times weekly with degludec. A third trial, Zinman 2011, included 62 patients treated with 3 times weekly degludec, but did not report patients achieving hemoglobin A\textsubscript{1C} targets and is excluded from our efficacy analysis. Daily timing of degludec also varied, with comparisons of fixed and flexible timing and of morning and evening administration.

Treatment duration across the 9 trials ranged from 16 to 52 weeks. Glargine concentration in each trial was 100 U/mL, but various formulations of degludec were tested, some 100 U/mL and some 200 U/mL. As for Type 1 diabetes, 1 trial\textsuperscript{62} in patients with Type 2 diabetes compared 2 molar concentrations of degludec, but both were equivalent to 100 U/mL. Most trials required or allowed additional treatment with non-insulin antidiabetic drugs, with some allowing DPP-4 inhibitors and others not; in 1 trial\textsuperscript{44} patients also received mealtime insulin aspart.

Table 4. Degludec compared with glargine in adults with Type 2 diabetes: study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample Size</th>
<th>Study Duration</th>
<th>Insulin Dosing</th>
<th>Additional Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garber, 2012\textsuperscript{44}</td>
<td>N=1,006</td>
<td>52 weeks</td>
<td>Starting dose: Degludec and glargine both 10 U and 100 U/mL</td>
<td>Mealtime insulin aspart, with or without pioglitazone and/or metformin</td>
</tr>
<tr>
<td>Hollander, 2015\textsuperscript{70}</td>
<td>N=1,006</td>
<td>52 weeks</td>
<td>Timing: once daily; degludec evening, glargine any time but same time daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Titration target: FPG 3.9 to &lt;5.0 mmol/L</td>
<td></td>
<td>Mealtime insulin aspart, with or without pioglitazone and/or metformin</td>
<td></td>
</tr>
<tr>
<td>Meneghini, 2013\textsuperscript{53}</td>
<td>N=687</td>
<td>26 weeks</td>
<td>Starting dose: Degludec flexible 19 U, degludec fixed 20 U, glargine 18 U\textsuperscript{b}; 10 U for insulin-naïve; all 100 U/mL</td>
<td>Oral antidiabetic drugs for patients treated with them before trial</td>
</tr>
<tr>
<td>BEGIN Basal-Bolus Type 2</td>
<td></td>
<td></td>
<td>Timing: once daily</td>
<td></td>
</tr>
<tr>
<td>BEGIN LOW VOLUME</td>
<td></td>
<td></td>
<td>Degludec flexible: MWF am, TuThSaSu evening, range 8 to 40 hours between doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Degludec fixed: evening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glargine: any time but same time daily</td>
<td></td>
</tr>
<tr>
<td>Gough, 2013\textsuperscript{45}</td>
<td>N=460</td>
<td>26 weeks</td>
<td>Starting dose: Degludec and glargine both 10 U; degludec 200 U/mL, glargine 100 U/mL</td>
<td>Metformin with or without a DPP-4 inhibitor</td>
</tr>
<tr>
<td>BEGIN FLEX T2</td>
<td></td>
<td></td>
<td>Timing: once daily; degludec evening, glargine any time but same time daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Titration target: FPG &lt; 5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Trial Name</td>
<td>Sample Size</td>
<td>Study Duration</td>
<td>Insulin Dosing</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
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</tr>
</tbody>
</table>
| Onishi, 2013  | BEGIN: ONCE ASIA | N=435 | 26 weeks | **Starting dose:** Degludec and glargine both 10 U and 100 U/mL  
**Timing:** once daily, degludec evening, glargine any time but same time daily  
**Titration target:** FPG 3.9 to <5.0 mmol/L | One or more oral antidiabetic drug as given before study, but DPP-4's discontinued |
| Osonoi, 2016  | BEGIN: ONCE | N=833 | 26 weeks | **Starting dose:** Degludec and glargine both 10 U and 100 U/mL  
**Timing:** once daily, degludec evening, glargine NR | Metformin |
| Pan, 2016  | BEGIN: ONCE | N=833 | 26 weeks | **Starting dose:** Degludec and glargine both 10 U and 100 U/mL  
**Timing:** once daily; degludec evening, glargine NR | Metformin |
| Zinman, 2011  | BEGIN Once Long | N=245 | 16 weeks | **Starting dose:** 20 U for 3x weekly regimen, 10 U for daily regimens  
Four study arms: degludec 3x weekly 900 nmol/mL, degludec daily 600 or 900 nmol/mL, glargine 600 nmol/mL; all equivalent to 100 U/mL  
**Timing:** 3 times weekly in one study arm (degludec, MWF) and once daily in 3 study arms (degludec and glargine)  
**Titration target:** FPG 4.0 to 6.0 mmol/L | Metformin |
| Zinman, 2012  | BEGIN Once Long 2 trials | N=1,030 | 52 weeks | **Starting dose:** Degludec and glargine both 10 U and 100 U/mL  
**Timing:** once daily, degludec evening, glargine any time but same time daily  
**Titration target:** FPG 3.9 to 4.9 mmol/L | Metformin with or without DPP-4 inhibitors |
| Rodbard, 2013 | BEGIN EASY AM  
BEGIN EASY PM (2 trials) | AM trial: N=460  
PM trial: N=467 | 26 weeks | **Starting dose:** degludec 20 U, glargine 10 U; degludec 200 U/mL, glargine 100 U/mL  
**Timing:** degludec 3 times weekly, glargine once daily  
AM trial: degludec before breakfast  
PM trial: degludec with evening meal  
**Glargine:** same time daily  
**Titration target:** FPG 3.9 to <5.0 mmol/L | Metformin with or without DPP-4 inhibitors |

**Abbreviations:** FPG, fasting plasma glucose; N, number of patients randomized; NR, not reported; U, international units (units) of insulin

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Six trials (Figure 2) provided moderate-strength evidence from more than 4,000 patients that glycemic control did not differ between patients treated with daily degludec and daily glargine. About the same proportion of patients in both groups achieved HbA1c less than 7% (pooled RR 0.96, 95% CI 0.90 to 1.03; I²=0%; Figure 2). Three of the trials also reported patients achieving goal hemoglobin A1c with no episodes of confirmed hypoglycemia, and...
provided low-strength evidence that rates for this outcome too did not differ between patients given degludec and glargine (pooled RR 1.0, 95% CI 0.88 to 1.1; I²=17%).

**Figure 2. Adults with Type 2 diabetes achieving hemoglobin A₁C ≤7% with degludec compared with glargine**

![Relative risk meta-analysis plot (random effects)](image)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garber 2012</td>
<td>0.99 (0.86, 1.15)</td>
</tr>
<tr>
<td>Gough 2013</td>
<td>0.93 (0.79, 1.11)</td>
</tr>
<tr>
<td>Meneghini 2013</td>
<td>0.91 (0.76, 1.09)</td>
</tr>
<tr>
<td>Onishi 2013</td>
<td>0.84 (0.68, 1.05)</td>
</tr>
<tr>
<td>Pan 2016</td>
<td>1.05 (0.92, 1.21)</td>
</tr>
<tr>
<td>Zinman 2012</td>
<td>0.96 (0.84, 1.10)</td>
</tr>
<tr>
<td>Combined [random]</td>
<td>0.96 (0.90, 1.03)</td>
</tr>
</tbody>
</table>

However, 2 trials (in 1 publication) found that treatment 3 times weekly with degludec had lower efficacy compared with daily glargine. The 3 times weekly regimen used a higher concentration of degludec (200 U/mL, FDA-approved along with 100 U/mL), compared with 100 U/mL daily glargine. Fewer patients met the goal of hemoglobin A₁C less than 7% when treated with degludec 3 times weekly (47% vs. 56%, pooled RR 0.84, 95% CI 0.74 to 0.95; I²=0%). Less than 1,000 patients were included in these comparisons, and we rated the strength of the evidence as low.

Two trials reported extension studies with 70% to 75% of randomized patients entering the extension period. Patients were not re-randomized, and received the same treatment throughout the main and extension trial periods. Total duration of trial and extension was 78 weeks in 1 study, and 2 years in the other. In each study, efficacy in the extension period was similar to that in the trial period, with no statistically significant differences in hemoglobin A₁C between degludec and glargine in either time period.

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

**Type 1 Diabetes**

Three good- or fair-quality open-label randomized controlled trials in adult patients with Type 1 diabetes compared degludec to glargine, as described in Key Question 1 above (Table 3). Formulations varied, but in each case both degludec and glargine concentrations were equivalent to 100 U/mL. One trial had a higher titration target than the other 2 (4 to 6 mmol/L fasting
plasma glucose compared with about 4 to 5 mmol/L), but targets did not differ across treatment arms. Timing of degludec administration also varied, with the BEGIN Flex T1 trial\(^6\) setting a range of 8 to 40 hours between degludec doses.

### Hypoglycemia

The 3 trials reported rates of severe hypoglycemia and of nocturnal hypoglycemia as episodes per patient-year of exposure, and reported rate ratios comparing degludec and glargine. We pooled these rate ratios across trials. There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given degludec and glargine.\(^46,51\) However, episodes of nocturnal hypoglycemia were more frequent, and rates were lower with degludec than with glargine (pooled rate ratio \(0.61; 95\%\) CI \(0.46\) to \(0.82\); \(I^2=55\%\); 3 RCTs, Low SOE). There was some statistical heterogeneity in these pooled results; however, each of the 3 trials showed lower rates of nocturnal hypoglycemia for degludec, results for each trial were statistically significant, and confidence intervals overlapped (Figure 3).

One trial\(^46\) included a 1-year main trial and an additional 1-year extension trial, in which patients were not re-randomized and received the same treatment regimens as in the main trial. Of the 629 patients randomized in the main trial, 75\% continued into the extension. Findings for adverse events in the extension period were similar to that in the main trial. There was no statistically significant difference in severe hypoglycemia between degludec and glargine in either time period, but rates of nocturnal hypoglycemia were lower for degludec over 2 years, as they had been over 1 year.

### Withdrawals due to Adverse Events

Few patients withdrew due to adverse events, with 27 withdrawals among 1,297 patients across the 3 trials. The evidence was insufficient to compare withdrawals due to adverse events in patient given degludec and glargine.

### Figure 3. Rates of nocturnal hypoglycemia in adult patients with Type 1 diabetes treated with degludec compared with glargine

#### Summary meta-analysis plot [random effects]

- Birkeland, 2011 D600
- Heller, 2012
- Mathieu, 2013 DFlex
- Combined

* ratio (95% confidence interval)
Other Harms
None of the 3 trials reported cancer diagnoses in the patients treated. Two trials\textsuperscript{46,51} reported major adverse cardiovascular events assessed by an event adjudication committee, but events were few (7 across the 2 trials) and not reported by treatment arm.

Type 2 Diabetes
We included 9 good- or fair-quality trials in more than 5,000 adult patients with Type 2 diabetes treated with degludec compared with glargine, as described in Key Question 1 above (Table 4; 9 trials in 8 primary publications).\textsuperscript{44,45,53-55,61-63} Three of the trials\textsuperscript{61,62} compared degludec given 3 times weekly to glargine given daily, and we analyzed these comparisons separately from those comparing daily degludec and glargine. The timing of degludec administration also varied across trials. In most cases degludec was given in the evening and glargine at any time in the day, but with that time kept consistent through the trial. The BEGIN FLEX T2 trial varied the degludec dose interval from 8 to 40 hours.\textsuperscript{53} Two trials that administered degludec 3 times weekly compared morning and evening administration (BEGIN: EASY AM and BEGIN: EASY PM, reported in 1 publication\textsuperscript{61}).

Hypoglycemia
Low-strength evidence from 3,927 patients in 6 trials\textsuperscript{44,45,54,55,62,63} showed no difference in rates of severe hypoglycemia between patients given daily degludec and daily glargine (pooled RR 0.55, 95% CI 0.25 to 1.2; \(I^2=19\%\)). In comparisons of degludec 3 times weekly to daily glargine in 1,047 patients in 3 trials, there were few episodes of severe hypoglycemia and evidence was insufficient to compare rates in patients given degludec and glargine.

Moderate-strength evidence from 4,612 patients with Type 2 diabetes in 7 randomized controlled trials showed that rates of nocturnal hypoglycemia were lower with daily degludec than with daily glargine. The difference was not statistically significant (and some heterogeneity was present) when analyzing whether each patient had any episode of nocturnal hypoglycemia (pooled RR 0.93, 95% CI 0.76 to 1.1; \(I^2=43\%\)). However, there were fewer episodes of nocturnal hypoglycemia per patient year in patients given daily degludec than in those receiving daily glargine (pooled rate ratio 0.71, 95% CI 0.59 to 0.85; \(I^2=0\%\); 6 RCTs; Figure 4).

Depending on the timing of degludec administration, the opposite result was found for degludec given 3 times weekly (2 trials in 1 publication\textsuperscript{61}). The BEGIN: EASY PM trial, with degludec given 3 times weekly with the evening meal, did not show a statistically significant difference in episodes of nocturnal hypoglycemia per patient year (Insufficient SOE.) However, in the BEGIN: EASY AM trial with the same design but with degludec administered before breakfast 3 times weekly, this regimen showed twice as many episodes of nocturnal hypoglycemia as daily glargine (rate ratio 2.1, 95% CI 1.1 to 4.2, Low SOE).

Two of these trials in patients with Type 2 diabetes reported an extension period, with 70% to 75% of patients from the main trial entering the extension, and a total duration of 78 weeks in 1 trial\textsuperscript{44,70} and 2 years in the other.\textsuperscript{63,67} Results for nocturnal hypoglycemia were similar in the extension and main trials, with lower rates over each time period for patients given degludec versus glargine. For severe hypoglycemia, 1 study\textsuperscript{67} showed lower rates with degludec over 2 years of treatment, but there was no difference in rates of severe hypoglycemia between treatments administered for 1.5 years or less.\textsuperscript{44,63,70}
Withdrawals Due to Adverse Events
Seven trials provided data on adverse events in 4,612 patients with Type 2 diabetes given daily degludec or glargine. We found low-strength evidence that withdrawals due to adverse events did not differ between patients given degludec and glargine (pooled RR 0.98, 95% CI 0.62 to 1.6; I²=0%).

Other Harms
Few patients in Type 2 diabetes trials died (18 patients in 8 trials) or were diagnosed with cancer (23 patients in 5 trials), and these outcomes were not prespecified or adjudicated. Major adverse cardiovascular events were assessed by adjudication committees in multiple trials, and reported in 4 trials (3 publications), but just 28 events occurred and evidence was inadequate to compare across treatment arms.

Figure 4. Rates of nocturnal hypoglycemia in adult patients with Type 2 diabetes treated with daily degludec compared with glargine

Summary meta-analysis plot [random effects]

- Garber 2012: 0.75 (0.58, 0.99)
- Gough 2013: 0.64 (0.30, 1.37)
- Meneghini 2013 (D Flex): 0.77 (0.44, 1.35)
- Onishi 2013: 0.62 (0.38, 1.04)
- Pan 2016: 0.77 (0.43, 1.37)
- Zinman 2012: 0.64 (0.42, 0.98)
- combined: 0.71 (0.59, 0.85)

Key Question 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?

Type 1 Diabetes
Included studies did not report outcomes by subgroup.

Type 2 Diabetes
The BEGIN: ONCE ASIA trial compared degludec and glargine in 435 patients with Type 2 diabetes living in 6 countries in Asia (Hong Kong, Japan, Malaysia, South Korea, Taiwan, and
Thailand). The trial duration was 26 weeks, and each drug was given once daily (Table 4). A secondary publication from this trial reported results for the subset of 133 patients living in Japan and found no differences in glycemic control or nocturnal hypoglycemia between patients in Japan and the larger study population in Asia.

There was also no difference when comparing results for Japan or Asia with those for all populations included in this report, though point estimates for relative risk were lowest for Japan and highest for all populations. For other outcomes (severe hypoglycemia, withdrawals due to adverse events, severe adverse events, and mortality), there were too few events among the 133 patients in Japan to compare rates across treatment arms, and to compare these with the larger populations.

**Insulin Detemir vs. Insulin Glargine**

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

**Type 1 Diabetes**

We found 2 fair-quality open-label randomized controlled trials (N=763) comparing detemir with glargine (combined with a short-acting insulin analog at mealtimes) in adults with Type 1 diabetes mellitus for 26 and 52 weeks (Table 3). Patients had been using long or intermediate-acting insulin with varying schedules, but neither study reported the proportion who had used either detemir or glargine prior to the study. Mean baseline hemoglobin A1C was 8.85% and 8.1%. Both studies were open-label, which could affect glycemic control outcomes via dosing and titration of insulin. These studies provided low-strength evidence that there was no difference between the insulins in hemoglobin A1C at 26 or 52 weeks. The difference in endpoint hemoglobin A1C was 0.01 (-0.13 to 0.16) at 52 weeks, and 0.03 (-0.25 to 0.19) at 26 weeks. One of the studies was conducted as a non-inferiority study, where an upper limit of the 95% confidence interval for difference between hemoglobin A1C at 52 weeks of <0.4% constituted noninferiority (equivalence). This criterion was met, and the insulins were considered equivalent for this outcome at 52 weeks.

Also at 52 weeks, there was no statistical difference between groups in the percent with hemoglobin A1C ≤7.0% without major hypoglycemia (31.9% vs. 28.9%; EPC calculated RR 1.1, 95% CI, 0.80 to 1.5). In both studies, the dosing titration schedules allowed more flexibility in the detemir arms due to the FDA approved dosing schedules allowing twice daily injections for detemir, but only once daily for glargine.

In children with Type 1 diabetes, we found a single very small, fair-quality 12-week crossover trial of glargine and detemir (Table 5). The objective of this trial was to assess changes in growth hormone and insulin-like growth factor-1, but also measured hemoglobin A1C. Both groups had hemoglobin A1C’s of 7.0 at baseline. Similar to the adults studies (above) the change over 12 weeks was very small and not different between groups (difference −0.02% ± 0.4% vs. 0.1 ± 0.3%; P=0.45). This evidence was insufficient to draw conclusions due to lack of confirmatory studies, methodological limitations and imprecise estimates due to the very small sample size.
Table 5. Studies of insulin detemir compared with glargine on hemoglobin A1C in patients with type 1 diabetes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample Size</th>
<th>Baseline HbA1C</th>
<th>Disease Duration</th>
<th>Baseline Medications for Diabetes</th>
<th>Assigned Insulin Dosing and Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heller, 2009, N=443, 52 weeks</td>
<td>HbA1C: 8.1% Duration: 17.2 years</td>
<td></td>
<td>Starting Dose: equivalent to total daily dose prior to trial; if pre-trial insulin given twice daily, total daily dose was reduced 30% and given once/day. Insulin Dose Timing: once daily, evening; detemir dose could be split into twice daily based on PG results. Titration: algorithm to mean fasting PG ≤108 mg/dL with no episodes of significant hypoglycemia. Glargine doses only titrated to pre-breakfast readings. Detemir dose could also be adjusted based on pre-dinner PG by dividing dose into twice daily.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pieber, 2007, N=320, 26 weeks</td>
<td>HbA1C: 8.85% Duration: 16.5 years</td>
<td></td>
<td>Starting dose: Detemir: split according to prior insulin split; total dose reduced 30% initially. Glargine: total daily dose combined and reduced 20% to 30% initially (aspart dose adjusted during week 1 to compensate). Timing: detemir twice daily; Glargine once daily (evening). Titration: algorithm to mean PG &lt;132 mg/dL. Doses for detemir were adjusted based on pre-breakfast and pre-dinner readings; glargine only on pre-breakfast readings.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cherubini, 2016, N=15, 12 weeks (crossover)</td>
<td>Mean age: 8.6 years HbA1C: 7.0% Duration: 4.2 years</td>
<td></td>
<td>Starting Dose: Detemir and Glargine: equivalent to total daily dose prior to trial given via pen device. Timing: detemir divided into twice daily; Glargine once daily (evening). Both groups received mealtime rapid acting insulin based on carbohydrate count.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HbA1C, hemoglobin A1C; PG, plasma glucose; N, number of patients; NR, not reported.

Type 2 Diabetes

We identified a good quality Cochrane review published in 201191 that included 4 trials26,29,31,34 comparing detemir and glargine in patients with Type 2 diabetes. We also identified 4 additional trials published since the review was published.24,27,40,43 The Cochrane review rated the risk of bias of the 4 trials as high due primarily to the lack of blinding, and we rated 2 of the newer trials poor-quality for concerns with randomization, blinding, and attrition.40,43 We rated the other 2 newer trials as fair quality, although they were also open-label. The total number of patients in the fair- or good-quality trials was 2,750, with 12 to 52 weeks of treatment. Characteristics of the aforementioned studies are listed in Table 6.
Table 6. Newer studies of insulin detemir compared with glargine on hemoglobin A1C in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Study Duration</th>
<th>Baseline HbA1C</th>
<th>Disease Duration</th>
<th>Prior Treatment</th>
<th>Insulin Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swinnen, 2011</td>
<td>Systematic Review (4 RCTs)</td>
<td>N=2,250</td>
<td>24 to 52 weeks</td>
<td>HbA1C: 8.4% to 8.7%</td>
<td>Duration: 9 to 14 years</td>
<td>Prior Treatment: 2 studies enrolled insulin-naïve patients; 75% taking metformin, and most also taking an oral secretagogue. All randomized to basal insulin only. 2 studies enrolled a mix of patients with insulin experience and oral medication only, prior medications not reported. ~20% oral only, 33% insulin only, 45% both. Patients assigned to basal and meal-time insulin (= aspart).</td>
<td>Insulin Dose Timing: patients initially assigned to once daily (evening) dosing of both insulins in 3 studies, with the option to divide the dose of detemir if necessary, while the fourth study assigned all patients on detemir to twice daily injections. Titratin: insulin doses titrated to target plasma glucose levels; fasting levels for glargine and fasting, or fasting and pre-dinner levels for detemir depending on the number of injections given. Oral Diabetes Medications: A mix of regimens, ranging from not changing regimen to stopping specific drugs (i.e., thiazolidinediones, secretagogues and alpha-glucosidase inhibitors) but maintaining others (e.g., metformin).</td>
</tr>
<tr>
<td>Meneghini, 2013</td>
<td>RCT</td>
<td>N=457</td>
<td>26 weeks</td>
<td>HbA1C: 7.9%</td>
<td>Duration: 8.2 years</td>
<td>Prior Treatment: metformin monotherapy at stable dose (27%) or metformin + second oral drug at maximum tolerated dose.</td>
<td>Insulin Dose Timing: patients initially assigned to 10 IU once daily (evening) dosing of both insulins. Titratin: insulin doses titrated to target fasting plasma glucose levels; fasting levels for both insulins using the same algorithm. Oral Diabetes Medications: only metformin continued (at same dose); others discontinued.</td>
</tr>
<tr>
<td>Fadini, 2011</td>
<td>Crossover RCT</td>
<td>N = 43</td>
<td>12 weeks</td>
<td>HbA1C: 8.8%</td>
<td>Duration: NR</td>
<td>Prior Treatment: 85% taking metformin, 85% taking secretagogues.</td>
<td>Insulin Dose Timing: patients initially assigned to 10 IU once daily (evening) dosing of both insulins. Titratin: insulin doses titrated to target fasting plasma glucose levels; fasting levels for both insulins using the same algorithm. Oral Diabetes Medications: continued; secretagogue evening doses recommended to be reduced if hypoglycemic fasting plasma glucose levels noted.</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1C, hemoglobin A1C; IU, international units; PG, plasma glucose; N, number of patients; NR, not reported.

There was low-strength evidence of no statistically significant difference in glycemic control between detemir and glargine based on 1 good-quality Cochrane review (based on 4 trials, 3 of which included a non-inferiority design) and 2 newer trials. The Cochrane review found no difference in hemoglobin A1C reduction (difference 0.07%, 95% CI -0.14% to 0.24%), which was the primary outcome in 3 of the trials. They also found no statistically significant difference in the proportion of patients achieving a hemoglobin A1C of 7% or less with (RR 0.97,
95% CI 0.76 to 1.00; I²=13%) or without (RR 0.96, 95% CI 0.81 to 1.14; I²=66%) hypoglycemia. Several sensitivity and subgroup analyses were conducted, which found that individual studies with variation in study population or design contributed to the heterogeneity in the meta-analysis, but concluded that there was not a statistically significant difference between the insulins in glycemic control. They noted the weaknesses in the evidence as the open-label designs, variation in injection frequency, and some variation in injection methods (pen versus vial) across studies, as well as wide confidence intervals.

In the newer randomized controlled trials, the parallel design, non-inferiority, trial (N=457) found a difference in the reduction of hemoglobin A₁C after 26 weeks of 0.30 (95% CI 0.14 to 0.46), favoring glargine. Using this as the outcome to detect non-inferiority with an upper limit of the 95% confidence interval of 0.4%, this finding precluded a finding of noninferiority. Similarly, this study found more patients achieved a hemoglobin A₁C of 7% or less with glargine (53%) than with detemir (38%; P=0.026). However, when limiting to those without any hypoglycemic events in the last 4 weeks, the numbers were similar (38% glargine and 32% detemir) and non-significant. The second study was a smaller (N=43), crossover design trial that found no difference between insulins at 12 weeks (in the first randomized sequence) in reduction in hemoglobin A₁C from baseline (detemir -1.3% versus glargine -1.6%, P=0.391). The proportion achieving hemoglobin A₁C of 7% or less was not reported.

Updating the meta-analyses presented in the Cochrane review for patients achieving a hemoglobin A₁C of 7% or less (Figure 5), we found a relative risk of 0.91 (95% CI 0.76 to 1.1; I²=75%). The statistical heterogeneity found in the Cochrane review meta-analysis was still present, reducing our confidence in this finding. Two studies found statistically significantly more patients achieved hemoglobin A₁C of 7% or less27,29 while the other 3 studies26,31,34 found no difference (1 study did not report this outcome).24 The reasons for these differences are not entirely clear but may be due to the wide variation in concomitant antidiabetic therapies and dosing/titration schedules for detemir and glargine. Analyzing this outcome only for patients who did not experience hypoglycemia alters the findings, resulting in a significantly lower proportion achieving the goal with detemir than with glargine (RR 0.87, 95% CI 0.77 to 0.97). However, 3 of the trials counted hypoglycemia that occurred only in the last 1 to 3 months of the trial, and the other 2 included hypoglycemia occurring at any time during the trial. Removing these last 2 trials from the analysis resulted in the finding becoming non-significant again (RR 0.89, 95% CI 0.75 to 1.0). There was no heterogeneity in either of these analyses. Based on the variation in these findings, we concluded that there was low-strength evidence of no difference between the insulins in achieving hemoglobin A₁C targets. The newer trials did not report data on change from baseline in hemoglobin A₁C to allow pooling with the older data.

**Figure 5. Patients achieving hemoglobin A₁C ≤7% with insulin detemir compared with glargine**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollander, 2008</td>
<td>0.98 (0.72, 1.37)</td>
</tr>
<tr>
<td>Rosenstock, 2008</td>
<td>1.00 (0.84, 1.18)</td>
</tr>
<tr>
<td>Raskin, 2009</td>
<td>0.75 (0.60, 0.94)</td>
</tr>
<tr>
<td>Swinnen, 2010</td>
<td>1.10 (0.97, 1.25)</td>
</tr>
<tr>
<td>Meneghini, 2013</td>
<td>0.73 (0.59, 0.90)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>0.91 (0.76, 1.08)</td>
</tr>
</tbody>
</table>

**Long-Acting Insulins**

24 of 47
Key Question 2. What is the comparative tolerability and frequency of adverse events with long-acting insulins for children and adults with diabetes mellitus?

**Type 1 Diabetes**

We found 2 open-label randomized controlled trials comparing detemir with glargine in adults with Type 1 diabetes mellitus (described above, see Table 5), 1 observational study that included both Type 1 and Type 2 patients but reported outcomes separately, and 2 small observational studies of pregnant women with Type 1 diabetes who used detemir or glargine for the entire pregnancy. All of these were rated fair-quality, although there were differences between the 2 randomized controlled trials in how the insulins were dosed – both schedule (once a day versus twice a day) and how they were titrated. The trials were open-label, which could affect the subjective outcome of nocturnal hypoglycemia and withdrawals due to adverse events. In the larger observational study (N=8,494 for Type 1 glargine and detemir), mean duration of diabetes was 16 years and 15 years and mean age was 48 years and 43 years for detemir and glargine, respectively. The baseline hemoglobin A1C was similar to the trials, 8%. In the studies of pregnant women, the mean duration of diabetes was 14 years and mean age was 30 years in one, and ranged from 9 years to 12 years duration and mean age of 26 years in the other. The baseline hemoglobin A1C (at 8 weeks gestation) was lower than the other studies, 6.6% in one study, and ranged from 6.9% to 7.3% in the other study.

In children with Type 1 diabetes, we found a single very small, fair-quality 12-week crossover trial of glargine and detemir (Table 3). The objective of this trial was to assess changes in growth hormone and insulin-like growth factor-1, but also reported that there were no episodes of severe hypoglycemia and no withdrawals due to adverse events over 12 weeks with either insulin. This evidence was insufficient to draw conclusions.

**Hypoglycemia**

Based on these studies, we conclude that there was low-strength evidence of no difference between the insulins in the risk of severe hypoglycemia. This assessment is based on 1 trial and 3 observational studies that did not find statistically significant differences in frequencies of events. The second trial (N=320), however, found a significant difference favoring detemir (Table 7) when reporting the outcome as patients with ‘at least one event’. This difference in findings may be based on the way the outcome was reported or due to differences in how the insulins were dosed and titrated. In the study finding a difference, doses were reduced at study initiation (30% for detemir and 20 to 30% for glargine), and insulin aspart was used in the glargine group to compensate during week 1. The large observational study using ICD-9 codes to identify severe hypoglycemia episodes in real-world settings may provide stronger evidence for this particular outcome.

For nocturnal hypoglycemia, 1 trial reported a small difference favoring glargine with no statistical analysis, and the other finding lower risk with detemir (Table 7). Differences in reporting and insulin dosing may again have affected these results. One small fair-quality observational study of pregnant women reported no episodes of severe nocturnal hypoglycemia occurred with either detemir or glargine.
Table 7. Effects of insulin detemir compared with glargine on hypoglycemia in adult patients with type 1 diabetes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Study Duration</th>
<th>Hypoglycemia Outcomes</th>
<th>Withdrawals Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heller, 2009</td>
<td>RCT</td>
<td>N=443</td>
<td>52 weeks</td>
<td>Severe: Mean episodes/patient-year 0.5 vs. 0.4 (P=NR)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Night: Mean episodes/patient-year: 9.2 vs. 8.1 (P=NR)</td>
<td></td>
</tr>
<tr>
<td>Pieber, 2007</td>
<td>RCT</td>
<td>N=320</td>
<td>26 weeks</td>
<td>Severe: (at least 1 episode) 1.9% vs. 7.8%; RR 0.28 (95% CI, 0.08 to 0.98)</td>
<td>Lower risk with detemir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Night: (at least 1 episode) 48.7% vs. 52.6%; RR 0.68 (95% CI, 0.46 to 0.99)</td>
<td></td>
</tr>
<tr>
<td>Laubner, 2014</td>
<td>Observational</td>
<td>N=8,494</td>
<td>1 year follow-up</td>
<td>Severe: Adjusted mean frequency per year 11.93 vs. 10.86 (P=0.43)</td>
<td>No difference</td>
</tr>
<tr>
<td>Todorova, 2010</td>
<td>Observational</td>
<td>N=90</td>
<td></td>
<td>Severe nocturnal: No episodes reported for detemir or glargine groups.</td>
<td>No difference</td>
</tr>
<tr>
<td>Callesen, 2013</td>
<td>Observational</td>
<td>N=113</td>
<td>Conception to end of pregnancy</td>
<td>Severe: At least 1 episode: 23% vs. 23%</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Withdrawals Due to Adverse Events
Based on 2 fair-quality randomized controlled trials,25,28 there was low-strength evidence of no difference between the insulins in withdrawals due to adverse events, when limiting to those thought to be related to the study drug.

Type 2 Diabetes
One Cochrane review of 4 randomized controlled trials and 2 newer randomized controlled trials (described above, Table 6) reported adverse events. The trials were open-label, which could affect the subjective outcome of nocturnal hypoglycemia and withdrawals due to adverse events. We included 8 observational studies to evaluate severe hypoglycemia outcomes.74,75,78-80,86,88 Five were fair-quality, 1 was good-quality84 and 1 was poor-quality for multiple reasons including high loss to follow-up and lack of statistical control for confounding.74 The mean ages in these studies ranged from 54.9 years to 69.5 years; baseline hemoglobin A1C values were higher than the trials and ranged from 9.4% to 9.8%. The mean duration of disease was 9.3 years to 14.7 years. Additionally, we included 4 observational studies reporting on cancer outcomes in relation to the use of detemir and glargine.82,83,85,87 These were fair- and good-quality85 studies of 197,561 adults (mean ages 60 to 72 years) with Type 2 diabetes.
Cancer
We found low-strength evidence of no difference between detemir and glargine in the risk for any cancer in the short-term.

Four retrospective cohort studies (N=115,858) evaluated the association of exposure to detemir or glargine (with or without oral medications) and a diagnosis of cancer.\textsuperscript{82,83,85} Hazard or odds ratios range from 0.97 to 1.02 for glargine and 0.96 to 1.14 for detemir, and all were not statistically significant compared with no insulin exposure. The limitations of these studies include the lack of direct comparison of the insulins, and more importantly, the short duration of follow-up (1 year to 4.7 years). Given the potentially long latency period for cancer development, these studies may not have captured important effects with longer exposure and follow-up.

While we also identified observational studies that reported on the association with breast cancer and cancer deaths, this evidence was insufficient to draw conclusions due to methodological limitations (noted above), lack of corroborating studies, and lack of direct comparison of the insulins.\textsuperscript{83,87}

Hypoglycemia
For severe and nocturnal hypoglycemia, we found low-strength evidence of no difference between the insulins.

A good quality Cochrane review,\textsuperscript{91} and 2 newer randomized controlled trials\textsuperscript{24,27} (summarized above) reported severe hypoglycemia. The Cochrane review found no statistically significant difference between the insulins on this outcome. Our updated analyses are similar. The pooled relative risk for severe hypoglycemia is 0.80 (95% CI 0.51 to 1.3; \textit{I}^2=0\%). Across 6 observational studies (N=91,171), no differences were found in the incidence of severe hypoglycemia, although the studies reported the frequency in varying ways that could not be pooled.\textsuperscript{75,78-80,86,88}

For nocturnal hypoglycemia, the Cochrane review found no difference between insulins (RR 1.02, 95% CI 0.90 to 1.16) for any nocturnal event and RR 1.00 (95% CI 0.92 to 1.09) for event rate per patient-year. Only 1 new trial reported this outcome, again with no difference between the groups (RR 1.29, 95% CI 0.92 to 1.82). Adding these results to the other 4 trials results in a pooled relative risk of 0.97 (95% CI 0.86 to 1.1; \textit{I}^2=22.6\%).

Withdrawals Due to Adverse Events
The risk of withdrawing from the study due to adverse events was greater with detemir than with glargine. The pooled relative risk was 2.13 (95% CI 1.38 to 3.28; \textit{I}^2=0\%; Figure 6). As can be seen in the figure, while the result is statistically significant only in 2 trials, the finding is consistent across the trials and this evidence is moderate strength. The reasons for higher withdrawal in the detemir groups are not clear.
Figure 6. Withdrawals from study due to adverse events: insulin detemir versus glargine

Study ID          RR (95% CI)
Hollander, 2008   1.96 (0.61, 6.40)
Rosenstock, 2008  2.09 (1.06, 4.16)
Raskin, 2009      1.71 (0.52, 5.69)
Swinnen, 2010     3.09 (1.37, 7.02)
Fadini, 2011      0.35 (0.00, 3.88)
Meneghini, 2013   1.67 (0.45, 6.28)
Overall Effect    2.13 (1.38, 3.28)

Mixed Population: Type 1 and Type 2 Diabetes

Hypoglycemic coma
A single, large (N=75,682), good-quality retrospective cohort study using Finnish national databases found the risk of hospitalization for hypoglycemic coma to be significantly lower (RR 17.9%, 95% CI 3.6% to 30.1%) with detemir than with glargine in patients who were not previously treated with insulin. Detemir also resulted in lower risk of hospitalization for recurrent hypoglycemic coma and first hypoglycemic coma. Although the study was good-quality, the evidence was insufficient to draw conclusions, and needs to be corroborated.

Key Question 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?

Type 1 Diabetes
Two fair-quality trials and 1 large observational study provided no information on relevant subgroups of patients, comparing detemir with glargine in patients with Type 1 diabetes.

Two small (N = 203) fair-quality observational studies of pregnant women with Type 1 diabetes provided information on how the insulins compared in effects on various adverse events in the mother (reported above in Key Question 2), and in the neonate. In both studies, women used detemir or glargine throughout their pregnancies. Both are small studies, with methodological or reporting flaws, and they have different findings. One was conducted in 2006 to 2008 in Bulgaria and reported on 30 women using detemir and 30 using glargine, and included a third group taking NPH insulin (not reported here). This study reported matching the women based on key characteristics, but ultimately had some differences at baseline and had unclear reporting on most quality criteria. For example, the duration of diabetes was 12 years in the detemir group and 9 years in the glargine group, and the women taking glargine had a higher frequency of history of spontaneous abortions (33.3% versus 10%). This study reported a higher incidence of perinatal mortality (5 of 30 pregnancies) in the glargine group than in the detemir group (3 of 30 pregnancies). The other study was conducted from 2007 to 2011 in Denmark and reported on 110 women who were taking detemir or glargine at the time of conception through the end of pregnancy, and also had some small differences at baseline including a lower
proportion of women in the glargine group who had no previous deliveries. The Danish study reported no perinatal deaths in either group. While the reporting differed, it appears that the glycemic control was slightly better in the Danish study. This study did not conduct statistical analyses to adjust for potential confounders, or use other methods to reduce potential indication bias, such as matching, and did not adjust the analyses for multiple statistical testing.

Outcomes related to neonatal birth weight also differed between the studies. The Bulgarian study found greater mean weight for infants of women using glargine (3,623 grams) than those whose mothers used detemir (3,076 grams). In the Danish study, these findings are reversed; neonates born to women using detemir had larger babies (3,490 grams versus 3,219 grams). The Bulgarian study additionally reported that 4 neonates in the glargine group were born with macrosomia (birth weight 4,500 grams or more), but does not report the rate in the detemir group. The Danish study reported that more infants born to mothers using detemir were large for gestational age than those born to mothers who used glargine (49% versus 30%). The studies reported outcomes related to gestational age differently, but again the results point in different directions. The Bulgarian study found that the glargine group delivered infants at 37.5 weeks (mean) compared with 36.2 weeks for women using detemir, while the Danish study reported a mean of 37 weeks in both groups.

The studies also differed in the mean dose of long-acting insulin used in late pregnancy. The Bulgarian study reported higher mean dose with glargine (29.7 units) than detemir (21.4 units) while the Danish study reported that women using detemir had a larger mean dose (0.62 IU/kg detemir versus 0.44 IU/kg glargine) and greater frequency of women using 2 or more injections per day than those using glargine (91% versus 60%).

In the Danish study, other outcomes, such as neonatal hypoglycemia, initial plasma glucose, gestational age, admittance to neonatal intensive care unit, or low Apgar scores were not found different between groups. The proportion of neonates requiring continuous positive airway pressure beyond 1 hour after birth was greater with detemir, but did not reach statistical significance (26% vs. 15%, \( P=0.18 \)). The Bulgarian study found no difference rates of infants with respiratory distress between groups, but post-natal hypoglycemia occurred more frequently in the glargine group (68% versus 33%).

Given these differences in findings, concerns over methodology, and the small size of the studies, the results are not sufficient to draw conclusions, and more study is needed.

B. Within Insulin Comparisons

**Insulin Degludec U200 vs. Insulin Degludec U100**

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

**Type 2 Diabetes**

We included 1 fair-quality, open-label randomized controlled trial comparing degludec U200 and degludec U100 in adult patients with Type 2 diabetes (N=373). The trial was 22-weeks in duration. Patients were randomized to degludec 200 U once per day, plus pre-trial oral antidiabetic drugs or degludec 100 U once per day, plus pre-trial oral antidiabetic drugs. During the trial treatment period, both arms were titrated once weekly, based on the mean of the preceding 3 consecutive days’ pre-breakfast self-measured plasma glucose measurements. The
insulin dose adjustments aimed for a pre-breakfast self-measured plasma glucose value between 70 mg/dL and 90 mg/dL (3.9 mmol/L and 5.0 mmol/L).

The trial provided insufficient evidence in comparing differences in glycemic control measured by hemoglobin A1C between degludec U200 and degludec U100 (hemoglobin A1C change estimated treatment difference: -0.11, 95% CI -0.28 to 0.05).

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

**Type 2 Diabetes**

One fair-quality, open-label randomized controlled trial comparing degludec U200 and degludec U100 in adult patients with Type 2 diabetes (N=373),\(^3^9\) as described in Key Question 1 above, was included.

Hypoglycemia

There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given degludec U200 and degludec U100 (RR 1.02, 95% CI 0.06 to 16.13).\(^3^9\) Evidence was also insufficient to compare rates of nocturnal hypoglycemia (RR 0.93, 95% CI 0.67 to 1.36).

Withdrawals Due to Adverse Events

The study did not report withdrawals due to adverse events.

**F-O Glargine vs. Glargine**

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

**Type 1 Diabetes**

We included 1 fair-quality, open-label, non-inferiority, randomized-controlled trial comparing F-O glargine and glargine in adults with Type 1 diabetes (N=535).\(^3^8\) This was a 24-week, multinational trial with a 28-week extension and 4-week post treatment follow-up period. The primary efficacy outcome was to test the non-inferiority (0.4% and then 0.3% margin) of F-O glargine to glargine as measured by change in HbA1c from baseline to 24 weeks. Patients were randomized to F-O glargine or glargine and started on the same dose at the same time of day as their pre-study basal insulin and mealtime insulin lispro. Insulin dose adjustments were carried out to achieve fasting plasma glucose ≤6.0 mmol/L and pre-prandial capillary blood glucose 3.9 mmol/L to 7.2 mmol/L. Subjects in the trial were titrated until 12 weeks, allowing for additional titration after 12 weeks for safety concerns.

The trial provided low-strength evidence that glycemic control did not differ between F-O glargine and glargine adults with Type 1 diabetes. At 24 weeks, hemoglobin A1C change from baseline was -0.35 for F-O glargine vs. -0.46 for glargine (LSM difference: 0.108, 95% CI -0.002 to 0.219). At 24 weeks, the percent of participants achieving a hemoglobin A1C <7% was 35% for F-O glargine vs. 32% for glargine (RR 1.07, 95% CI 0.84 to 1.36). There were also no differences at 52 weeks: the hemoglobin A1C change from baseline was -0.26 versus -0.28 (LSM difference: 0.020, 95% CI -0.099 to 0.140) and the percent of participants achieving hemoglobin A1C <7% at 52 weeks was 30% versus 25% (RR 1.20, 95% CI 0.92-1.59).
**Type 2 Diabetes**

We included 1 fair-quality, non-inferiority, randomized controlled trial comparing F-O glargine and glargine adults with Type 2 diabetes (N=756). This was a 24-week, multinational trial with a 4-week post treatment follow-up period. The starting dose for all insulin-naïve patients was 10 U/day, while patients entering the study on glargine used a dose equivalent to their pre-study glargine dose. Doses were titrated by adding 1 unit daily until fasting plasma glucose levels reached ≤5.6 mmol/L. Patients in the trial were titrated until 12 weeks, allowing for additional titration after 12 weeks for safety concerns. The non-inferiority margin was -0.4.

The trial provided low-strength evidence that glycemic control did not differ between F-O glargine and glargine adults with Type 2 diabetes. The mean change in hemoglobin A1C at week 24 was -1.29% for F-O glargine versus -1.34% for glargine (LS mean difference: 0.052, 95% CI -0.07 to 0.18), which met the criteria for noninferiority. The proportion of patients achieving a hemoglobin A1C <7% was 49% with F-O glargine and 53% for glargine (P>0.05). In patients who were insulin naïve and those who were glargine-experienced, these findings were consistent.

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

**Type 1 Diabetes**

One fair-quality, open-label, randomized controlled trial comparing F-O glargine and glargine adults with Type 1 diabetes (N=535), as described in Key Question 1 above, was included.

**Hypoglycemia**

There were few episodes of severe hypoglycemia, and evidence was insufficient to draw conclusions about rates in adult patients with Type 1 diabetes given F-O glargine and glargine (24 weeks: 0.06 ± 0.52 events/person/year for F-O glargine vs. 0.09 ± 0.50 events/person/year for glargine; 52 weeks: 0.07 ± 0.46 events/person/year for F-O glargine vs. 0.08 ± 0.46 events/person/year for glargine). Evidence was also insufficient to draw conclusions about rates of nocturnal hypoglycemia (24 weeks: 18.3 ± 23.6 events/person/year for F-O glargine vs. 18.4 ± 21.5 events/person/year for glargine; 52 weeks: 16.1 ± 20.2 events/person/year for F-O glargine vs. 17.3 ± 19.5 events/person/year for glargine).38

**Withdrawals Due to Adverse Events**

Few patients withdrew due to adverse events, and evidence was insufficient to draw conclusions about withdrawals due to adverse events in participants given F-O glargine and glargine. Withdrawals due to adverse events was not reported at 24 weeks, and at 52 weeks, the percentages were 1% for F-O glargine versus 2% for glargine (RR 0.33, 95% CI 0.08 to 1.42).38

**Type 2 Diabetes**

One fair-quality, non-inferiority, randomized-controlled trial comparing F-O glargine and glargine adults with Type 2 Diabetes (N=756), as described in Key Question 1 above, was included.

**Hypoglycemia**

There were few episodes of severe hypoglycemia, and evidence was insufficient to draw conclusions about rates in adult patients with Type 2 diabetes given F-O glargine and glargine
(mean events/patient/1 year: 0.04 ± 0.66 for F-O glargine vs. 0.01 ± 0.16 for glargine; incidence <1% vs. <1%). Evidence was also insufficient to draw conclusions about rates of nocturnal hypoglycemia (mean events/patient/year: 7.6 ± 11.8 for F-O glargine vs. 8.1 ± 14.6 for glargine; incidence: 57% vs. 54%; P=0.462).57

Withdrawals Due to Adverse Events
Few patients withdrew due to adverse events, and evidence was insufficient to draw conclusions about withdrawals due to adverse events in participants given F-O glargine and glargine (RR 0.55, 95% CI 0.21 to 1.48).57

Insulin Glargine U300 vs. Insulin Glargine U100
Key Question 1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with diabetes mellitus?

Type 1 Diabetes
We included 4 fair-quality trials32,33,36,48,49,52 that compared glargine U300 to glargine U100 in patients with Type 1 diabetes. Two were small trials, with 20 to 59 patients,32,36,49 while the EDITION JP 152 and EDITION 448 trials were larger, enrolling 243 patients and 549 patients, respectively. All 4 trials included adults only. The EDITION 4, EDITION JP 1, and NCT01676233 trials used modified TactiPen® and SoloSTAR® pen injectors for the administration of insulin. The NCT01658579 trial used commercially available insulin syringes because an insulin pen that could deliver the small volumes of glargine U300 required for this study was not available when the study was being conducted.36 Table 8 shows additional trial characteristics.

Table 8. Insulin glargine U300 versus U100 in adults with Type 1 diabetes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample Size</th>
<th>Study Duration</th>
<th>Baseline HbA1c</th>
<th>Disease Duration</th>
<th>Treatment History</th>
<th>Insulin Dosing</th>
<th>Additional Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergenstal, 201736</td>
<td>N=59</td>
<td>16 weeks</td>
<td>7.5%</td>
<td>22 years</td>
<td>Insulin-experienced</td>
<td>Starting dose: 0.30 to 0.31 units/kg/day</td>
<td>Mealtime insulin analogues used prior to screening were continued</td>
</tr>
<tr>
<td>Sanofi, 201532</td>
<td>N=59</td>
<td>16 weeks</td>
<td>8.1%</td>
<td>21 years</td>
<td>Insulin-experienced</td>
<td>Starting dose: 0.37 to 0.38 units/kg/day</td>
<td>Mealtime insulin</td>
</tr>
<tr>
<td>NCT01658579</td>
<td>N=20</td>
<td>8.4 weeks</td>
<td>8.2%</td>
<td>NR</td>
<td>Insulin-experienced</td>
<td>Starting dose: 0.21 to 0.23 units/kg/day</td>
<td>Mealtime insulin</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Trial Name</td>
<td>Sample Size</td>
<td>Study Duration</td>
<td>Baseline HbA1C</td>
<td>Disease Duration</td>
<td>Treatment History</td>
<td>Insulin Dosing</td>
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<tr>
<td>Matsushisa, 2016</td>
<td>EDITION JP 1</td>
<td>N=243</td>
<td>6 months</td>
<td>8.1%</td>
<td>Insulin-experienced</td>
<td>Starting dose: 0.28 to 0.30 units/kg/day</td>
<td>Timing: once daily, evening</td>
</tr>
</tbody>
</table>

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin, type A1c; N, number of patients; NR, not reported; U100, glargine 100 units/mL; U300, glargine 300 units/mL

Two studies reported the proportion of patients reaching the hemoglobin A1C goal of less than 7.0% at 6 months, which allowed for pooling of results. These studies provided low-strength evidence that the proportion of patients reaching the target HbA1C <7.0% was similar between patients receiving glargine U300 and patients receiving glargine U100 (pooled RR 1.0, 95% CI 0.73 to 1.37).

Four trials reported glycemic control measured as the difference in the change in percent hemoglobin A1C from baseline to 8.4 weeks, 16 weeks or 6 months. These studies were consistent in their findings that both glargine concentrations yielded small improvements in glycemic control over the study period (HbA1C least squares mean difference, range -0.44% to -0.28% for U300 and -0.44% to -0.22% for U100). We were able to pool findings from these 4 studies, which provided low-strength evidence that glycemic control was similar between glargine U300 and glargine U100 (weighted mean difference: 0.02%, 95% CI -0.10% to 0.15%; I²=25.6%).

**Type 2 Diabetes**

Four fair-quality trials comparing glargine U300 to glargine U100 in adult patients with Type 2 diabetes met inclusion criteria; all were in the EDITION series of trials: EDITION 1, EDITION 2, EDITION 3, and EDITION JP 2. The EDITION 1, 2, and 3 trials included about 800 patients treated for 6 months in the main trial period, and also included a 6-month treatment extension period. The EDITION JP 2 trial was smaller, including only 241 Japanese participants. Baseline glycemic control was similar across the 4 trials, and all 4 used pen devices to administer either insulin concentration once daily, with a titration target of 80 to 100 mg/dL (Table 9). Other patient characteristics and additional therapies differed across trials. EDITION 3 included only insulin-naïve patients, while the other 3 trials included insulin-experienced patients. EDITION 1 patients received mealtime insulin with or without metformin, while EDITION 2 and 3 and EDITION JP 2 patients received only oral antidiabetic agents.
### Table 9. Insulin glargine U300 compared with glargine U100 in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Trial Name</th>
<th>Sample Size</th>
<th>Baseline HbA1c</th>
<th>Disease Duration</th>
<th>Treatment</th>
<th>Insulin Dosing</th>
<th>Additional Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riddle, 2014</td>
<td>EDITION 1</td>
<td>N=804</td>
<td>8.2%</td>
<td>16 years</td>
<td>Insulin-experienced</td>
<td>Starting dose: baseline basal insulin dose for patients on glargine or once-daily NPH; dose reduced by ~20% for those taking NPH &gt; once daily</td>
<td>Timing: once daily, evening</td>
</tr>
<tr>
<td>Riddle, 2015</td>
<td>EDITION 2</td>
<td>N=811</td>
<td>8.2%</td>
<td>13 years</td>
<td>Insulin-experienced</td>
<td>Starting dose: baseline basal insulin dose for patients on glargine or once-daily NPH; dose reduced by ~20% for those taking NPH &gt; once daily</td>
<td>Timing: once-daily, evening</td>
</tr>
<tr>
<td>Yki-Jarvinen</td>
<td>EDITION 3</td>
<td>N=862</td>
<td>8.5%</td>
<td>9.8 years</td>
<td>Insulin-naive</td>
<td>Starting dose: 0.2 U/kg body weight</td>
<td>Timing: once daily, evening</td>
</tr>
<tr>
<td>Bolli, 2015</td>
<td>EDITION JP2</td>
<td>N=241</td>
<td>8.0%</td>
<td>14 years</td>
<td>Insulin-experienced</td>
<td>Starting dose: baseline basal insulin dose for patients on glargine (once or twice daily), detemir (once daily), or NPH (once daily), or 80% of NPH at baseline for those previously receiving twice daily NPH</td>
<td>Timing: once daily, evening</td>
</tr>
</tbody>
</table>

**Abbreviations:** FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin, type A1c; mo, month; N, number of patients; NPH, Neutral Protamine Hagedorn insulin; U100, glargine 100 units/mL; U300, glargine 300 units/mL.

Despite these differences, the relative effects of glargine U300 and glargine U100 on benefits and harms were similar across the 4 trials, allowing their results to be pooled. An unpublished manuscript included in a dossier submission used individual patient data to pool results from the 3 EDITION trials; however, this manuscript generally did not report the outcomes of interest in this review, or measures of statistical significance. Therefore we conducted study-level meta-analyses instead and report their results here.

The 4 trials provided moderate-strength of evidence that glycemic control measured by hemoglobin A1c did not differ between glargine U300 and glargine U100. After 6 months of treatment, the proportion of patients with hemoglobin A1c less than 7.0% was 35% for both glargine U300 glargine U100 (pooled RR 1.0, 95% CI 0.92 to 1.1, I^2=0%). Rates differed
between trials; the lowest proportions of patients reached target in EDITION 2 (25.6% for U300 and 23.0% for U100) and EDITION JP 2 (25.0% for U300 and 24.2% for U100), in which insulin-experienced patients were given oral agents but not mealtime insulin in addition to glargine. The highest response rate was in EDITION 3 (43.1% for U300 and 42.1% for U100), in which insulin-naïve patients were given glargine in addition to oral agents taken at baseline.

These 4 trials also reported glycemic control measured as the difference in change in the percent hemoglobin A1C from baseline to 6 months. Both glargine concentrations improved glycemic control over the study period (HbA1C least squares mean difference, range -1.42% to -0.45% for U300 and -1.46% to -0.55% for U100). We were able to pool findings from these 4 studies, which provided moderate-strength evidence that glycemic control was similar between glargine U300 and glargine U100 (weighted mean difference: 0.04%, 95% CI -0.05% to 0.12%, I²=0).

EDITION 1 and EDITION 2 have completed 6-month extension periods in which patients continued to be treated as initially randomized. Attrition over 12 months was 12% in EDITION 1 and 22% in EDITION 2, and was non-differential between insulin concentrations. In EDITION 1, glycemic control improved more for glargine U300 than for glargine U100; the difference between glargine U300 and glargine U100 in mean change in hemoglobin A1C from baseline to 12 months was –0.17% (95% CI –0.30% to –0.05%). This differs from the finding in the initial 6 months of the study, where mean hemoglobin A1C decreased similarly in the two treatment groups (difference in mean change in hemoglobin A1C from baseline to 6 months = –0.00%, 95% CI –0.11 to 0.11). In EDITION 2, glargine concentration did not affect glycemic control, with a difference in mean change in hemoglobin A1C of -0.06% (95% CI -0.22% to 0.10%). This finding was seen in both the initial 6-month trial period and the 6-month extension period.

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

**Type 1 Diabetes**

4 fair-quality trials comparing glargine U300 to glargine U100 in patients with Type 1 diabetes met inclusion criteria; a detailed description of these trials is included in Key Question 1 (Table 8). The 6-month EDITION 4 trial enrolled 549 patients, the 6-month EDITION JP 1 trial enrolled 243 patients, the 16-week trial included 59 patients, and the 8.4-week trial included 20 patients.

These 4 trials provided low-strength evidence that the rates of severe hypoglycemia were similar between glargine U300 and glargine U100 (pooled RR 0.77, 95% CI 0.56 to 1.05; I²=23.5%).

Three trials provided moderate-strength evidence that the rates of nocturnal hypoglycemia were similar between patients taking glargine U300 and glargine U100 (pooled RR 0.91, 95% CI 0.80 to 1.05; I²=39.1%). The fourth trial reported ratios of annualized rates of nocturnal hypoglycemia categorized by degree of hypoglycemia. This study reported that the annualized rate of “confirmed” nocturnal hypoglycemia (≤70 mg/dL) was similar between those taking glargine U300 and those taking glargine U100 (RR 0.62, 95% CI 0.35 to 1.11). However, this study found that the annualized rate of severe nocturnal hypoglycemia (<54 mg/dL) was lower in those treated with glargine U300 than those treated with glargine U100 (RR 0.45, 95% CI 0.24 to 0.82).
Withdrawals due to adverse events were uncommon. Four trials\(^\text{36,48,49,52}\) provided low-strength evidence that the rate of withdrawals due to adverse events was similar between glargine U300-treated patients and glargine U100-treated patients (pooled RR 1.13, 95% CI 0.35 to 3.66; \(I^2=0\%\)).

**Type 2 Diabetes**

The 4 fair-quality EDITION trials described in Key Question 1 (EDITION 1, 2, 3, and EDITION JP 2; Table 9) compared glargine U300 with glargine U100 in about 2,700 patients treated for 6 months. Three trials provided moderate-strength of evidence that rates of nocturnal hypoglycemia were lower with glargine U300 than with glargine U100 in patients with Type 2 diabetes (37% vs. 50%; pooled RR 0.74; 95% CI, 0.66 to 0.82; \(I^2=0\%\)). Other adverse events occurred less frequently, and rates did not differ between glargine concentrations. Low-strength evidence did not find differences between glargine U300 and glargine U100 in severe hypoglycemia based on 4 trials (2.3% vs. 2.6%; pooled RR 0.88, 95% CI 0.55 to 1.4; \(I^2=0\%\)), or withdrawals due to adverse events (1.5% vs. 1.3%; pooled RR 1.2; 95% CI, 0.60 to 2.2; \(I^2=0\%\)).

The 6-month treatment extension periods in EDITION 1 and EDITION 2\(^\text{64-66}\) showed no differences from baseline to 12 months between glargine U300 and glargine U100 in severe hypoglycemia (2 trials; EPC pooled RR 0.94, 95% CI, 0.60 to 1.5; \(I^2=0\%)^\text{64,65}\) or withdrawals due to adverse effects (1 trial; EPC calculated RR 0.75, 95% CI, 0.36 to 1.5).\(^\text{65}\) There was also no statistically significant difference in nocturnal hypoglycemia over 12 months in the EDITION 2 trial\(^\text{64,66}\) though this estimate was closer to statistical significance (RR 0.86; 95% CI, 0.73 to 1.01).

**Insulin Glargine U100 Pen vs. Insulin Glargine U100 Vial**

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

**Type 1 or Type 2 Diabetes**

One RCT comparing glargine delivered via pen versus vial in indigent or Medicaid patients with Type 1 or Type 2 diabetes met inclusion criteria for this review.\(^\text{58}\) However, this trial was rated poor-quality due to a lack of reporting of specific randomization technique and allocation concealment, the open-label nature of the study, and the level of attrition of patients. Therefore, this study was not analyzed further.

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

**Type 1 Diabetes**

No studies comparing glargine delivered via pen versus vial in patients with Type 1 diabetes met inclusion criteria.

**Type 2 Diabetes**

We included a meta-analysis that pooled results from 6 observational studies comparing glargine administered by pen versus vial and syringe in patients with Type 2 diabetes, and 1 additional study not included in the meta-analysis.\(^\text{76,77,90}\) Although standard quality assessment tools are not available for individual patient data (IPD) meta-analyses that are not based on a systematic
review, we note that it described methods for included studies similar to those of other fair-quality studies, and analyzed patient-level data, eliminating duplicate patient records and using multivariate analysis to further adjust for confounding factors.

The aforementioned studies used data from U.S. health plan administrative claims databases, and identified a total of 24,564 patients with Type 2 diabetes initiating treatment with glargine using either a pen or a vial and syringe. Each study used the same 4 ICD-9 codes to identify episodes of hypoglycemia; 3 of the codes specified hypoglycemia, though the fourth was less specific (250.8, diabetes with other specified manifestations). Because events defined by ICD-9 code each involved a healthcare encounter, we considered all episodes to be severe (i.e., requiring assistance from another individual).

These studies provided low-strength evidence that rates of severe hypoglycemia were lower with glargine administered in a pen than with glargine administered using a vial and syringe. Over 1 year of follow-up, the adjusted odds ratio across 6 studies in the IPD analysis was 0.74 (95% CI 0.66 to 0.83). The difference was not statistically significant in a single study in 1,466 patients published separately, but the risk estimate was consistent with results of the IPD analysis (0.74, 95% CI 0.46 to 1.18). The pooled analysis also provided low-strength evidence of fewer episodes of severe hypoglycemia per patient in patients using pens than in those using vial and syringe to administer glargine (0.14 vs. 0.22 episodes per patient-year, adjusted \( P<0.0001 \)).

**Type 1 or Type 2 Diabetes**

As noted above, we found 1 trial in patients with either Type 1 or Type 2 diabetes comparing glargine delivered via pen versus vial that was poor quality.58

**C. Fixed-dose Combination Products**

**Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Degludec**

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

**Type 2 Diabetes**

We included 1 fair-quality, open label, treat-to-target trial comparing FDCP degludec/aspart versus degludec in adult patients with Type 2 diabetes (N=274).56 This was a 26-week, multinational trial conducted at 48 sites in five countries. Patients were randomized 1:1 to receive FDCP degludec/aspart 100 U/mL subcutaneous injection twice daily or degludec 100 U/ml 2 to 4 times/day. Both groups also received insulin aspart (prandial) 100 U/mL subcutaneous injection. Insulin dose was titrated weekly to a self-monitored pre-breakfast/pre-evening meal plasma glucose target of 71 mg/dL to 90 mg/dL (4 mmol/L to 5 mmol/L).

The trial provided insufficient evidence in comparing differences in glycemic control measured by hemoglobin A1C between FDCP degludec/aspart, and degludec. Percent change in hemoglobin A1C levels from baseline to week 26 was -1.31% for FDCP degludec/aspart compared with -1.50% for degludec (estimated treatment difference: 0.18%, 95% CI -0.04 to 0.41). The percent of patients achieving HbA1C <7.0% at 26 weeks was 56.5% for FDCP degludec/aspart compared with 59.6% for degludec (OR 0.83, 95% CI 0.50 to 1.38).
Key Question 2. What is the comparative frequency of adverse events with long-acting insulins for children and adults with diabetes mellitus?

**Type 2 Diabetes**

One fair-quality, open label, treat-to-target trial comparing FDCP degludec/aspart vs. degludec in adult patients with Type 2 diabetes (N=274),\(^{56}\) as described in Key Question 1 above, was included.

**Hypoglycemia**

There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given FDCP degludec/aspart and degludec (0.47 events/patient-years of exposure for FDCP degludec/aspart vs. 0.24 events/patient-years of exposure for degludec).\(^{56}\) Evidence was also insufficient to compare rates of nocturnal hypoglycemia (Rate ratio 0.80, 95% CI 0.50 to 1.29).

**Withdrawals Due to Adverse Events**

Few patients withdrew due to adverse events, and evidence was insufficient to compare withdrawals due to adverse events in patient given FDCP degludec/aspart and degludec (RR 0.12, 95% CI 0.01-1.28).\(^{56}\)

**Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Detemir**

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

**Type 1 Diabetes**

We included 1 fair-quality, randomized controlled trial comparing FDCP degludec/aspart and detemir in adult patients with Type 1 diabetes (N=548).\(^{47}\) This was a 26-week, multinational trial. Degludec/aspart FDCP 100 U/mL was given once per day with aspart given at the remaining meals. Patients in the detemir arm administered detemir once per day with aspart at mealtimes. In both treatment arms, doses were adjusted to a pre-breakfast target of 4 mmol/L to 5 mmol/L.

The trial provided low-strength evidence that glycemic control did not differ between FDCP degludec/aspart and detemir in adult patients with Type 1 diabetes. Mean hemoglobin A\(_1C\) reduction was -0.75% for FDCP degludec/aspart compared with -0.70% for detemir (estimated treatment difference: -0.05, 95% CI -0.18 to 0.08). The proportion of participants achieving hemoglobin A\(_1C\) <7% was 24.6% for FDCP degludec/aspart compared with 20.3% for detemir (RR 1.21, 95% CI 0.86 to 1.70).

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

**Type 1 Diabetes**

One fair-quality randomized controlled trial comparing FDCP degludec/aspart with detemir in adult patients with Type 1 diabetes (N=548),\(^{47}\) as described in Key Question 1 above, was included.
Hypoglycemia
There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given FDCP degludec/aspart and detemir (RR 1.19, 95% CI 0.58 to 2.41). Evidence was also insufficient to compare rates of nocturnal hypoglycemia. There were 3.71 compared with 5.72 episodes/person/year in patients receiving FDCP degludec/aspart and detemir, respectively (RR 0.63, 95% CI 0.49 to 0.81).

Withdrawals Due to Adverse Events
Few patients withdrew due to adverse events, and evidence was insufficient to compare withdrawals due to adverse events in patient given FDCP degludec/aspart and detemir (RR 0.66, 95% CI 0.17 to 2.63).

Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Glargine

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

Type 2 Diabetes
We included 1 fair-quality, open-label, parallel-group, treat-to-target trial comparing FDCP degludec/aspart vs. glargine in adult patients with Type 2 diabetes (N=530). This was a 26-week, multi-national trial conducted in 8 countries. Participants completed the 26 week core trial, and then entered a 26-week extension phase. FDCP degludec/aspart was administered via a pen injection once per day with breakfast. Glargine U100 was administered once per day at the same time every day. Both arms received metformin, but any previous treatments were discontinued at randomization. Dose adjustments of basal insulin were based on the participant’s before-breakfast value, and a titration algorithm provided in the study was used.

The trial provided low-strength evidence that glycemic control did not differ between FDCP degludec/aspart and glargine in adult patients with Type 2 diabetes. Mean hemoglobin A1C change from baseline at week 26 was -1.65% for FDCP degludec/aspart compared with -1.72% for glargine U100 (estimated treatment difference: 0.03%, 95% CI -0.14 to 0.20). At week 52, the estimated treatment difference was -0.08% (95% CI -0.26 to 0.09). The percent of patients achieving <7.0% hemoglobin A1C at week 26 was 45.9% for FDCP degludec/aspart compared with 45.6% for glargine (OR 0.95, 95% CI 0.66 to 1.35). The difference at week 52 was 33.1% for FDCP degludec/aspart compared with 29.7% for glargine (OR 1.13, 95% CI 0.77 to 1.66).

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

Type 2 Diabetes
One fair-quality, open-label, parallel-group, treat-to-target trial comparing FDCP degludec/aspart compared with glargine in adult patients with Type 2 diabetes (N=530), as described in Key Question 1 above, was included.

Hypoglycemia
There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given FDCP degludec/aspart and glargine (0.8% for degludec/insulin aspart vs. 0.8%
for glargine U100; 0.01 events/patient-year of exposure for both). Evidence was also insufficient to compare rates of nocturnal hypoglycemia, although treatment ratio favored degludec/insulin aspart (RR 0.25, 95% CI 0.14 to 0.47; \(P<0.000\)).

**Withdrawals Due to Adverse Events**

Few patients withdrew due to adverse events, and evidence was insufficient to compare withdrawals due to adverse events in patients given FDCP degludec/aspart and glargine (RR 1.65, 95% CI 0.44 to 6.22).50

**APPLICABILITY OF THE EVIDENCE**

The evidence in this report is applicable primarily to adults, with approximately two-thirds of the evidence applicable to patients with Type 2 diabetes. The mean age across the trials was 59 years for patients with Type 2 diabetes and 44 years for those with Type 1 diabetes, with mean durations of diabetes of 11 years and 19 years, respectively. In both groups the mean baseline hemoglobin A1C was 8.5%. The trials generally excluded patients with diabetes complications (e.g., retinopathy, neuropathy).

**LIMITATIONS OF THE EVIDENCE**

As with other types of research, the limitations of this systematic review are important to recognize. Methodological limitations of the review within the defined scope included the exclusion of studies comparing one of the analog long-acting insulins to neutral protamine Hagedorn (NPH) insulin and studies published in languages other than English, and not being able to search additional electronic databases. While the search of the US Food and Drug Administration documents and request for information from the manufacturers of the drugs is an important step in searching for unpublished studies and supplemental data, another possible limitation is the lack of a specific search for gray literature.

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. For many outcomes the cumulative sample sizes were inadequate to determine differences. The observational studies limitations included the frequent lack of clearly valid outcome measures and methods of ascertainment, as well as some studies not controlling for potential confounding (e.g., indication and new user biases). 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.
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