Long-Acting Insulins for Type 1 and Type 2 Diabetes

Update 2 Final Report

July 2018

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.

Authors:
Marian McDonagh, PharmD
Rebecca Holmes, MD, MS
Frances Hsu, MS
Melissa Fulton, BS
Chandler Weeks, BS

Suggested Citation:
McDonagh M, Holmes, R, Hsu F, Fulton M, Weeks C. Long-acting Insulins. Update 2 Final Report, prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University, Portland, Oregon, July 2018.

Conflict of Interest Disclosures:
No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Table of Contents

Overview 4
Key Findings 4
Background 5
Key Questions 6
Inclusion Criteria 6
Review Procedures 7
Findings 8
Insulin Degludec Comparisons 8
Insulin Degludec vs. Insulin Detemir 8
Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Detemir 9
Insulin Degludec vs. Insulin Glargine 11
Insulin Degludec U200 vs. Insulin Degludec U100 15
Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Glargine 16
Fixed-dose Combination Product (FDCP) Degludec/Aspart compared with Degludec 17
Insulin Detemir Comparisons 17
Insulin Detemir vs. Insulin Glargine 17
Insulin Glargine Comparisons 23
Follow-on Glargine vs. Glargine 23
Insulin Glargine U300 vs. Insulin Glargine U100 24
Insulin Glargine U100 Pen vs. Insulin Glargine U100 Vial 27
Summary 28
References 29

Overview

Overall 71 studies were included, with 12 added in Update 2 (mostly fair quality, funded by pharmaceutical manufacturers and open-label). Significant differences are limited to risk for hypoglycemia: degludec < glargine, glargine U300 < U100, glargine via pen < vial and syringe.

Key Findings

Insulin Degludec Comparisons

Versus Insulin Detemir

- Type 1 DM: No significant difference in glycemic control (2 RCTs, SOE: low). Evidence from a 52-week extension trial in adults did not change these findings.

Versus Insulin Glargine

- *Type 1 DM:* No significant difference in glycemic control at 16 to 52 weeks (4 RCTs, SOE: Moderate). Incidence of nocturnal hypoglycemia was **significantly lower** with degludec than with glargine (4 RCTs, pooled rate ratio 0.68, 95% CI 0.56 to 0.81; SOE: Moderate).
- *Type 2 DM:* No significant differences in glycemic control (9 RCTs, SOE: High), or adverse event withdrawals (9 RCTs, SOE: Low, 16 weeks - 2 years) Hypoglycemia **significantly less** with degludec (nocturnal: 9 RCTs, pooled rate ratio 0.71, 95% CI 0.63 to 0.79 and severe: 9 RCTs, 3.3% vs. 5.1% of patients, RR 0.72, 95% CI 0.54 to 0.96; SOE: Moderate). No significant difference in cardiovascular events (4 RCTs), deaths (8 RCTs), and cancer (6 RCTs).

Insulin Detemir Comparisons

Versus Insulin Glargine

- *Type 1 DM:* No significant differences in glycemic control, severe hypoglycemic events or withdrawal due to adverse events at 26 or 52 weeks (2 RCTs, SOE: Low).
- *Type 2 DM:* No significant differences in glycemic control (6 RCTs, 12 - 52 weeks), severe or nocturnal hypoglycemia (6 RCTs, 6 cohort studies; SOE: Low). Adverse event withdrawals **significantly greater** with detemir (6 RCTs, pooled RR 2.1; 95% CI, 1.4 to 3.3; SOE: Moderate). Evidence does not support a difference in risk of any cancer (4 studies) or breast cancer (3 studies; SOE: Low).

Insulin Glargine Comparisons

Follow-On Glargine vs. Glargine

- Type 1 and 2 DM: No significant difference in glycemic control (1 RCT each, SOE: Low).

Insulin Glargine U300 vs. Insulin Glargine U100

- *Type 1 DM:* No significant differences in glycemic control, severe hypoglycemia, adverse event withdrawals (4 RCTs, N=871, 2, 6 and 12 months; SOE: Low) or nocturnal hypoglycemia (2- 12 months, SOE: Moderate)
- *Type 2 DM:* No significant differences in glycemic control, severe hypoglycemia or adverse event withdrawals. (4 RCTs, 6-12 months; SOE: Moderate, Low) Nocturnal hypoglycemia **significantly less frequent** with U300 (3 RCTs, pooled RR 0.74, 95% CI 0.66 to 0.82) at 2 to 6 months, not different at 12 months (SOE: Moderate).

Insulin Glargine U100 Pen vs. Insulin Glargine U100 Vial

Type 2 DM: Severe hypoglycemia **significantly less frequent** with pen than vial /syringe (pooled RR 0.72; 95% CI, 0.65 to 0.79, 7 cohort studies; SOE: Moderate)

Background

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] 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]

Endogenous insulin is secreted at a relatively constant basal rate over 24 hours, with increased secretion after meals.[2] 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, and have a flat pharmacokinetic profile without a peak that could cause hypoglycemia.[2] Insulin glargine at doses of 0.4 units/kg to 0.5 units/kg has a duration of action of about 20 to 24 hours without a peak, and is approved for use once daily.[1] 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] Insulin degludec has a longer duration of action, > 42 hours, with a flat pharmacodynamic profile at doses from 0.4 to 0.8 units/kg. It is approved for use once daily.[3]

With persistent hyperglycemia, glucose attaches irreversibly to proteins including hemoglobin, at a rate dependent on plasma glucose concentration. Glycated hemoglobin, or HbA_{1c}, 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.[4] Based on the results of landmark studies, the American Diabetes Association's 2015 Standards of Medical Care in Diabetes suggests that "a reasonable HbA_{1c} goal for many nonpregnant adults is <7%," for both Type 1 and Type 2 patients.[5]

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.[5] 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 insulins, which could in theory affect mitogenic activity and cancer risk.[1]

Key Questions

- What is the comparative efficacy, effectiveness and harms of long-acting insulins for children and adults with diabetes mellitus?
    - Are there differences in efficacy or effectiveness when a given insulin is administered via vial & syringe or using a pen device?
    - Are there differences in efficacy or effectiveness between a given originator insulin and any follow-on insulins?
- Are there subgroups of patients based on demographics (age – older versus younger adults, racial groups, gender), comorbidities (drug-disease interactions [e.g., obesity, renal dysfunction]), or other medications (drug-drug interactions) for which long-acting insulins differ in efficacy/effectiveness or frequency of adverse events?

Inclusion Criteria

Populations:

- Adults or children with Type 1 or Type 2 diabetes mellitus.

Interventions:

Table 1. Included interventions in Update 2 Report

Drug	Trade name,	Form	Frequency	Approved
Follow-on insulin glargine	Semglee™	Vial or pen	Once daily[C]	Submitted to FDA September 2017[a]
Follow-on insulin glargine	Lusduna Nexvue	Pen	Once daily[C]	7/19/2017 (tentative)[b]
Follow-on insulin glargine (U100)	Basaglar®	Pen	Once daily	12/16/2015
Insulin degludec (U100, U200)	Tresiba®	Pen	Once daily	9/25/2015
Insulin degludec/insulin aspart	Ryzodeg® 70/30	Pen	Once or twice daily	9/25/2015
Insulin glargine U300	Toujeo®	Pen	Once daily	2/25/2015
Insulin detemir	Levemir®	Vial or pen	Once or twice daily	10/19/2005
Insulin glargine U100	Lantus®	Vial or pen	Once daily	4/20/2000

[a]Lantus® patent owner (Sanofi) initiated a patent infringement suit in October 2017.
[b]Lantus® patent owner (Sanofi) has initiated a patent infringement suit lawsuit (September 2016).
[c]Presumed frequency, FDA approved label not currently available.

In Update 2, we excluded any trials or trial arms of 3 times weekly degludec; the FDA has approved daily degludec dosing instead.

Comparators:

- An included long-acting insulin vs. another included long-acting insulin (including Fixed-Dose Combination Products).

- Long-acting insulin in one formulation/device vs. same drug in another formulation/device (e.g. vial/syringe versus pen).

Outcomes:

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

Setting:

- Outpatient.

***Study** Designs:*

- RCTs of at least 8 weeks' duration with head-to-head comparisons of included drugs.
- For harms, comparative observational studies (N≥1,000).
- Systematic reviews (with search dates ending after last DERP report search dates)
    - *Excluded: Placebo-controlled trials, pooled analyses combining selected studies without systematically identifying, assessing and combining all relevant studies.*

Review Procedures

We followed systematic review methodology and procedures developed specifically for DERP[6] and that are in accordance with current guidance, for example, using dual review for study inclusion, quality assessments and data abstraction.[7] See Appendix A for further details.

Literature Search. Literature searches, including Medline and the Cochrane Library databases, were conducted thru February 2018.

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. When conducting meta-analyses, we use data points (such as event rates), and not estimates of effect that were reported in the study publication (such as relative risks and confidence intervals). As a result, the estimates produced by meta-analysis software may differ slightly to those presented in the published paper. Specific methods used can be found in our DERP Methods Manual.[6] The I^2 statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity in effects between studies.[8,9] For cross-over trials, we consider data from the first assigned sequence (only) when results are reported by sequence. This avoids risk of carryover effects bias.

Findings

Based on screening 2,534 records, this report cumulatively includes 71 studies (in 90 publications): 49 head-to-head trials[10-58] (in 68 publications) [10-77]19 observational studies[78-96], 2 pooled analyses,[97,98] and 1 systematic review.[99] These include 9 new head-to head trials[10,11,31-34,53-55] (in 19 publications) [10,11,31-34,53-55,60,62,64,66-71,75] and 3 new observational studies[79,91,95] included as part of Update 2. Across the original report, Update 1 and Update 2, we have received dossiers from 3 pharmaceutical manufacturers regarding 6 products: Eli Lilly (Basaglar®), Novo Nordisk (Levemir®, Tresiba®, and Ryzodeg®), and Sanofi (Lantus®; Toujeo®).

In total, observational studies included 428,693 patients and randomized control trials included 29,702 patients. The majority of the studies were fair quality, 74%, with good quality and poor quality studies representing 13% each. Sample sizes ranged from 15 to 7,637 and RCT study durations ranged from 16 weeks to 2 years. Table 2 shows the cumulative and new evidence for Update 2 according to insulins compared. Appendix D shows the flow of studies through the selection process, and Appendix E lists the included study citations. A list of studies excluded after full-text review and reasons for exclusion is provided in Appendix F. Please see Appendix G for strength of evidence tables. We found very little comparative evidence of the efficacy/effectiveness or harms of long-acting insulins in children with diabetes.

Table 2. Overview of Cumulative and New RCT and Observational Study Evidence

	Degludec	Detemir	Glargine	FDCP – Degludec/Asp	F-O Glargine	Degludec U200	Glargine U300	Glargine Vial
Degludec		2 (0)	16 (6)	1(0)				
Detemir			29 (4)	2 (1)				
Glargine				2 (1)	2 (0)			
Degludec U100						1 (0)		
Glargine U100							10 (0)	
Glargine Pen								3 (0)

Drug comparison with new evidence in green, numbers in ( ) = new studies. Systematic reviews or pooled analyses not included.

Insulin Degludec Comparisons

Insulin Degludec vs. Insulin Detemir

Type 1 Diabetes

We included 2 fair-quality RCTs comparing degludec and detemir in patients with Type 1 diabetes.[19,52] Both were 26-week, multinational trials. One was conducted in children and adolescents (N=350; 1 to 17 years).[52] 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).[19] Degludec 100 U/mL was given once per day and detemir 100 U/mL was given once or twice per day, both with aspart 100 U/mL given at mealtimes. Patients in both treatment arms were titrated individually once a week to a plasma glucose of 3.9 to 4.9 mmol/L.

Glycemic Control

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 HbA_{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 HbA_{1c} reduction (95% CI -0.23 to 0.05). The proportion of adults achieving HbA_{1c} <7% was 41.1% for degludec compared with 37.3% for detemir (OR 1.27, 95% CI 0.77 to 2.0).

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).[52]

Evidence of differences in rates of hypoglycemia was also insufficient in adult patients given degludec and detemir).[19] 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)[52], and in adults (RR 1.51, 95% CI 0.22 to 10.54).[19]

Subgroup analyses

A subgroup analysis of patients enrolled in Japan in the RCT conducted in adults found similar results to the overall study (described above). [71]

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

Type 1 Diabetes

We included 2 fair-quality, RCTs comparing FDCP degludec/aspart (70/30) and detemir in patients with Type 1 diabetes, 1 in adults and 1 in children and adolescents.[11,26] The trial in adults (N=548) was a 26-week, multinational trial. Degludec/aspart FDCP 100 U/mL was given once per day with aspart given at the remaining meals.[26] 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. In this update, we have added a secondary publication of the 12-month extension data from this trial. [62] The trial in children and adolescents was presented at a conference in 2015 but has not been formally published.

We received additional unpublished information on the study from the manufacturer (NovoNordisk)[11] and also used data reported on ClinicalTrials.gov. [70]

Glycemic Control

In adults, there is low-strength evidence that glycemic control did not differ between FDCP degludec/aspart and detemir in adult patients with Type 1 diabetes at 26 weeks, or at 52 weeks. At 26 weeks, the mean HbA_{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), and at 52 weeks was -0.65% vs. -0.56% (estimated treatment difference -0.10%, 95% CI -0.24 to 0.03). The proportion of participants achieving HbA_{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) at 26 weeks, and at 52 weeks was 22.4% vs. 17.0% (odds ratio 1.56, 95% CI 0.94 to 2.59).

In children and adolescents, there is low-strength evidence that glycemic control did not differ between FDCP degludec/aspart and detemir in children or adolescent patients with Type 1 diabetes at 16 weeks.[11] The mean HbA_{1c} reduction was -0.27% for degludec/aspart FDCP compared with -0.23% for detemir. The estimated treatment difference was -0.04, 95% CI -0.23 to 0.15. The proportion of participants achieving HbA_{1c} <7% was not reported.

Hypoglycemia

In adults, there were few episodes of severe hypoglycemia, and no significant difference was found between FDCP degludec/aspart and detemir at 26 weeks (RR 1.19, 95% CI 0.58 to 2.41).[26] Similarly, at 52 weeks the event rates were small and no significant difference was found (episodes/person/year 0.3 vs. 0.6, event rate 0.98, 95% CI 0.54 to 0.79).[62] In children and adolescents, the event rates for severe hypoglycemia were also low (0.26 versus 0.07 episodes/patient/year) and while the absolute rates favored detemir, the estimated rate ratio was not significantly different (3.2, 95% CI 0.88 to 11.66).[11] This evidence is insufficient to draw conclusions, mainly due to too few events and lack of corroborating evidence.

In adults, the incidence and rate ratios of nocturnal hypoglycemia favor the FDCP, but the relative risk was not significantly different. 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) at 26 weeks. At 52 weeks there were 3.09 vs. 5.41 episodes/person/year; RR 0.62 (95% CI 0.48 to 0.79).[62] In children there was no difference between groups; 5.77 versus 5.40 episodes/patient/year (estimated rate ratio 1.09, 95% CI 0.81 to 1.48).[11] This evidence is also insufficient to draw conclusions, mainly due to too few events and lack of corroborating evidence.

Withdrawals Due to Adverse Events

Few patients withdrew due to adverse events at 26 or 52 weeks, and the relative risk was not significantly different between patients given FDCP degludec/aspart and detemir (1.1% vs. 1.6%, RR 0.66 (95% CI 0.17 to 2.63) at 26 weeks, and 1.9% vs 1.6%; RR 1.16 (95% CI 0.30 to 4.43) at 52 weeks; EPC-calculated relative risks). Similarly, in children, there was not a difference in withdrawals due to adverse events at 16 weeks, with only 1 withdrawal in the FDCP group and none in the detemir group.[11] This evidence is insufficient to draw conclusions, mainly due to too few events.

Insulin Degludec vs. Insulin Glargine

Type 1 Diabetes

Glycemic control

We included 4 randomized controlled trials comparing degludec to glargine in adult patients with Type 1 diabetes.[13,24,32,35] Three trials were rated fair quality,[13,32,35] and 1 (BEGIN Basal-Bolus Type 1, N=629) was rated good quality for objective outcomes that are less affected by the open-label design.[24] One additional trial included 18 children, but reporting was unclear and we rated it as poor quality and do not present its results.[53] The four trials in adults included a total of 1,801 participants treated for 16 to 52 weeks, with patients in each trial receiving bolus insulin aspart in addition to basal insulin. One trial[13] 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. The BEGIN Flex T1 trial[35] compared degludec administered at a fixed time daily to "forced flexible" timing where the interval between doses ranged from 8 to 40 hours.

The 4 trials provided moderate-strength evidence that glycemic control did not differ between degludec and glargine in adults with Type 1 diabetes. Three of the trials,[13,24,35] reported the decrease in HbA_{1c} (percent glycated hemoglobin) from baseline to the end of treatment, and there was no statistically significant difference between degludec and glargine (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 et al[35] (with fixed daily timing) and in Birkeland et al[13] (600 µmol/L, the FDA-approved formulation of 100 U/mL degludec). One trial also reported the percent of patients reaching the goal of HbA_{1c} ≤7%, which did not differ between those treated with degludec and glargine (RR 0.93, 95% CI 0.76 to 1.2).[24] SWITCH1 was a double-blinded crossover trial that reported HbA_{1c} at the end of the first 32-week treatment period, with no statistically significant difference between degludec and glargine (Appendix G, Table G-3).[32]

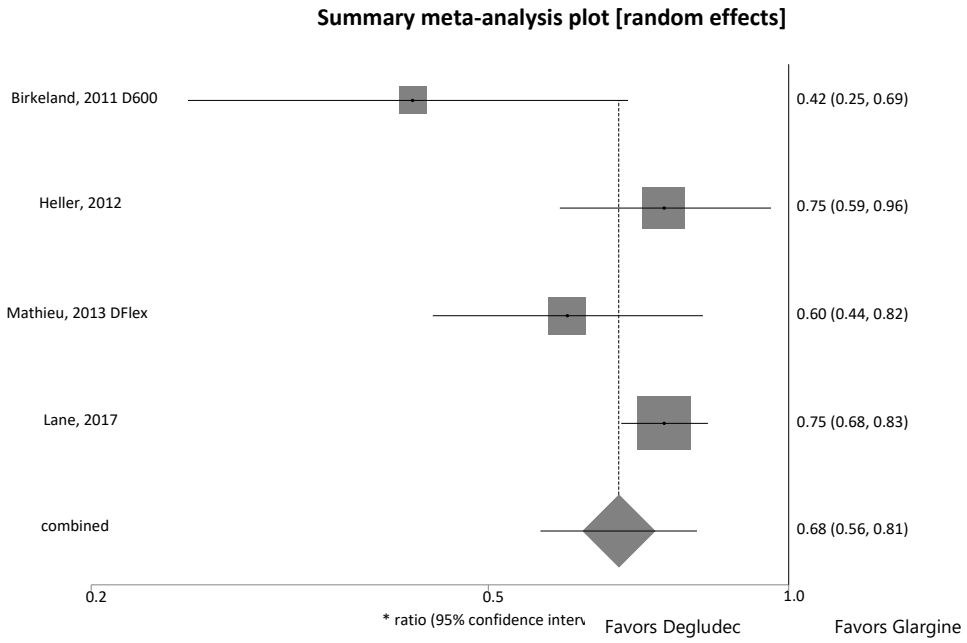
Two trials included an extension study where patients continued on the insulin assigned during the trial.[24,35,59] Neither trial re-randomized participants, and in both 75% of patients randomized in the main trial continued into the extension. Treatment was extended to 2 years in 1 study[24,59] and 1 year in the other.[35] In both studies, efficacy in the extension period was similar to that in the main trial, with no statistically significant differences in HbA_{1c} between degludec and glargine in either time period.

Hypoglycemia

The 4 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. There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given degludec and glargine.[13,24,32,35] However, episodes of nocturnal hypoglycemia were less frequent with degludec than with glargine (pooled rate ratio 0.68; 95% CI 0.56 to 0.81; I^2=53%; 4 RCTs, Figure 1). Although statistical heterogeneity was moderate in the meta-analysis, each of the 4 trials found significantly lower rates of nocturnal hypoglycemia with degludec, and confidence intervals overlapped, such that our confidence in these findings is moderate.

A 1-year trial[24] had an additional 1-year extension, 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.

Figure 1. Nocturnal hypoglycemia event rates in adult patients with Type 1 diabetes treated with degludec compared with glargine



Withdrawals due to Adverse Events

Few patients withdrew due to adverse events, with 37 withdrawals among 1,737 patients across the 4 trials. The evidence was insufficient to compare withdrawals due to adverse events in patients given degludec and glargine, mainly due to too few events.

Other Harms

None of the 4 trials reported cancer diagnoses in the patients treated. Three trials[24,32,35] reported major adverse cardiovascular events assessed by an event adjudication committee, but events were few (11 across the 3 trials) and could not be compared across treatment arms.

Type 2 Diabetes

Ten good- or fair-quality trials compared treatment with degludec and glargine in a total of more than 13,000 adult patients with Type 2 diabetes (Appendix G, Table G-3).[22,23,34,37,41,42,54,55,57,58] An additional trial in 44 patients was rated poor quality, and we do not discuss its results.[10] Over half of all patients in the 10 good- or fair-quality trials were enrolled in the DEVOTE trial.[34,100] The FDA approved insulin degludec in 2015 contingent on the manufacturer completing a clinical trial to rule out major adverse cardiovascular event (MACE) rates higher than an active control, because of concerns about cardiovascular harms identified in

a meta-analysis of earlier trial results.[101] DEVOTE randomized 7,637 patients with Type 2 diabetes and elevated cardiovascular risk to degludec or glargine, and continued until ≥ 633 adjudicated MACE events occurred (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Interim results supported the 2015 approval, and final results were published in 2017 and are included in this update report.

Daily timing of degludec varied, with comparisons of fixed and flexible timing and of morning and evening administration. Treatment duration across trials ranged from 16 weeks to a median of 2 years in DEVOTE.[34] 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 noted in Type diabetes (above), 1 trial[57] 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[22] patients also received mealtime insulin aspart.

Glycemic control

Nine trials provided high-strength evidence from almost 13,000 patients that glycemic control did not differ between patients treated with daily degludec and daily glargine.[22,23,34,37,41,42,54,55,58] About the same proportion of patients in both groups achieved $HbA_{1c} \leq 7\%$ (7 trials, N=4,716, pooled RR 0.97, 95% CI 0.91 to 1.03; $I^2=0\%$; Appendix H, Figure H-1).[22,23,37,41,42,54,58] Three of the trials also reported patients achieving goal HbA_{1c} 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; $I^2=17\%$).[41,42,58] The DEVOTE[34] and SWITCH2[55] trials together included more than 8,000 patients, and neither trial found a statistically significant difference in mean HbA_{1c} at the end of treatment with degludec compared with glargine.

Two trials reported extension studies[22,58,63,74] 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,[22,63] and 2 years in the other.[58,74] In each study, efficacy in the extension period was similar to that in the trial period, with no statistically significant differences in HbA_{1c} between degludec and glargine in either time period.

Hypoglycemia

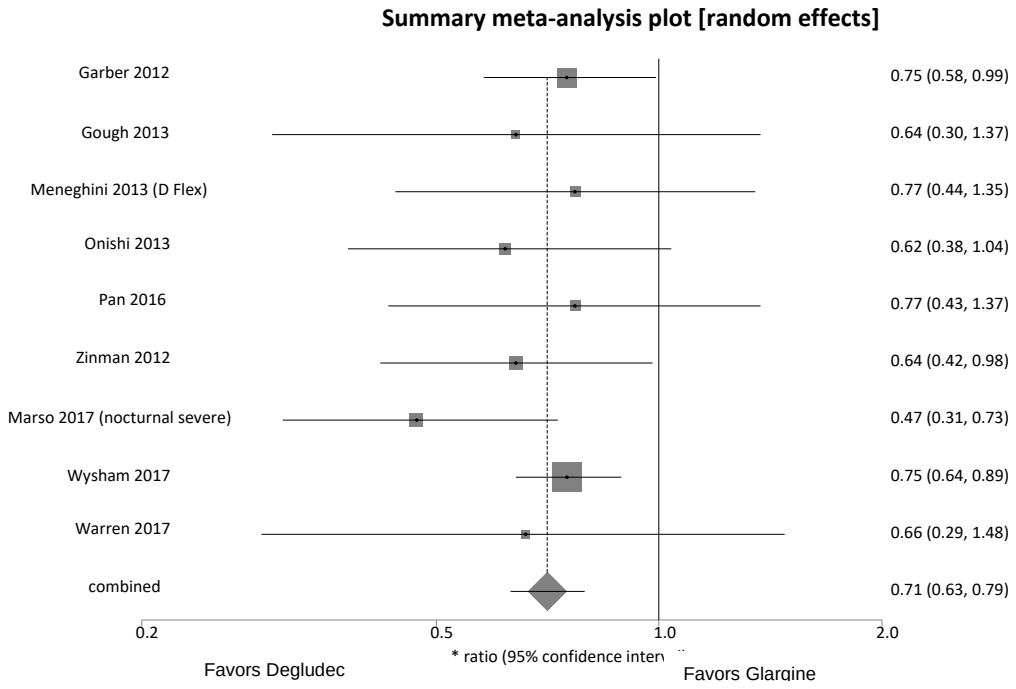
Moderate-strength evidence from 13,182 patients in 9 trials[22,23,34,41,42,57,58 54,55] showed that fewer patients experienced severe hypoglycemia among those given degludec compared with patients treated with glargine (3.3% vs. 5.1%, pooled RR 0.72, 95% CI 0.54 to 0.96; $I^2=12.5\%$; see Appendix H, Figure H-2). In terms of the number of severe hypoglycemia events per patient, rates were also lower with degludec than with glargine, though there was some heterogeneity across the 3 studies reporting this outcome (pooled rate ratio 0.50, 95% CI 0.32 to 0.80, $I^2=42.1\%$; see Appendix H, Figure H-3).[34,55,58]

Moderate-strength evidence from 13,867 patients with Type 2 diabetes in 10 randomized controlled trials showed that rates of nocturnal hypoglycemia were lower with daily degludec than with daily glargine. The difference was of borderline statistical significance (and some

heterogeneity was present) when analyzing whether each patient had any episode of nocturnal hypoglycemia (pooled RR 0.84, 95% CI 0.71 to 1.0; I^2=47.4%). However, there were fewer episodes of nocturnal hypoglycemia per patient year in patients given daily degludec than in those receiving daily glargine (9 RCTs, pooled rate ratio 0.71, 95% CI 0.63 to 0.79; I^2=0%; Figure 2).

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[22,63] and 2 years in the other.[58,74] 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[74] 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.[22,58,63]

Figure 2. Nocturnal hypoglycemia event rates in adult patients with Type 2 diabetes treated with daily degludec compared with glargine



Withdrawals Due to Adverse Events

Nine trials provided data on adverse events in 5,470 patients with Type 2 diabetes given daily degludec or glargine.[22,23,37,41,42,54,55,57,58] 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 0.64 to 1.5; I^2=0%; Appendix H, Figure H-4).

Other Harms

In most trials of LAIs in patients with Type 2 diabetes, mortality and cancer outcomes were not prespecified or adjudicated, but the addition of the large DEVOTE trial provided enough data to assess these outcomes. In 8 trials reporting mortality, 450 patients died with no difference in death rates between degludec and glargine (RR 0.90, 95% CI 0.75 to 1.07; I^2=0%; Appendix H, Figure H-5).[22,23,34,37,41,42,55,58] Six trials provided low-strength evidence that cancer rates were also

similar between treatments (RR 0.91, 95% CI 0.66 to 1.24, I^2=1.7%; Appendix H, Figure H-6).[22,23,34,37,42,58] Major adverse cardiovascular events were assessed by adjudication committees in multiple trials, and reported in 4 trials[34,42,55,58]; as discussed above, the DEVOTE trial was designed specifically to assess this outcome. The 4 trials provided moderate-strength evidence that cardiovascular events did not differ between degludec and glargine (0.92, 95% CI 0.80 to 1.06; I^2=0%; Appendix H, Figure H-7).

Subgroup Analyses

DEVOTE analyzed the effects of degludec and glargine on cardiovascular events and severe hypoglycemia within subgroups including demographics, disease severity, baseline cardiovascular risk, comorbidity, and geographic location.[34] Geographic location was the only subgroup that changed the effect of treatment on cardiovascular outcomes (*P*=0.0052 for the interaction of treatment and subgroup). For patients in Africa and Asia, MACE rates were lower among those treated with degludec compared with glargine (RR 0.30, 95% CI 0.12 to 0.77 for Africa, RR 0.42, 95% CI 0.22 to 0.81 for Asia). For patients in Europe and the Americas, there was no difference in cardiovascular event rates between treatments.

For severe hypoglycemia, multiple patient characteristics changed the effect of treatment on outcome: sex (*P*=0.038), ethnicity (*P*=0.040), baseline cardiovascular risk (*P*=0.014), and geographic location (*P*=0.034). For women, patients who were not Hispanic or Latino, those with established baseline cardiovascular disease, and patients in the United States, rates of severe hypoglycemia were lower with degludec than with glargine. For men, Hispanic or Latino patients, those with risk factors for (but not established) cardiovascular disease, and those outside the U.S., there was no statistically significant difference in hypoglycemia rates between degludec and glargine.

The BEGIN: ONCE ASIA trial[41] 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. A secondary publication from this trial[72] 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 Degludec U200 vs. Insulin Degludec U100

Type 2 Diabetes

We included 1 fair-quality, open-label RCT comparing degludec U200 and degludec U100 in adult patients with Type 2 diabetes (N=373).[15] 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 treatment period, both

insulins 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).

Glycemic Control

The trial provided insufficient evidence in comparing differences in glycemic control measured by HbA_{1c} between degludec U200 and degludec U100 (HbA_{1c} change estimated treatment difference: -0.11, 95% CI -0.28 to 0.05).

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).[15] Evidence was also insufficient to compare rates of nocturnal hypoglycemia (RR 0.93, 95% CI 0.67 to 1.36).

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

Type 2 Diabetes

We included 2 fair-quality, open-label trials comparing FDCP degludec/aspart to glargine in adult patients with Type 2 diabetes (N=992).[30,31] Both trials were multi-national and treated patients for 26 weeks. In one trial, after completing the 26-week core trial patients entered a 26-week extension phase.[30] Both drugs were given once daily via a pen injection. Patients treated with glargine did not receive insulin aspart.

Glycemic control

The trials provided moderate-strength evidence that glycemic control did not differ between FDCP degludec/aspart and glargine in adult patients with Type 2 diabetes. Mean HbA_{1c} change from baseline to week 26 was -0.97 to -1.65% for FDCP degludec/aspart compared with -1.00 to -1.72% for glargine U100 (estimated treatment difference was not statistically significant for either trial). One trial reported results at week 52,[30] when the estimated treatment difference was -0.08% (95% CI -0.26 to 0.09). Across both trials, the percent of patients achieving <7.0% HbA_{1c} at week 26 was 43% for degludec/aspart compared with 41% for glargine (RR 1.04, 95% CI 0.90 to 1.21). The difference at week 52 in one trial was 33.1% for FDCP degludec/aspart compared with 29.7% for glargine (OR 1.13, 95% CI 0.77 to 1.66).[30]

Hypoglycemia

There were few episodes of severe hypoglycemia, and evidence was insufficient to compare rates in patients given FDCP degludec/aspart and glargine (0.50% for degludec/aspart vs. 1.11% for glargine).[30,31] Evidence was also insufficient to compare rates of nocturnal hypoglycemia. The earlier trial suggested lower rates of nocturnal hypoglycemia with degludec/aspart than with glargine (7.5% vs. 20%, RR 0.37, 95% CI 0.23 to 0.60).[30] However the second trial did not confirm these results, suggesting no difference in nocturnal hypoglycemia between treatments (degludec/aspart 19% vs. glargine 21%, RR 0.91, 95% CI 0.63 to 1.31).[31] Attempts to pool these data resulted in significant statistical heterogeneity (I^2 > 80%), such that we do not present a meta-analysis of these findings.

Withdrawals Due to Adverse Events

Few patients withdrew due to adverse events, and evidence was insufficient to draw conclusions on withdrawals in patients given degludec/aspart and glargine (RR 1.21, 95% CI 0.35 to 4.20).[30,31]

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

Type 2 Diabetes

One fair-quality, 26-week open label trial compared FDCP degludec/aspart (twice daily) versus degludec (2-4 times daily + aspart at meals) in adult patients with Type 2 diabetes (N=274).[46] Insulin was titrated weekly to pre-breakfast/evening meal plasma glucose target of 71 to 90 mg/dL. The findings below are insufficient to draw conclusions due to too few events and lack of corroborating evidence.

Glycemic Control

There was no significant difference in glycemic control between groups. Percent change in HbA_{1c} 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 HbA_{1c} <7.0% at 26 weeks was also not significantly different (56.5 versus 59.6%, OR 0.83, 95% CI 0.50 to 1.38).

Hypoglycemia

There were few episodes of severe hypoglycemia (0.47 events/patient-years of exposure for FDCP degludec/aspart vs. 0.24 events/patient-years of exposure for degludec) and there was no significant difference in nocturnal hypoglycemia (rate ratio 0.80, 95% CI 0.50 to 1.29).[46]

Withdrawals Due to Adverse Events

There was no significant difference in the number of patients withdrawing due to adverse events between groups (RR 0.12, 95% CI 0.01 to 1.28).[46]

Insulin Detemir Comparisons

Insulin Detemir vs. Insulin Glargine

Type 1 Diabetes

We found 2 fair-quality open-label RCTs (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 (see Evidence Table 1).[25,43] 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. Mean baseline HbA_{1c} was similar between groups.

In additional to these trials, we found 1 observational study that included both Type 1 and Type 2 patients but reported adverse outcomes separately, and 2 small observational studies of pregnant women with Type 1 diabetes who used detemir or glargine for the entire pregnancy.[25,43,80,87,92] All of these were rated fair-quality. In the larger observational study (N=8,494 for Type 1 glargine and detemir),[87] 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 HbA_{1c} 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,[80] and ranged from 9 years to 12 years duration and mean age of 26 years in the other.[92] The baseline HbA_{1c} (at 8 weeks gestation) was lower than the other studies, 6.6% in one study,[80] and ranged from 6.9% to 7.3% in the other study.[92]

Glycemic Control

These studies provided low-strength evidence that there was no difference between the insulins in HbA_{1c} at 26 or 52 weeks. The difference in endpoint HbA_{1c} was 0.01 (-0.13 to 0.16) at 52 weeks,[25] and 0.03 (-0.25 to 0.19) at 26 weeks.[43] One of the studies was conducted as a non-inferiority study, where an upper limit of the 95% confidence interval for difference between HbA_{1c} at 52 weeks of <0.4% constituted noninferiority (equivalence).[25] 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 HbA_{1c} ≤7.0% without major hypoglycemia (31.9% vs. 28.9%; EPC calculated RR 1.1, 95% CI, 0.80 to 1.5).[25] In children with Type 1 diabetes, we found a single very small, fair-quality 12-week crossover trial that found no significant difference in the mean change in HbA_{1c} (difference −0.02% vs. 0.1; P=0.45).[18] This evidence was insufficient to draw conclusions due to lack of confirmatory studies, methodological limitations and the very small sample size.

Hypoglycemia

There was low-strength evidence of no significant difference in the risk of severe hypoglycemia, based on 4 studies.[25,80,87,92] Only 1 small study (N=320), found a significant difference favoring detemir. 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.[43] 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.[87] Findings on nocturnal hypoglycemia were similarly not consistently different between insulins.

Withdrawals Due to Adverse Events

Based on 2 fair-quality RCTs,[25,43] 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.

Adverse Neonatal Outcomes

Two small (N = 203) fair-quality observational studies of women with Type 1 diabetes who used detemir or glargine throughout pregnancy provided information on adverse events in the neonate.[80,92] Both are small studies, with methodological or reporting flaws, and have different findings. The findings are summarized in Table 3. A Bulgarian study found a few outcomes were worse with detemir, while a Danish study found a few were worse with glargine. The clinical implications of the magnitude of the findings are not clear for either study due to their small size and methodological shortcomings and the evidence is insufficient to draw conclusions.

Table 3. Neonatal outcomes with maternal use of Detemir versus Glargine during pregnancy

Study	Insulin daily dose	Gestational age (weeks)	Birth Weight (grams)	Other
Todorova–Ananieva , 2010[92] Bulgaria N = 60	21.4 units vs. 29.7 units	36.2 vs. 37.5	3,076 vs. 3,623 Macrosomia: (≥4,500 grams) 0% vs. 13%	Requiring continuous positive airway pressure beyond 1 hour: 26% vs. 15%, *P*=0.18 NSD: Respiratory distress
Callesen, 2013 [80] Denmark N = 113	0.62 IU/kg vs. 0.44 IU/kg	Mean of 37 in both groups	3,490 vs. 3,219 Large for gestational age: 49% vs. 30%	Hypoglycemia: 68% vs. 33% NSD: neonatal hypoglycemia, admittance to neonatal ICU, low Apgar scores

NSD, not statistically significant

Type 2 Diabetes

We identified a good quality Cochrane review published in 2011[99] that included 4 trials[27,44,47,50] comparing detemir and glargine in patients with Type 2 diabetes. We also identified 5 additional trials published since the review was published (see Evidence Table 1).[17,20,21,33,38] The Cochrane review rated the risk of bias of the 4 trials as high due primarily to the lack of blinding, and we rated 3 of the newer trials poor-quality for concerns with randomization, blinding, and attrition.[17,20,33] 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. We included 8 observational studies to evaluate severe hypoglycemia outcomes.[81,82,86,87,89,93,94,96] Six were fair-quality, 1 was good-quality[86] and 1 was poor-quality for multiple reasons including high loss to follow-up and lack of statistical control for confounding.[81] The mean ages in these studies ranged from 54.9 years to 69.5 years; baseline HbA_{1c} 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.[78,84,88,90] These were fair- and good-quality[88] studies of 197,561 adults (mean ages 60 to 72 years) with Type 2 diabetes.

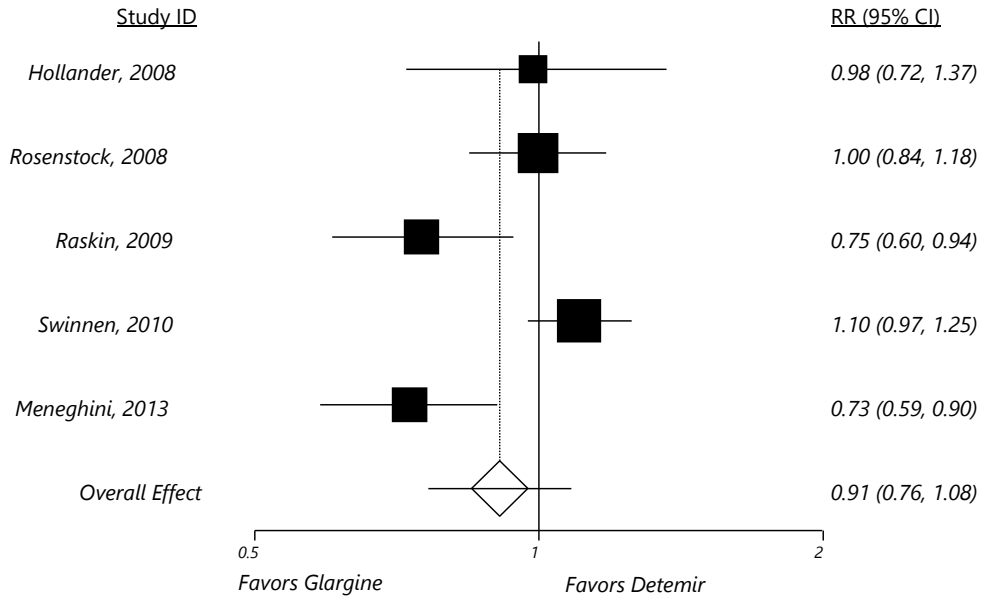
Glycemic Control

There was low-strength evidence of no significant difference in glycemic control between detemir and glargine based on 1 good-quality Cochrane review[99] (4 trials, 3 of which used a non-inferiority design)[27,44,47,50] and 2 newer trials.[21,38] The Cochrane review found no significant difference in HbA_{1c} reduction (difference 0.07%, 95% CI -0.14% to 0.24%). They also found no significant difference in the proportion of patients achieving an HbA_{1c} of ≤7% with (RR 0.97, 95% CI 0.76 to 1.00; I^2=13%) or without (RR 0.96, 95% CI 0.81 to 1.14; I^2=66%) hypoglycemia. Sensitivity and subgroup analyses found that individual studies with variation in study population or design contributed to the heterogeneity in the meta-analysis.

Updating the meta-analyses for patients achieving an HbA_{1c} <7% with newer evidence, we found no significant difference (relative risk 0.91, 95% CI 0.76 to 1.1; I^2=75%, Figure 3). 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 HbA_{1c} of ≤7%,[38,44] while the other 3 studies[27,47,50] found no difference (1 study did not report this outcome).[21] The reasons for these differences may be due to the variation in concomitant antidiabetic drugs and dosing/titration schedules for the insulins. 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). Three of the trials only counted hypoglycemia that occurred 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 HbA_{1c} targets. The newer trials did not report data on change from baseline in HbA_{1c} to allow pooling with the older data.

Figure 3. Proportion achieving HbA_{1c} ≤7% with detemir versus glargine



Cancer

We found low-strength evidence of no increased risk and no difference in risk for any cancer or breast cancer between detemir and glargine. Evidence on cancer mortality with glargine or detemir was limited and insufficient to draw conclusions.

Three retrospective cohort studies, and 1 case-control study (N=240,101) evaluated the association of exposure to detemir or glargine (+/- oral medications) with a diagnosis of (any) cancer (Table 4)[78,79,84,88] Three studies compared use of detemir or glargine to non-use, with means of 1 to 4.7 years of use. [78,84,88] These studies found no significant increased risk with either insulin. The newest study is much larger, good quality, and directly compares the insulins.[79] In

the overall population, there was no significant increase in risk for 7 of 8 duration categories (≤ 0.5 years to > 6 years), no difference in all 8 in men and in 6 of 8 for women. With concerns over the latency period for cancer development, and the lack of multiple studies making direct comparisons or with longer durations of follow-up, our confidence in these findings is low; future studies could alter the findings.

Three retrospective cohort studies (N=212,419) reported on the risk of breast cancer with detemir and glargine (Table 4).[79,84,95] Overall, these studies were not able to differentiate the insulins, or to show definitively whether there is increased risk of breast cancer with either insulin. The largest, best quality, study finds no difference in direct comparison between insulins.[79] While the smallest study finds increased risk with glargine versus NPH, and no significant difference with detemir versus NPH, there were no direct comparisons of the 2 LAIs.[95] The third study finds no increased incidence with either insulin compared with non-use.[84] These studies have different methods of analysis and differing comparisons, such that our confidence in the finding of no increased risk or difference in risk of breast cancer is low; future studies could alter the findings.

A single cohort study (N = 9,363) reported on cancer mortality, using propensity score matching, and found that the risk was not significantly different between detemir and glargine (hazard ratio 0.67, 95% CI 0.38 to 1.18).[90] The median duration of insulin use was only 1.7 years in this study. This evidence is insufficient to draw conclusions.

Table 4. Risk of Cancer with Detemir and Glargine

Study	Comparison	Analysis type	Findings
Risk of Any Cancer			
But, 2017 (Good) N = 129,572	Glargine versus detemir use	Multivariate regression (Relative risks)	NSD for 7 of 8 durations of use (overall population). Men: NSD for all 8 durations Women: small increased risk with glargine at <0.5 and >6 years, NSD in other 6 durations of use.
Buchs, 2011 (Fair) N = 36,342)	Use versus non-use (incidence)	Cox proportional hazards (Hazard Ratios)	Glargine: 1.01 (95% CI 0.995 - 1.026) Detemir: 1.03 (95% Ci 0.989 - 1.001)
Fagot, 2013 (Fair) N = 70,027	Use versus non-use (incidence)	Cox proportional hazards (Hazard Ratios)	Glargine: 0.99 (95% CI 0.89 - 1.09) Detemir: 0.96 (95% CI 0.86 - 1.08)
Simo, 2013 (Good) N = 4,160	Use versus non-use (incidence)	Logistic regression (Odds Ratios)	Detemir: 1.11 (95% CI 0.71 to 1.74) Glargine: 0.97 (95% CI 0.64 to 1.49)
Risk of Breast Cancer			
But, 2017 (Good) N = 129,572	Glargine versus detemir	Multivariate regression (Relative risks)	NSD for 8 durations of use. 3-4 years: 0.95 (0.47 – 1.91)
Wu, 2017 (Fair) N = 12,820	Versus NPH	Cox proportional hazards (Hazard Ratios)	**Glargine: 1.44 (**95% CI **1.11 – 1.88)** Detemir: 1.17 (95% CI 0.77 – 1.77)
Fagot, 2013 (Fair) N = 70,027	Versus non-use (incidence)	Cox proportional hazards (Hazard Ratios)	Glargine: 1.02 (95% CI 0.71 - 1.47) Detemir: 1.14 (95% CI 0.79 - 1.64)

Hypoglycemia

For severe and nocturnal hypoglycemia, we found low-strength evidence of no difference between the insulins. A good quality Cochrane review,[99] and 2 newer RCTs[21,38] 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; I^2=0%).

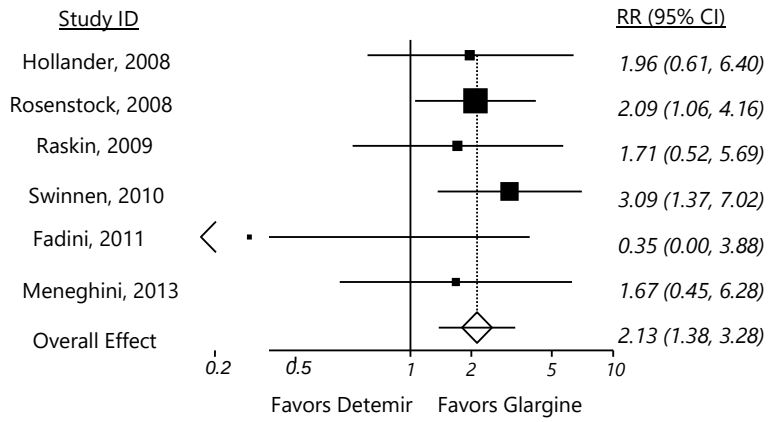
Six of 8 observational studies (N=178,252) found no significant difference in the incidence of severe hypoglycemia, typically defined as requiring emergency department or inpatient treatment, although the studies reported the frequency in varying ways that could not be pooled.[82,87,89,93,94,96] The 2 studies finding a difference, were both conducted in Finland, were good quality, and included some patients with Type I DM.[86,91] One of these, a study evaluating the risk for first hospital admission due to severe hypoglycemia (N = 11,399), found that the risk was slightly, but significantly, lower with detemir than glargine (absolute incidence 1.95% vs. 2.96%; event rate/1000 person-years 12.4 vs. 17.8, adjusted hazard ratio 0.76, 95% CI 0.58 to 0.99).[91] The second study (N=75,682), evaluated the risk of hospitalization for hypoglycemic coma, and found it to be lower with detemir (RR 17.9%, 95% CI 3.6% to 30.1%) in patients who were not previously treated with insulin.[86]

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).[38] Adding these results to the other 4 trials results in a pooled relative risk of 0.97 (95% CI 0.86 to 1.1; 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; I^2=0%; Figure 4). 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 4. Withdrawals from study due to adverse events: insulin detemir versus glargine



Insulin Glargine Comparisons

Follow-on Glargine vs. Glargine

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 (Element 1; N=535).[14] 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 HbA_{1c} 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 glucoses 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.

Glycemic Control

The trial provided low-strength evidence that F-O glargine was non-inferior to glargine on glycemic control in adults with Type 1 diabetes. At 24 weeks, HbA_{1c} 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 HbA_{1c} <7% was 35% for F-O glargine vs. 32% for glargine (RR 1.07, 95% CI 0.84 to 1.36). At 52 weeks F-O glargine was also non-inferior to glargine in glycemic control: the HbA_{1c} 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 HbA_{1c} <7% at 52 weeks was 30% versus 25% (RR 1.20, 95% CI 0.92-1.59).[14]

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).[14]

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).[14]

Type 2 Diabetes

We included 1 fair-quality, non-inferiority, comparing F-O glargine and glargine adults with Type 2 diabetes (N=756).[48] 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.

Glycemic Control

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 HbA_{1c} 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 HbA_{1c} <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.

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%; $P=0.462$).[48]

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).[48]

Insulin Glargine U300 vs. Insulin Glargine U100

Type 1 Diabetes

We included 4 fair-quality trials[12,28,29,36] that compared glargine U300 to glargine U100 in patients with Type 1 diabetes for 4 to 6 months. Two were small trials, with 20 to 59 patients,[12,29] while the EDITION 1[36] and EDITION 4[28] trials were larger, enrolling 243 patients and 549 patients, respectively. All 4 trials included adults only. Three of the trials used pen injectors for the administration of insulin, [28,29,36] while 1 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.[12] In Update 2, we added 12-month data from EDITION 4,[64] and 12-month data and an additional 6-month extension for EDITION JP-1.[68] Study details are in Evidence Table 1.

Glycemic Control

Based on EDITION 4 and EDITION JP-1, there is low-strength evidence that the proportion of patients reaching the target HbA_{1c} <7.0% at 6 months was similar between patients receiving glargine U300 and patients receiving glargine U100 (pooled RR 1.0, 95% CI 0.73 to 1.37).[28,36] The 2 publications of extended follow-up of these trials did not report this outcome.[64,68]

Four trials reported no significant difference in glycemic control measured by the difference in the change in percent HbA_{1c} from baseline to 8.4 weeks,[29] 16 weeks[12] or 6 months.[28,36] The ranges in HbA_{1c} least squares mean difference were -0.44% to -0.28% for U300 and -0.44% to -

0.22% for U100). The pooled estimate across these trials was a weighted mean difference of 0.02%, 95% CI -0.10% to 0.15% (I^2=25.6%). The 12 month data for EDITION 4 also show no difference between groups: % change in HbA_{1c} -0.20% vs. -0.22% (LS mean difference: 0.02, 95% CI -0.13 to 0.17).[64] The 6-month extension of EDITION JP-1 also found no difference between the concentrations, and that the initial decrease in HbA_{1c} was maintained; the mean HbA_{1c} at the end of the extension was 7.9% with U300 and 7.8% with U100).[68]

Hypoglycemia

Four trials[12,28,29,36] 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; I^2=23.5%). Extension study reports from EDITION 4 and EDITION JP-1 analyzed severe hypoglycemic events using different definitions and according to different times of day but did not find significant differences between U300 and U100.[64,68])

Three trials[28,29,36] 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; I^2=39.1%). The fourth trial[12] 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). The two extension study reports also analyzed nocturnal hypoglycemia according to different thresholds. EDITION JP-1 found the risk of nocturnal hypoglycemia <54 mg/dL to be significantly lower with glargine U300 than with U100, while the extension of the larger EDITION 4 study did not.[64,68] Combining these data does not find a significant effect (RR 0.92, 95% CI 0.80 to 1.05).

Withdrawals due to Adverse Events

Withdrawals due to adverse events were uncommon. Four trials[12,28,29,36] 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%). The extension studies of EDITION 4 and EDITION JP-1 also did not find differences in the rate of withdrawal due to adverse events.[64,68]

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,[45,73] EDITION 2,[56,76,77] EDITION 3,[16] and EDITION JP 2.[51] 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 (Evidence Table 1). 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.

In Update 2, we included data on extensions of EDITION 3 (12-month data),[60] EDITION JP-2 (12 month data plus an additional 6 month extension),[75] and an analysis of EDITION 2 and 3 data according to risk levels.[66]

Glycemic Control

The 4 trials provided moderate-strength of evidence that HbA_{1c} did not differ between glargine U300 and glargine U100. After 6 months of treatment, the proportion of patients with HbA_{1c} < 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 the difference in change in the percent HbA_{1c} from baseline to 6 months.[16,45,51,56] Both glargine concentrations improved glycemic control over the study period (HbA_{1c} 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%, I^2=0). Two of these trials reported outcomes at 12 months, with no differences being found between the insulin concentrations.[60,75] In one trial, mean change from baseline in HbA_{1c} was slightly lower, and the overall means for percent HbA_{1c} were slightly higher at 12 months in both groups.[60]

All 4 trials have completed 6-month extension periods in which patients continued to be treated as initially randomized.[45,51,60,73,75-77] In EDITION 2, 3, and JP-1, the finding of no difference at 6 months in mean change in HbA_{1c} from baseline was maintained at 12 months. In EDITION 1, there was a small, but significant difference in mean change in HbA_{1c} from baseline to 12 months (–0.17%, 95% CI –0.30% to –0.05%). This differs from the finding in the initial 6 months of the study, where mean HbA_{1c} decreased similarly in the two treatment groups (–0.00%, 95% CI –0.11 to 0.11).[45] The proportion of patients with HbA_{1c} <7% was not reported in these extension study publications.

Hypoglycemia

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 the 4 EDITION trials reported no differences in incidence of severe hypoglycemia, nocturnal hypoglycemia defined as < 54 mg/dL, or withdrawal due to adverse events over 12 months of treatment. .[60,73,75,77] Nocturnal hypoglycemia defined as <70 mg/dL was significantly less frequent with the U300 concentration in 2 trials,[75,77] and not significantly different in 2 others.[60,73] Pooling these data results in no significant difference between the insulin concentrations (events/patient/year RR 0.78, 95% CI 0.59 to 1.03, I2 = 49%; Appendix H Figure H-8).

Subgroup Analyses

A post-hoc analysis using patient-level data from the EDITION 2 and 3 RCTs evaluated hypoglycemia according to patient risk levels.[66] The study used the Healthcare Effectiveness Data and Information Set (HEDIS) clinical performance measures to assign risk, with patients ≤65 years, with no comorbidities and a HbA_{1c} target of <7% as low-risk, and patients > 65 years, or with one or more HEDIS-defined comorbidity and a target HbA_{1c} of <8% as high risk. The composite of patients achieving HbA_{1c} target without confirmed or severe hypoglycemia over 6 months was not found to be significantly different between glargine U300 and U100, although the authors emphasize a trend that favored U300.

Insulin Glargine U100 Pen vs. Insulin Glargine U100 Vial

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.[49] 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. 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,[83,98] and 1 additional observational study not included in the meta-analysis.[85]

The 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).

Hypoglycemia

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 was 0.74 (95% CI 0.66 to 0.83) and the incidence per-patient-per year of exposure was also significantly lower in patients using pens than in those using vial and syringe to administer glargine (0.14 vs. 0.22 episodes per patient-year, adjusted $P<0.0001$).[98] The findings of 1 additional observational study are consistent with these findings.[85]

Summary

A total of 71 studies were included (90 publications), with 12 new studies this update (including 5 new 12-month extension studies of RCTs). Across the comparisons, there were no significant differences in glycemic control. Differences in adverse events were found in a few comparisons: degludec has lower risk of hypoglycemia than glargine (nocturnal hypoglycemia in Type 1 patients, and both nocturnal and severe hypoglycemia in Type 2 patients), adverse event withdrawals were greater with detemir than glargine in Type 2 patients, glargine U300 had lower risk of nocturnal hypoglycemia than U100 in the short-term (only), and glargine given via pen injector was associated with lower risk of severe hypoglycemia than via vial and syringe (observational evidence). Evidence on other harms (e.g. cancer, neonatal effects) or the comparative harms of fixed-dose combination degludec/aspart 70/30 was insufficient to draw conclusions.

REFERENCES

1. McCulloch DK, Nathan DM, Mulder JE. General principles of insulin therapy in diabetes mellitus2015; http://www.uptodate.com/contents/general-principles-of-insulin-therapy-in-diabetes-mellitus?source=search_result&search=general+principles+diabetes&selectedTitle=4%7E150.
2. Arnolds S, Kuglin B, Kapitza C, Heise T. How pharmacokinetic and pharmacodynamic principles pave the way for optimal basal insulin therapy in type 2 diabetes. *Int J Clin Pract*. 2010;64(10):1415-1424.
3. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clin Pharmacokinet*. 2014;53(9):787-800.
4. McCulloch DK, Nathan DM, Wolfsdorf JI, Mulder JE. Estimation of blood glucose control in diabetes mellitus. 2015; http://www.uptodate.com/contents/estimation-of-blood-glucose-control-in-diabetes-mellitus?source=search_result&search=estimation+of+blood+glucose+control&selectedTitle=1%7E150.
5. American Diabetes Association. Standard of Medical Care in Diabetes - 2015. *Diabetes Care*. 2015;38(S1).
6. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the drug effectiveness review project. *BMC Med Res Methodol*. 2012;12:140.
7. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
8. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
9. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj*. 2003;327(7414):557-560.
10. Aso Y, Suzuki K, Chiba Y, et al. Effect of insulin degludec versus insulin glargine on glycemic control and daily fasting blood glucose variability in insulin-naive Japanese patients with type 2 diabetes: I'D GOT trial. *Diabetes Res Clin Pract*. 2017;130:237-243.
11. Battelino T, Deeb L, Diamantopoulous P. Efficacy and safety of a fixed dose combination of insulin degludec/insulin aspart in children and adolescents with type 1 diabetes. *Poster presented at: 54th European Society for Paediatric Endocrinology*. 2015.
12. Bergenstal R, Bailey T, Rodbard D, et al. Comparison of Insulin Glargine 300U/mL and 100U/mL in Adults With Type 1 Diabetes: Continuous Glucose Monitoring Profiles and Variability Using Morning or Evening Injections. *Diabetes Care*. 2017;[Epub ahead of print].
13. Birkeland KI, Home PD, Wendisch U, et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. *Diabetes Care*. 2011;34(3):661-665.
14. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab*. 2015;17(8):726-733.
15. Bode BW, Chaykin LB, Sussman AM, et al. Efficacy and Safety of Insulin Degludec 200 U/mL and Insulin Degludec 100 U/mL in Patients with Type 2 Diabetes (Begin: Compare). *Endocr Pract*. 2014;20(8):785-791.
16. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17(4):386-394.
17. Cander S, Oz Gul O, Sitki Dizdar O, Aydin T, Ersoy C. The effect of basal analog insulin on the glycemic variability in type 2 diabetics. *Turkish Journal of Endocrinology and Metabolism*. 2014;18(2):33-38.
18. Cherubini V, Pintaudi B, Iannilli A, Pambianchi M, Ferrito L, Nicolucci A. Long-acting Insulin Analogs Effect on gh/igf Axis of Children with Type 1 Diabetes: a Randomized, Open-label, Two-period, Cross-over Trial. *Exp Clin Endocrinol Diabetes*. 2016;124(5):276-282.
19. Davies MJ, Gross JL, Ono Y, et al. Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obes Metab*. 2014;16(10):922-930.
20. Elisha B, Azar M, Taleb N, Bernard S, Iacobellis G, Rabasa-Lhoret R. Body Composition and Epicardial Fat in Type 2 Diabetes Patients Following Insulin Detemir Versus Insulin Glargine Initiation. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2016;48(1):42-47.
21. Fadini GP, de Kreutzenberg SV, Mariano V, et al. Optimized glycaemic control achieved with add-on basal insulin therapy improves indexes of endothelial damage and regeneration in type 2 diabetic patients with macroangiopathy: a randomized crossover trial comparing detemir versus glargine. *Diabetes Obes Metab*. 2011;13(8):718-725.

22. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1498-1507.
23. Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care*. 2013;36(9):2536-2542.
24. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1489-1497.
25. Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. *Clin Ther*. 2009;31(10):2086-2097.
26. Hirsch IB, Bode B, Courreges JP, et al. Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. *Diabetes Care*. 2012;35(11):2174-2181.
27. Hollander P, Cooper J, Bregnhoj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther*. 2008;30(11):1976-1987.
28. Home PD, Bergenstal RM, Bolli GB, et al. New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). *Diabetes Care*. 2015;38(12):2217-2225.
29. Jinnouchi H, Koyama M, Amano A, et al. Continuous Glucose Monitoring During Basal-Bolus Therapy Using Insulin Glargine 300 U mL(-1) and Glargine 100 U mL (-1) in Japanese People with Type 1 Diabetes Mellitus: A Crossover Pilot Study. *Diabetes Ther*. 2015;6(2):143-152.
30. Kumar A, Franek E, Wise J, Niemeyer M, Mersebach H, Simo R. Efficacy and Safety of Once-Daily Insulin Degludec/Insulin Aspart versus Insulin Glargine (U100) for 52 Weeks in Insulin-Naive Patients with Type 2 Diabetes: A Randomized Controlled Trial. *PLoS ONE*. 2016;11(10):e0163350.
31. Kumar S, Jang HC, Demirag NG, Skjoth TV, Endahl L, Bode B. Efficacy and safety of once-daily insulin degludec/insulin aspart compared with once-daily insulin glargine in participants with Type 2 diabetes: a randomized, treat-to-target study. *Diabet Med*. 2017;34(2):180-188.
32. Lane W, Bailey TS, Gerety G, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. *Jama*. 2017;318(1):33-44.
33. Makino H, Tanaka A, Hosoda H, et al. Effect of basal insulin therapy on vascular endothelial function and adipokine profiles in people with Type 2 diabetes. *Diabet Med*. 2016;33(12):1737-1743.
34. Marso SP, McGuire DK, Zinman B, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. *N Engl J Med*. 2017;377(8):723-732.
35. Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab*. 2013;98(3):1154-1162.
36. Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). *Diabetes Obes Metab*. 2016;18(4):375-383.
37. Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care*. 2013;36(4):858-864.
38. Meneghini L, Kesavadev J, Demissie M, Nazeri A, Hollander P. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15(8):729-736.
39. NCT01658579. Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 1 Diabetes Mellitus on Basal Plus Mealtime Insulin *ClinicalTrialsgov*. 2015.
40. NCT01683266. Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 1 Diabetes Mellitus (EDITION IV) (). *ClinicalTrialsgov*. 2015.
41. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, Park S. Insulin degludec compared with insulin glargine in insulin-naive patients with type 2 diabetes: A 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *Journal of Diabetes Investigation*. 2013;4(6):605-612.

42. Pan C, Gross JL, Yang W, et al. A Multinational, Randomized, Open-label, Treat-to-Target Trial Comparing Insulin Degludec and Insulin Glargine in Insulin-Naive Patients with Type 2 Diabetes Mellitus. *Drugs R D*. 2016;16(2):239-249.
43. Pieber TR, Treichel HC, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. *Diabet Med*. 2007;24(6):635-642.
44. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2009;25(6):542-548.
45. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014;37(10):2755-2762.
46. Rodbard HW, Cariou B, Pieber TR, Endahl LA, Zacho J, Cooper JG. Treatment intensification with an insulin degludec (IDeg)/insulin aspart (IAsp) co-formulation twice daily compared with basal IDeg and prandial IAsp in type 2 diabetes: a randomized, controlled phase III trial. *Diabetes Obes Metab*. 2016;18(3):274-280.
47. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia*. 2008;51(3):408-416.
48. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus) in patients with type 2 diabetes who were insulin-naive or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab*. 2015;17(8):734-741.
49. Seggelke SA, Hawkins RM, Gibbs J, Rasouli N, Wang CC, Draznin B. Effect of glargine insulin delivery method (pen device versus vial/syringe) on glycemic control and patient preferences in patients with type 1 and type 2 diabetes. *Endocr Pract*. 2014;20(6):536-539.
50. Swinnen SG, Dain MP, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care*. 2010;33(6):1176-1178.
51. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes Obes Metab*. 2016;18(4):366-374.
52. Thalange N, Deeb L, Iotova V, et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2015;16(3):164-176.
53. Urakami T, Mine Y, Aoki M, Okuno M, Suzuki J. A randomized crossover study of the efficacy and safety of switching from insulin glargine to insulin degludec in children with type 1 diabetes. *Endocr J*. 2017;64(2):133-140.
54. Warren ML, Chaykin LB, Jabbour S, et al. Insulin Degludec 200 Units/mL Is Associated With Lower Injection Frequency and Improved Patient-Reported Outcomes Compared With Insulin Glargine 100 Units/mL in Patients With Type 2 Diabetes Requiring High-Dose Insulin. *Clin Diabetes*. 2017;35(2):90-95.
55. Wysham C, Bhargava A, Chaykin L, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. *Jama*. 2017;318(1):45-56.
56. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014;37(12):3235-3243.
57. Zinman B, Fulcher G, Rao PV, et al. Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. *Lancet*. 2011;377(9769):924-931.
58. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012;35(12):2464-2471.
59. Bode BW, Buse JB, Fisher M, et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN() Basal-Bolus Type 1): 2-year results of a randomized clinical trial. *Diabet Med*. 2013;30(11):1293-1297.
60. Bolli GB, Riddle MC, Bergenstal RM, et al. Glycaemic control and hypoglycaemia with insulin glargine 300U/mL versus insulin glargine 100U/mL in insulin-naive people with type 2 diabetes: 12-month results from the EDITION 3 trial. *Diabetes Metab*. 2017;43(4):351-358.
61. Davies M, Sasaki T, Gross JL, et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: A 1-year treat-to-target trial. *Diabetes Obes Metab*. 2016;18(1):96-99.

62. Hirsch IB, Franek E, Mersebach H, Bardtrum L, Hermansen K. Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal-bolus treatment in people with Type 1 diabetes: 1-year results from a randomized clinical trial (BOOST T1). *Diabet Med*. 2017;34(2):167-173.
63. Hollander P, King AB, Del Prato S, et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. *Diabetes Obes Metab*. 2015;17(2):202-206.
64. Home PD, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia during 12months of randomized treatment with insulin glargine 300U/mL versus glargine 100U/mL in people with type 1 diabetes (EDITION 4). *Diabetes Obes Metab*. 2018;20(1):121-128.
65. Home PD, Meneghini L, Wendisch U, et al. Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes. *Diabet Med*. 2012;29(6):716-720.
66. Lingvay I, Chao J, Dalal MR, Meneghini LF. Efficacy and Safety of Insulin Glargine 300 U/mL Versus Insulin Glargine 100 U/mL in High-Risk and Low-Risk Patients with Type 2 Diabetes Stratified Using Common Clinical Performance Measures. *Diabetes Technol Ther*. 2017;19(5):315-322.
67. Marso SP, McGuire DK, Zinman B, et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) - DEVOTE 1. *Am Heart J*. 2016;179(pp 175-183).
68. Matsuhisa M, Koyama M, Cheng X, et al. Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300U/mL compared with glargine 100U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension). *Diabetes Res Clin Pract*. 2016;122:133-140.
69. NCT00978627. Comparison of NN5401 Plus Insulin Aspart With Insulin Detemir Plus Insulin Aspart in Type 1 Diabetes (BOOST). *ClinicalTrialsgov*. 2017.
70. NCT01835431. A Trial Investigating the Efficacy and Safety of Insulin Degludec/Insulin Aspart Once Daily Plus Insulin Aspart for the Remanining Meals Versus Insulin Detemir Once or Twice Daily Plus Meal Time Insulin Aspart in Children and Adolescents With Type 1 Diabetes Mellitus. *ClinicalTrialsgov*. 2015.
71. Ono Y, Nishida T, Hyllested-Winge J, Seino H, Sasaki T. A comparison of IDeg + IAsp versus IDet + IAsp in subjects with type 1 diabetes: subgroup analysis of Japanese subjects. *Diabetology international*. 2016;7(4):404-412.
72. Osonoi T, Onishi Y, Nishida T, Hyllested-Winge J, Iwamoto Y. Insulin degludec versus insulin glargine, both once daily as add-on to existing orally administered antidiabetic drugs in insulin-naive Japanese patients with uncontrolled type 2 diabetes: subgroup analysis of a pan-Asian, treat-to-target phase 3 trial. *Diabetology International*. 2016;7(2):141-147.
73. Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab*. 2015;[Epub ahead of print].
74. Rodbard HW, Cariou B, Zinman B, et al. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med*. 2013;30(11):1298-1304.
75. Terauchi Y, Koyama M, Cheng X, et al. Glycaemic control and hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 2 diabetes using basal insulin plus oral anti-hyperglycaemic drugs (EDITION JP 2 randomised 12-month trial including 6-month extension). *Diabetes Metab*. 2017;43(5):446-452.
76. Yki-Jarvinen H, Bergenstal RM, Bolli GB. Less nocturnal hypoglycaemia and weight gain with new insulin glargine 300 U/ml vs 100 U/ml: 1-year results in people with type 2 diabetes using basal insulin and OADs (EDITION 2) [abstract]. Diabetologia 2014;57(suppl 1):S387. Abstract 946. In:2014.
77. Yki-Jarvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab*. 2015;17(12):1142-1149.
78. Buchs AE, Silverman BG. Incidence of malignancies in patients with diabetes mellitus and correlation with treatment modalities in a large Israeli health maintenance organization: a historical cohort study. *Metabolism*. 2011;60(10):1379-1385.
79. But A, De Bruin ML, Bazelier MT, et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. *Diabetologia*. 2017;60(9):1691-1703.
80. Callesen NF, Damm J, Mathiesen JM, Ringholm L, Damm P, Mathiesen ER. Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: comparison of glycaemic control and pregnancy outcome. *J Matern Fetal Neonatal Med*. 2013;26(6):588-592.

81. Damci T, Emral R, Svendsen AL, Balkir T, Vora J, group Ss. Lower risk of hypoglycaemia and greater odds for weight loss with initiation of insulin detemir compared with insulin glargine in Turkish patients with type 2 diabetes mellitus: local results of a multinational observational study. *BMC Endocr Disord*. 2014;14:61.
82. Davis KL, Tangirala M, Meyers JL, Wei W. Real-world comparative outcomes of US type 2 diabetes patients initiating analog basal insulin therapy. *Curr Med Res Opin*. 2013;29(9):1083-1091.
83. Davis S, Wei W, Garg S. Clinical impact of initiating insulin glargine with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract*. 2011;17(6):845-852.
84. Fagot JP, Blotiere PO, Ricordeau P, Weill A, Alla F, Allemand H. Does insulin glargine increase the risk of cancer compared with other basal insulins?: A French nationwide cohort study based on national administrative databases. *Diabetes Care*. 2013;36(2):294-301.
85. Grabner M, Chu J, Raparla S, Quimbo R, Zhou S, Conoshenti J. Clinical and economic outcomes among patients with diabetes mellitus initiating insulin glargine pen versus vial. *Postgrad Med*. 2013;125(3):204-213.
86. Haukka J, Hoti F, Erasto P, Saukkonen T, Makimattila S, Korhonen P. Evaluation of the incidence and risk of hypoglycemic coma associated with selection of basal insulin in the treatment of diabetes: a Finnish register linkage study. *Pharmacoepidemiol Drug Saf*. 2013;22(12):1326-1335.
87. Laubner K, Molz K, Kerner W, et al. Daily insulin doses and injection frequencies of neutral protamine hagedorn (NPH) insulin, insulin detemir and insulin glargine in type 1 and type 2 diabetes: a multicenter analysis of 51964 patients from the German/Austrian DPV-wiss database. *Diabetes Metab Res Rev*. 2014;30(5):395-404.
88. Simo R, Plana-Ripoll O, Puente D, et al. Impact of glucose-lowering agents on the risk of cancer in type 2 diabetic patients. The Barcelona case-control study. *PLoS ONE*. 2013;8(11):e79968.
89. Solomon MD, Vijan S, Forma FM, Conrad RM, Summers NT, Lakdawalla DN. The impact of insulin type on severe hypoglycaemia events requiring inpatient and emergency department care in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2013;102(3):175-182.
90. Strandberg AY, Hoti FJ, Strandberg TE, Christopher S, Haukka J, Korhonen P. All-Cause and Cause-Specific Mortality among Users of Basal Insulins NPH, Detemir, and Glargine. *PLoS ONE*. 2016;11(3):e0151910.
91. Strandberg AY, Khanfir H, Makimattila S, Saukkonen T, Strandberg TE, Hoti F. Insulins NPH, glargine, and detemir, and risk of severe hypoglycemia among working-age adults. *Ann Med*. 2017;49(4):357-364.
92. Todorova–Ananieva K, Konova E, Guenova M. Pregnancy Outcomes in Women with Type 1 Diabetes Treated with Long Acting Insulin Analogs. A Case Control Study. *Acta Medica Bulgarica*. 2010;XXXVII(2):21-31.
93. Tsai ST, Pathan F, Ji L, et al. First insulinization with basal insulin in patients with Type 2 diabetes in a real-world setting in Asia. *J Diabetes*. 2011;3(3):208-216.
94. Wei W, Zhou S, Miao R, et al. Much ado about nothing? A real-world study of patients with type 2 diabetes switching Basal insulin analogs. *Adv Ther*. 2014;31(5):539-560.
95. Wu JW, Azoulay L, Majdan A, Boivin JF, Pollak M, Suissa S. Long-Term Use of Long-Acting Insulin Analogs and Breast Cancer Incidence in Women With Type 2 Diabetes. *J Clin Oncol*. 2017;35(32):3647-3653.
96. Xie L, Wei W, Pan C, Du J, Baser O. A real-world study of patients with type 2 diabetes initiating basal insulins via disposable pens. *Adv Ther*. 2011;28(11):1000-1011.
97. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab*. 2015;17(9):859-867.
98. Xie L, Wei W, Pan C, Baser O. Real-world rates, predictors, and associated costs of hypoglycemia among patients with type 2 diabetes mellitus treated with insulin glargine: results of a pooled analysis of six retrospective observational studies. *J Med Econ*. 2013;16(9):1137-1145.
99. Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2011(7):CD006383.
100. Marso SP, McGuire DK, Zinman B, et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) - DEVOTE 1. *Am Heart J*. 2016;179:175-183.
101. Food and Drug Administration. NDA Approval Letter. *https://wwwaccessdatafdagov/drugsatfda_docs/appletter/2015/203314Orig1s000ltrpdf*. 2015;Accessed on May 1, 2018.