Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Single-Ingredient, Long-Acting Insulins

Insulin Degludec (Tresiba)
Insulin Determir (Levemir)
Insulin Glargine (Basaglar, Lantus, Toujeo)

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Executive Summary

The long acting-insulin analogs (LAIAs) include insulin degludec (Tresiba), insulin detemir (Levemir), and insulin glargine (Basaglar, Lantus, and Toujeo). Each LAIA is available in a U-100 multi-dose vial or injector pen. Concentrated products include Tresiba (insulin degludec) U-200 FlexTouch pen, and Toujeo (insulin glargine) U-300 SoloStar or Max SoloStar pens. Basaglar is a biosimilar product that produces the same clinical effects as the originator insulin glargine, Lantus.

The LAIAs are used to improve glycemic control in adults and children with diabetes mellitus. Insulin degludec is indicated for patients ≥ 1 year of age with T1DM or T2DM. Insulin glargine U-100 products are indicated for adults with T2DM or pediatric and adult patients with T1DM. Insulin detemir is indicated for adults and pediatric patients with diabetes mellitus. Insulin glargine U-300 is indicated only for adults. Dosing is individualized according to the patient’s metabolic needs and glycemic targets; adjustments may be required during acute illness, or when there are changes in the patient’s activity level, meal patterns, renal/hepatic functioning, or to concomitant medications.

The 2019 American Diabetes Association (ADA) guideline and the 2018 Consensus Report by the ADA and the European Association for the Study of Diabetes highlight the importance of individualizing therapy. The ADA guideline notes that the longest-acting products, degludec and insulin glargine U-300 may have lower hypoglycemia risk compared to U-100 glargine in T1DM. For patients with T2DM, decision points are specified according to patient-specific co-morbidities. When choosing a basal insulin for patients with atherosclerotic cardiovascular disease (ASCVD), heat failure (HF), or chronic kidney disease (CKD), prescribers may consider that degludec and U-100 glargine have demonstrated safety in cardiovascular disease; ASCVD, HF, and CKD, altogether, affect about 15% to 25% of patients with T2DM. For patients at a low risk of hypoglycemia or who have relaxed A1c goals, the ADA guideline suggests that patients can be safely treated with lower cost insulins such as neutral protamine Hagedorn (NPH) and regular human insulin. Otherwise, when patients have a compelling need to minimize hypoglycemia, the ADA treatment algorithm specifies the following basal insulin options in order of lowest hypoglycemia risk (degludec/glargine U-300 < glargine U-100/detemir < NPH insulin). Regarding concentrated insulin products, the ADA notes that “…concentrated preparations may be more comfortable for the patient and may improve adherence for patients with insulin resistance who require large doses of insulin.”

The objective of this report is to determine whether there are key efficacy or safety differences between the single-ingredient, long-acting insulins for outpatient management of T1DM, T2DM, or gestational diabetes mellitus (GDM) based on direct comparative evidence. Following literature searches for systematic reviews of randomized controlled trials in Embase and Medline, we included evidence from 9 SRs, all published within the last 3 years, that describe treatment comparisons.

Although degludec treatment was found to produce modest reductions in fasting blood glucose beyond the effect of detemir (for T1DM) or glargine (for T1DM and T2DM), the LAIAs similarly controlled A1c which is generally a better measure for evaluating sustained glycemic effect over the previous 3 months compared to looking at fasting blood glucose only at two different time points (eg, at the end-of-study vs. baseline).
Common adverse reactions for the LAIAs include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain. Differences were found between LAIAs, particularly with respect to nocturnal hypoglycemia in favor of degludec and U-300 glargine, and with respect to weight gain in favor of detemir. Degludec treatment resulted in lower rates of confirmed nocturnal hypoglycemia (<56 mg/dL) compared to detemir for patients with T1DM, and lower rates of overall nocturnal hypoglycemia compared to glargine for patients with T1DM or T2DM. Rates of severe hypoglycemia and overall hypoglycemia were also lower with degludec compared to glargine for patients with T2DM. Body weight gain was lower with detemir compared to degludec for patients with T1DM, and compared to glargine for patients with T2DM.

Compared to glargine U-100 in adults with T1DM, treatment with U-300 glargine resulted in a lower risk of confirmed nocturnal hypoglycemia (BG<54 mg/dL); yet, products were similar with respect to confirmed nocturnal hypoglycemia (BG <70 mg/dL), any nocturnal hypoglycemia, and severe hypoglycemia. Compared to glargine U-100 in adults with T2DM, the U-300 formulation tended to demonstrate a lower risk of confirmed nocturnal hypoglycemia (<70 mg/dL); however, the difference was less clear since the statistical significance depended on the meta-analysis method used (fixed versus random-effects). Additionally, there were no differences found for confirmed nocturnal hypoglycemia (BG <54 mg/dL) or for overall nocturnal hypoglycemia at month 12 for adults with T2DM.

According to the Medicaid fee-for-service utilization data, the majority of patients who received an LAIA in 2018 used insulin glargine U-100 products (vial and pen), followed by insulin detemir. Prescription fills for insulin degludec and U-300 glargine were very low relative to the usage of other LAIA products. Insulin degludec and U-300 glargine prescribing currently requires a prior authorization request, with a variety of scenarios allowing for attainment of these therapies. Considering the safety differences regarding hypoglycemia outcomes in favor of degludec and U-300 glargine, these agents may be reserved for patients that are determined by their provider to be at higher risk of hypoglycemia (eg, patients with a history of hypoglycemia, hypoglycemia unawareness, renal failure, etc.), or for patients who have experienced other scenarios of treatment failure and/or adverse effects with a preferred LAIA product.
Introduction

Basal insulins are generally administered to control blood glucose in-between meals and overnight (ie, during fasting state) and are classified into two categories: (a) intermediate-acting insulin (neutral protamine Hagedorn [NPH]), and (b) long-acting insulin analogs (LAIA). This report will focus on the single-ingredient, LAIA products containing insulin degludec (Tresiba), insulin detemir (Levemir), and insulin glargine (Basaglar, Lantus, and Toujeo). Table 1 details the specific formulations, indications, and dosing for these products. From here on, the letter “U” followed by a number stands for the insulin concentration as insulin units per milliliter (eg, U-300 means 300 units/mL).

Each active ingredient (insulin degludec, detemir, and glargine) is available in a U-100 multi-dose vial or injector pen. Basaglar is a biosimilar of the originator insulin glargine, Lantus. Biosimilar products produce the same clinical effect as the reference product and are considered interchangeable by the US Food and Drug Administration (FDA). Available concentrated products include Tresiba (insulin degludec) U-200 FlexTouch pen, and Toujeo (insulin glargine) U-300 SoloStar or Max SoloStar pens. Concentrated products allow for administration of a smaller volume per dose compared to using a U-100 product at the same unit dose. The American Diabetes Association (ADA) notes that “[t]hese concentrated preparations may be more comfortable for the patient and may improve adherence for patients with insulin resistance who require large doses of insulin.”

Insulin degludec is indicated for patients ≥ 1 year of age with T1DM or T2DM. Insulin detemir is indicated for adults and pediatric patients with diabetes mellitus. Insulin glargine U-100 products are indicated for adults with T2DM or pediatric and adult patients with T1DM. Insulin glargine U-300 is indicated only for adults. Product labeling describes that insulin detemir and glargine U-100 products have not been studied in pediatric patients with T2DM or in children with T1DM who are <2 years of age for Levemir or <6 years of age for Basaglar and Lantus.

Insulin detemir is approved for use as a once or twice daily, subcutaneous injection. Insulin glargine U-100 is labeled as a once-daily injection; although, in practice it is commonly used twice daily since the duration of action can be less than 24 hours in some patients. Insulin degludec and glargine U-300 are administered once daily. Dosing is individualized according to the patient’s metabolic needs and glycemic targets; dose adjustments may be required during acute illness or when there are changes in the patient’s activity level, meal patterns, renal/hepatic functioning, or to concomitant medications.

The research objective of this report is to determine whether there are key efficacy or safety differences between the single-ingredient LAIA for the outpatient management of T1DM, T2DM, or gestational diabetes mellitus (GDM), based on direct comparative evidence. A thorough discussion of related topics (eg, appropriate diagnosis, use of other medications for diabetes management, or management of cardiovascular-related comorbidities, etc.) is beyond the scope of this report—see the full guidelines referenced throughout this report regarding related topics.

The Utah Medicaid Preferred Drug List (PDL) includes Lantus (vial and pen) and Levemir (vial and pen) as preferred LAIA products. Non-preferred products include Basaglar, Toujeo, and Tresiba. Patients may receive a non-preferred product if they have demonstrated trial and failure of a preferred agent, among other scenarios.
<table>
<thead>
<tr>
<th>Agents (Approval Year)</th>
<th>Indications and Administration Information</th>
</tr>
</thead>
</table>
| Insulin Degludec (2015) | Indicated for patients ≥1 year of age with T1DM or T2DM; not recommended in pediatric patients requiring less than 5 units  
Administration: SQ injection into the thigh, deltoid, or abdomen; rotate injection sites  
Dosed once daily, at any time of day for adults and at the same time each day for children. Individualize dose; may titrate up every 3 to 4 days based on patient’s metabolic needs, blood glucose monitoring, and glycemic goals.  
Initiation  
T1DM Insulin-naive: Initiate at one-third to one-half of the total daily insulin dose required, administered once daily; the remainder of total daily dose should be given as a short-acting insulin, in divided doses at meal times (general rule for initial total daily insulin dose, 0.2 to 0.4 units/kg)  
T2DM Insulin-naive: initiate as 10 units once daily  
T1DM or T2DM Insulin-experienced:  
- Adults: use the same total daily unit dose as the previous basal insulin dose  
- Pediatric patients: Use 80% of the previous basal insulin total daily unit dose as degludec  
Do not mix with other insulins  
Tresiba U-100 pen delivers doses in 1 unit increments and up to 80 units per injection; Tresiba U-200 pen delivers doses in 2 unit increments and up to 160 units per injection  
Opened or unrefrigerated Tresiba products expire in 56 days |
| Insulin Detemir (2005) | Indicated for glycemic control in adult and pediatric patients with diabetes mellitus. Safety and efficacy is established for adults with T1DM or T2DM, and for pediatric patients 2 years or older with T1DM.  
Administration: SQ injection into the thigh, deltoid, or abdomen; rotate injection sites  
Dosing once or twice daily; if dosed once daily, give with the evening meal or at bedtime. Individualize and titrate dose based on patient’s metabolic needs, blood glucose monitoring, and glycemic goals.  
Initiation  
T1DM, insulin-naive: Initiate as approximately one-third of the total daily insulin dose required; the remainder of total daily dose should be given as a rapid or short-acting insulin in divided doses at meal times.  
T2DM insulin-naive inadequately controlled on oral antidiabetic agents or GLP-1 agonists: initiate as 10 units (or 0.1 to 0.2 units/kg)  
Converting from insulin glargine or NPH:  
- From insulin glargine: conversion can be done by a unit to unit basis  
- From NPH: May convert on a 1:1 basis, however, some patients with T2DM may require more insulin glargine than NPH  
Do not mix with other insulins  
Levemir pen can deliver from 1 to 80 units per injection  
Opened or unrefrigerated Levemir products expire in 42 days |
Table 1. Long-acting Insulin Products

<table>
<thead>
<tr>
<th>Agents (Approval Year) Formulations</th>
<th>Indications and Administration Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Glargine</strong> (Lantus 2000; Basaglar 2015; Toujeo 2015)</td>
<td></td>
</tr>
<tr>
<td>Solution, 10mL Vial Lantus U-100</td>
<td>Basaglar and Lantus suggested to improve glycemic control in adults with T1DM or T2DM, and in pediatric patients with T1DM. Safety and effectiveness have not been established in patients younger than 6 years of age with T1DM or in children with T2DM. Dosed once daily, at the same time each day. Individualize dose and titrate based on patient’s metabolic needs, blood glucose monitoring results, and glycemic goals. Initiation</td>
</tr>
<tr>
<td><strong>T1DM:</strong> Initiate as approximately one-third of the total daily insulin dose required; the remainder should be given as prandial insulin.</td>
<td></td>
</tr>
<tr>
<td><strong>T2DM, insulin-naïve patients:</strong> initiate as 10 units (or 0.2 units/kg).</td>
<td></td>
</tr>
<tr>
<td><strong>Converting from other insulins:</strong></td>
<td></td>
</tr>
<tr>
<td>• From Toujeo U-300: dose Basaglar or Lantus as 80% of the Toujeo dose</td>
<td></td>
</tr>
<tr>
<td>• From once daily NPH: dose Lantus once daily in a 1:1 ratio of the total NPH dose</td>
<td></td>
</tr>
<tr>
<td>• From twice daily NPH: dose Basaglar or Lantus once daily, as 80% of the total NPH dose</td>
<td></td>
</tr>
<tr>
<td>Do not mix with other insulins</td>
<td></td>
</tr>
<tr>
<td>Lantus and Basaglar pen devices can deliver 1 to 80 units per injection.</td>
<td></td>
</tr>
<tr>
<td>Opened or unrefrigerated Lantus and Basaglar products expire in 28 days.</td>
<td></td>
</tr>
<tr>
<td>Toujeo U-300</td>
<td></td>
</tr>
<tr>
<td>Solution Pen-injector, 1.5mL Toujeo SoloStar U-300</td>
<td></td>
</tr>
<tr>
<td>Solution Pen-injector, 3mL Basaglar KwikPen U-100</td>
<td></td>
</tr>
<tr>
<td>Lantus SoloStar U-100 Toujeo Max SoloStar U-300</td>
<td></td>
</tr>
<tr>
<td>Indicated to improve glycemic control in adults with diabetes mellitus. Dosing is once daily, at the same time every day. Individualize dose and titrate dose based on patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal. When changing patients to Toujeo, glucose must be monitored closely in the first weeks of therapy and dose adjustments of other anti-hyperglycemic concomitant therapies may be required as the full effect of Toujeo may not manifest till about 5 days after initiation. Titrate the dose no more frequently than every 3 to 4 days. Initiation</td>
<td></td>
</tr>
<tr>
<td><strong>T1DM, insulin-naïve patients:</strong> Initiate as approximately one-third to one half of the total daily insulin dose required; the remainder of total daily dose should be given as a short-acting insulin divided between each daily meal. The total daily dose required for insulin naïve patients is generally 0.2 to 0.4 units/kg.</td>
<td></td>
</tr>
<tr>
<td><strong>T2DM, insulin-naïve patients:</strong> initiate as 10 units (or 0.2 units/kg).</td>
<td></td>
</tr>
<tr>
<td><strong>Converting from other insulins:</strong></td>
<td></td>
</tr>
<tr>
<td>• From U-100 once daily, intermediate- or long-acting regimens: dose Toujeo as 1:1 ratio of the U-100 intermediate- or long-acting product. Expect the need for up titration of Toujeo if converting a patient previously controlled on Lantus.</td>
<td></td>
</tr>
<tr>
<td>• From twice daily NPH: dose Toujeo once daily, as 80% of the total NPH dose</td>
<td></td>
</tr>
<tr>
<td>Do not mix with other insulins</td>
<td></td>
</tr>
<tr>
<td>Opened, unrefrigerated Toujeo products expire in 56 days</td>
<td></td>
</tr>
<tr>
<td>Toujeo Solostar can deliver 1 to 80 units per injection. Toujeo Max Solostar pen delivers doses in 2 unit increments, up to 160 units per injection. The Max Solostar pen is recommended for patients requiring at least 20 units of basal insulin per day.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GLP-1 RA, glucagon-like peptide 1; NPH, neutral protamine Hagedorn; SQ, subcutaneous; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus
Methods

Systematic Literature Search

Search strategies were developed for the systematic reviews (SRs) in Embase and Ovid-Medline; databases were searched up to December 22\textsuperscript{nd} and 24\textsuperscript{th}, respectively. The complete search strategies, terms, and syntax are available in Applicences A and B. Strategies consisted of controlled vocabularies, such as Medical Subject Headings (MeSH), and keyword phrases. Independently derived filters by an Informational Scientist were used to identify SRs. In Embase, we excluded conference abstracts. Results were limited to English language. We also screened the reference lists and other relevant websites for further information:


II. For professional prescribing information (ie, product labeling) we searched the drug sponsor’s website for each brand product, or websites such as Drugs@FDA and dailymed.nlm.nih.gov/dailymed/ if there was no sponsor website available (packaged inserts searched on December 17\textsuperscript{th}, 2018).

III. Evidence-based drug information databases, Micromedex and Lexicomp

Screening

Two reviewers independently screened publication titles and abstracts for inclusion. Conflicts were resolved by consensus between reviewers. The full text for all citations receiving 2 inclusion votes were retrieved. The lead author made the final determination for inclusion upon full-text review. Figure 1 on page 18 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

Considered for inclusion was evidence presented in SRs, based on head-to-head randomized controlled trials (RCTs) that compared efficacy or safety outcomes between the LAIAs for the outpatient management of patients with T1DM, T2DM, or GDM. Direct, pair-wise meta-analysis statistical data was included, while mixed- or indirect-comparative statistical data (ie, network meta-analyses) was excluded. We considered studies in which the same insulin delivery mode was used for the comparator arm (eg, continuous subcutaneous insulin infusion [CSII] or by multiple daily doses [MDD], but not one arm CSII versus another arm as MDD) and with matching concomitant antihyperglycemic agents in the comparator arm. We focused on evidence from trials with treatment lasting at least 12 weeks, since lesser durations would confound effects on A1c, a measure reflective of glycemic control over the past 3 months. SRs including the most up-to-date evidence was included; SR publications were excluded if they missed more recently published RCTs.
Disease Overview

Patients with diabetes mellitus have impaired glucose homeostasis that leads to hyperglycemia, hypertriglyceridemia, ketoacidosis, and tissue catabolism.\(^1\) Adequate glycemic control reduces microvascular complications (eg, retinopathy, nephropathy) and macrovascular complications (eg, myocardial infarction, stroke) that result from chronic hyperglycemia.\(^3\) In T1DM, insulin-producing, pancreatic beta-cells are destroyed by autoimmune processes (or idiopathic cause) and patients require exogenous insulin to thrive.\(^15\) The estimated prevalence of T1DM in the United States is approximately 3 million patients.\(^16\) Patients with T2DM have varying degrees of insulin resistance and insufficiency of insulin secretion.\(^1\) Early on in the disease, patients with T2DM are usually managed with oral antihyperglycemic therapies, unless patients are markedly symptomatic or with a very high hemoglobin A1c (A1c) or blood glucose at diagnosis— requiring insulin expediently.\(^1\) While lifestyle management is at the core of T2DM treatment, the disease is progressive and eventually many patients will require exogenous insulin.\(^3,15\) The Centers for Disease Control and Prevention estimates that more than 30 million Americans have diabetes with the majority of cases (90% to 95%) being T2DM.\(^17\)

In the ambulatory setting, patients requiring insulin therapy may receive bolus, prandial insulin (ie, rapid- or short-acting insulin for the management of the post-prandial glucose rise), usually in combination with a basal insulin (ie, insulin that controls blood glucose in-between meals), and with or without other non-insulin antihyperglycemic agents.\(^1\) For patients with T1DM especially, rapid-acting insulins may be used alone in a continuous infusion pump as the patient’s complete insulin regimen.\(^1\)

A1c “...has strong predictive value for diabetes complications...,” so is used as the major tool to evaluate glycemic control in patients with diabetes.\(^1\) A1c reflects the average blood glucose over approximately the preceding 3 months (ie, how well patients have been controlled over this period).\(^1\) Treatment guidelines recommend individualizing the patient’s A1c goal with consideration of patient-specific factors such as their age, duration of disease, co-morbidities, motivation, self-management ability, preferences, risk for hypoglycemia, and their hypoglycemia awareness.\(^1,18\) Once insulin therapy is initiated, appropriate control of fasting blood glucose generally relates the optimization of the basal insulin regimen; however, in some situations it can also depend on dosage/duration of action of the prandial insulin used. For patients requiring prandial insulin for the management of post-prandial blood glucose, the dose and timing must be tailored to match the patient’s carbohydrate intake, pre-meal glucose levels, and anticipated activity.\(^1\)

**Table 2** lists the glycemic targets described in American treatment guidelines for the management of diabetes along with other glycemic targets for fasting and post-prandial blood glucose levels.
Table 2. Glycemic Targets per ADA and AACE/ACE Guidelines

### ADA Diabetes Care Guideline, 2019

**Adults, non-pregnant**
- A1c target is generally <7%
- A lower A1c target of <6.5% can be set for individuals at low risk for hypoglycemia, polypharmacy, or other adverse effects. Such patients may include those with shorter duration of diabetes, T2DM treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease
- A1c target of <8% may be appropriate in individuals with a history of severe hypoglycemia, advanced macro- or micro-vascular complications, extensive comorbidities, long-standing diabetes and inability to achieve lower threshold targets
- Pre-prandial capillary plasma glucose target is 80-130 mg/dL, but can set to a more or less stringent goal per the patient’s needs
- Peak postprandial capillary plasma glucose (1-2 hours after beginning of the meal) target is <180 mg/dL, but can be set to a more or less stringent goal per patient need

**Older Adults**
- A1c target of <7.5 for older adults who are otherwise healthy older adults (eg, few coexisting chronic diseases, intact cognitive function and functional status)
- A1c goal of <8% or <8.5% for older adults with multiple coexisting chronic illnesses, cognitive impairment, functional dependence

**Children and Adolescents with T1DM**
- A1c target of 7.5% should be considered but goals should be individualized based on patient/caregiver needs/situation; a lower goal (<7%) is reasonable if it can be achieved without hypoglycemia
- Before meals serum glucose goal is 90 – 130 mg/dL and the bedtime/overnight goal is 90-150 mg/dL

**Pregnant Women**
- A1c goal of 6%-6.5% to reduce the risk of congenital anomalies; the goal can be set to <6% if it can be achieved without hypoglycemia, or can be relaxed to <7% to prevent hypoglycemia

### AACE/ACE T2DM Management Guideline, 2018

**Adults with T2DM**
- General A1c target is ≤6.5% if it can be achieved without significant hypoglycemia or other complications.
- An A1c target of >6.5%-8% is recommended for those in whom the lower target cannot be achieved without adverse outcomes (eg, patients with history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing T2DM with difficulty controlling A1c goal despite intensive effort)

Abbreviations: A1c, glycosylated hemoglobin A1c; AACE/ACE, American Academy of Endocrinologists and American College of Endocrinology; ADA, American Diabetes Association; T2DM, type 2 diabetes mellitus
Basal Insulin Pharmacotherapy

Preferences Specified Among ADA and AACE/ACE Guidelines Regarding Basal Insulins

The 2019 ADA guideline along with the 2018 Consensus Report by the ADA and the European Association for the Study of Diabetes highlight the importance of individualizing therapy. The ADA guideline notes that the longest-acting products, degludec and insulin glargine U-300 may have lower hypoglycemia risk compared to U-100 glargine in the type 1 and type 2 diabetes population; yet, authors do not go as far to prefer one product over another for patients with T1DM. For patients with T2DM, decision points are specified according to patient-specific co-morbidities. Atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and chronic kidney disease (CKD), altogether, affect about 15% to 25% of patients with T2DM. When choosing a basal insulin for patients with any of these conditions (ASCVD, HF, CKD) prescribers should consider that degludec and U-100 glargine have demonstrated safety in cardiovascular disease; other basal agents have not been studied in large prospective cardiovascular outcomes trials.

For patients who are at lower risk of hypoglycemia or who have relaxed A1c goals or high insulin resistance, the ADA suggests that patients can be safely treated with lower cost insulins such as NPH and regular human insulin. Otherwise, when patients have a compelling need to minimize hypoglycemia, the ADA treatment algorithm specifies the following basal insulin options in order of lowest hypoglycemia risk (degludec/glargine U-300 < glargine U-100/detemir < NPH insulin).

The 2018 Academy of Endocrinologists and American College of Endocrinology (AACE/ACE) guideline supports the use of LAIAs over the use of NPH for all patients with type 2 diabetes because the former have a relatively flat serum insulin concentration and are associated with less hypoglycemia. Both the ADA and AACE/ACE groups agree that pharmacologic therapy should follow a patient-centered approach when choosing medications, considering antihyperglycemic efficacy, key patient factors (eg, comorbidities, cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, side effects, tolerability, ease of use, adherence, patient preferences, and cost.

Each group considers cost a parameter in the selection of therapy but approach it differently. AACE/ACE considers minimizing the risk of hypoglycemia a priority over medication cost concerns. They describe the cost of the medication to be only a part of the total cost of care and recommend selecting agents with the best safety and efficacy. In contrast, the ADA considers that cost be a consideration in medication choices and specifies medication preferences in relation to patient-specific co-morbidities or demonstration of compelling need.

Type 1 Diabetes Mellitus

The majority of patients with T1DM should be treated with multiple daily doses of prandial insulin and basal insulin, or by continuous subcutaneous insulin infusion (CSII). Children and adolescents, especially, should be treated with intensive insulin regimens (ie, multiple daily doses of insulin or CSII). The ADA recommends considering CSII for all children and adolescents with T1DM, especially in children under 7 years of age. Insulin pumps can improve glycemic control and reduce hypoglycemia in children. CSII devices have features that can benefit patients, especially children who may have...
unpredictable eating and exercise patterns. While the ADA does not specifically recommend one LAIA product over another, authors comment that degludec and glargine U-300 may have lower hypoglycemia risk compared to U-100 glargine in patients with T1DM, citing 1 RCT for each comparison.

Type 2 Diabetes Mellitus

Metformin is the recommended first-line antihyperglycemic agent for all patients without contraindications. For newly diagnosed patients whose A1c is ≥1.5% above target or for patients who are not achieving their target A1c after 3 months of metformin monotherapy, the ADA recommends dual-therapy with metformin. Addition of the second glucose-lowering agent is selected according to patient co-morbidities, hypoglycemia risk, impact of potential weight gain, and patient preferences. For patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, the recommended second agent should be selected from specific glucagon-like peptide 1 (GLP-1) agonists and sodium-glucose co-transporter 2 inhibitors (SGLT2-I) with proven cardiovascular risk reduction; otherwise, the second therapy can be selected from any of the following drug classes: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors, or basal insulins. Early initiation of insulin is recommended if at presentation the patient’s A1c is ≥10%, blood glucose is ≥300 mg/dL, or if the patient is symptomatic.

In general, basal insulin can be added on to oral therapies or injectable GLP-1 agonists if patients are not meeting their A1c target with non-insulin regimens specified among the ADA or AACE/ACE treatment algorithms. Basal therapy is usually initiated at 10 units/day or 0.1-0.2 units/kg/day. The ADA notes the following potential treatment-effect differences among basal insulins: a) U-100 detemir and glargine may modestly reduce the risk of nocturnal and symptomatic hypoglycemia compared to NPH but the persistence of reduction is questionable; and b) when used in combination with oral antihyperglycemic agents, glargine U-300 and degludec may pose less risk of hypoglycemia compared to U-100 glargine.

If glycemic targets are not achieved with a basal insulin-containing regimen (or if the basal dose exceeds 0.5 units/kg/day), combination injectable therapy with basal insulin plus either prandial insulin or a GLP-1 agonist (if not already on one) should be considered. When combination injectable regimens are employed, metformin is continued, while sulfonylureas and DPP-4 inhibitors are usually discontinued to reduce complexity and cost of the patient’s regimen. Providers must balance the potential benefits of a more intensive or complex regimen approach with the risk of hypoglycemia and weight gain.

Type 2 Diabetes Mellitus in Pediatric Patients

According to the ADA treatment algorithm, there are generally 2 scenarios in which pediatric patients with T2DM may be started on basal insulin: 1) if patients are not meeting their A1c goal with metformin monotherapy, or 2) if patients are asymptomatic (without acidosis or without ketosis) with hyperglycemia and A1c ≥8.5% at diagnosis. If patients remain uncontrolled with basal insulin titrated up to 1.5 units/kg/day, then prandial insulin is added or patients may be converted to pump therapy.

Pregnant Women with Diabetes

Treatment of pregnant women with diabetes improves perinatal outcomes, reducing perinatal risks such as fetal anomalies, preeclampsia, macrosomia, and neonatal hypoglycemia associated with uncontrolled
diabetes in pregnancy. Insulin is the first-line therapy for gestational onset diabetes mellitus (GDM) and for pregnant women with pre-existing type 1 or type 2 diabetes because it does not cross the placenta. Efficacy of oral agents is generally insufficient and/or ineffective during pregnancy; safety evidence on their long-term use in pregnant women is also lacking. The ADA cites a 2017 Cochrane Review by O’Neil et al describing no clear superiority of any specific insulin regimen over another for diabetes management during pregnancy.

Table 3. American Guideline Recommendations Regarding the Use of Basal Insulins

<table>
<thead>
<tr>
<th>Professional Organization</th>
<th>Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association</td>
<td><strong>Type 1 DM</strong></td>
</tr>
</tbody>
</table>
| Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes; 2019 | Insulin is the mainstay therapy, starting with 0.4-1 units/kg/day
- Most patients with T1DM should be treated with concomitant basal insulin with multiple daily injections of prandial insulin, or by continuous subcutaneous insulin infusion (Level A recommendation).
- U-300 glargine or degludec may pose less hypoglycemia risk compared with U-100 glargine in patients with type 1 diabetes.
| Management considerations | Insulin requirements are higher during puberty.
- Balance intensive therapy (ie, multiple-dose insulin regimens or CSIII) with hypoglycemia risk. |
| Basal Insulin (NPH or LAIA) | **Type 2 DM** |
| | With the progressive nature of T2DM, patients often require insulin-containing regimens.
- Consider early initiation of insulin for newly diagnosed patients who are symptomatic and with A1c ≥10% or blood glucose ≥300 mg/dL
- For patients without atherosclerotic cardiovascular disease or chronic kidney disease who are not reaching their A1c target with metformin alone or who are diagnosed with an A1c ≥ 1.5% above goal, consider dual therapy with metformin plus an additional agent (eg, sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 receptor agonist [GLP-1 agonist], sodium-glucose co-transporter 2 inhibitor [SGLT2-I], or basal insulin)
  - For patients with atherosclerotic cardiovascular (CV) disease, heart failure or chronic kidney disease, adding an agent shown to reduce major CV events is recommended.
  - For GLP-1 RAs with proven CVD benefit, the strongest evidence is for liraglutide>semaglutide> exenatide extended release.
  - For SGLT-2i agents with proven CVD benefit, the evidence is modestly stronger for empagliflozin> canagliflozin.
- Basal Insulin (NPH or LAIA)
  - Initiate at 10 units/day or 0.1-0.2 units/kg/day; patient self-titration is more effective. Alternatively, may adjust by 2 units every 3 days, to reach FBG target. If patients experience hypoglycemia without a clear cause, decrease dose by 10-20%.
  - If A1c targets are not met despite having basal insulin titrated to an acceptable fasting blood glucose or if dose is >0.5 units/kg/day, consider combination injectable therapy.
### Table 3. American Guideline Recommendations Regarding the Use of Basal Insulins

<table>
<thead>
<tr>
<th>Professional Organization</th>
<th>Statements</th>
</tr>
</thead>
</table>
| ❖ **Guideline**                                                                            | ✷ May use NPH or LAIA for basal therapy. LAIAs provided a modest advantage with respect to nocturnal hypoglycemia compared to NPH in clinical trials, although their benefit in real world settings has been less clear. Management considerations  
   ✷ “A patient-centered approach should be used to guide the choice of pharmacologic agents,” taking into consideration efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, administration method, cost, and patient preferences.  
   ✷ With combination oral therapy, U-300 glargine or degludec may have lower hypoglycemia risk compared with U-100 glargine.                                                                                     |
| **American Diabetes Association**                                                          | ✷ For older adults at increased risk of hypoglycemia, ADA generally prefers medication classes with low risk of hypoglycemia.  
   ✷ A once-daily basal insulin dosing is associated with minimal side effects which may be a reasonable option in many older patients.  
   ✷ Consider simplifying regimens of multiple daily injections that may be too complex for patients with diabetes complications, life-limiting coexisting chronic illnesses, or limited functional status.                                                                                                           |
| ❖ Older Adults: Standards of Medical Care in Diabetes—2019                                 | ✷ “The majority of children and adolescents with type 1 diabetes should be treated with intensive insulin regimens, either via multiple daily injections or continuous subcutaneous insulin infusion”  
   ✷ Basal insulin should be initiated for the following  
     a) Patients with T2DM not reaching their A1c goal with metformin monotherapy  
     b) Symptomatic patients (but without acidosis or without ketosis) who have an A1c≥8.5% at diagnosis. Metformin should also be started and up-titrated for these patients. Insulin may be weaned off or to lower doses once metformin starts working and bases on glucose levels  
   ✷ Initiate basal insulin generally at 0.5 units/kg/day, titrating up to a maximum of 1.5 units/kg/day to achieve A1c control.  
   ✷ If patients reach 1.5 units/kg/day and a still not achieving their A1c target, start multiple daily injections with concomitant prandial insulin or insulin pump therapy.                                                                                                                   |
| **American Diabetes Association**                                                          | ✷ When the patient is not reaching their individualized A1c goal with combination non-insulin therapies, basal insulin should be added as a single dose.  
   ✷ Long-acting analogs are preferred over NPH since the analogs have been shown to have a lower risk of hypoglycemia.  
   ✷ Authors explain that compared to detemir and U-100 glargine, the longer-acting products, degludec and glargine U-300, demonstrate a more stable pharmacokinetic and pharmacodynamic profile, and lower rates of severe and confirmed hypoglycemia (including nocturnal hypoglycemia) compared to detemir and U-100 glargine.                                                                                                           |
| ❖ Consensus Statement by the American Association on Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

Patients who remain uncontrolled while receiving combination therapy with basal insulin and oral agents or GLP-1 agonists may then require prandial insulin. Additionally, prandial insulin should be considered when the total daily dose of basal insulin is greater than 0.5 units/kg since the risk of hypoglycemia increases considerably beyond this dose without much additional A1c reduction.

Abbreviations: A1c, glycosylated hemoglobin A1c; ADA, American Diabetes Association; CSII, continuous subcutaneous insulin infusion therapy; DM, diabetes mellitus; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; GLP-1, glucagon-like peptide 1; LAIA, long acting insulin analog; MDI, multiple daily injections; NPH, neutral protamine Hagedorn; PK, pharmacokinetics; PPG, post prandial glucose; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus
Pharmacology

Insulin analogs bind to insulin receptors in peripheral sites of skeletal muscle and adipose tissue stimulating glucose uptake and protein synthesis, while also inhibiting hepatic glucose production, lipolysis in adipocytes, and proteolysis.\(^8\)\(^{-10}\) Compared to the intermediate-acting insulin, NPH, LAIAs exert a less pronounced peak in the serum concentration curve; U-300 glargine and degludec are peakless. Of the LAIAs, insulin degludec has the longest half-life (25 hours), followed by U-300 glargine (19 hours) at a dose of 0.4 units/kg. Nonetheless, there is considerable variability in the pharmacodynamics of insulins between individuals, within the same individual, or based on the dose administered.\(^8\)\(^{-10}\)

The concentrated products (Tresiba U-200 and Toujeo U-300) allow for a smaller administration volume compared to using a U-100 insulin product at the same dose. The ADA guideline notes that “[t]hese concentrated preparations may be more comfortable for the patient and may improve adherence for patients with insulin resistance who require large doses of insulin.”\(^3\) Comparing U-100 and U-200 degludec, the total and maximum insulin exposure at steady state and the total glucose-lowering effect over 24 hours is comparable between products when administered at the same units/kg dose.\(^20\) Glargine U-300 was shown to have a longer duration of action than U-100 glargine when dosed at the same units/kg.\(^21\) However, on a unit-to-unit basis, compared to U-100 glargine, the U-300 product results in a lower exposure and a lower glucose-lowering effect compared to an equivalent dose of U-100 (27% lower glucose-lowering effect at steady-state after 8 daily injections of U-300 compared to U-100).\(^9\),\(^21\)

Although the serum concentration of insulin detemir and glargine U-100 products have a relatively constant concentration profile over 24 hours, as demonstrated in glucose clamp studies, pharmacodynamics can vary considerably between individuals.\(^7\),\(^8\) Some patients may need to dose insulin detemir or glargine U-100 twice daily to achieve basal insulin coverage throughout the day because they may not experience 24 hour duration of action with these agents (>45% of patients on detemir and >10% of patients on glargine may need twice daily dosing).\(^14\),\(^22\) Based on a very small RCT (N=54) comparing pharmacodynamic and kinetic profiles, insulin detemir was reported to have lower within-subject variability versus U-100 glargine in patients with type 1 diabetes.\(^23\)

Insulin degludec (Tresiba) and insulin glargine U-300 (Toujeo) products have durations of action that can persist well past 24 hours (depending on the dose for Toujeo): the duration of effect was >42 hours for degludec at 0.4 units/kg and was 16, 28, and 36 hours for glargine U-300 dosed at 0.4 units/kg, 0.6 units/kg, and 0.9 units/kg respectively.\(^9\),\(^10\) A small pharmacodynamic study of 54 patients suggests that the within-subject variability in the day-to-day glucose lowering effect of insulin degludec is 4 times less than with U-100 glargine (based on indirect comparison).\(^24\)

Table 4 provides a summary of pharmacodynamic and kinetic parameters for the LAIAs. Regarding table 4 formatting, some parameters were provided with respect to a certain weight-based dosing (eg, values appear in line with doses), while some parameters were provided without specification of the dose (eg, values that are aligned with the drug name). Table 5 provides additional information pertaining to special populations.
Table 4. Pharmacodynamic and Kinetic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Tmax (hours)</th>
<th>Peak</th>
<th>T1/2</th>
<th>Duration of action</th>
<th>Steady State (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Degludec</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tresiba</td>
<td>0.4 units/kg SQ</td>
<td>9</td>
<td>12</td>
<td>25</td>
<td>&gt;42</td>
</tr>
<tr>
<td><strong>Insulin Detemir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levemir</td>
<td>6-8</td>
<td>8-10</td>
<td>5-7</td>
<td>range 7.6 to &gt; 24</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(dose dependent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin Glargine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basaglar</td>
<td>0.5 units/kg</td>
<td>12</td>
<td>12</td>
<td>&gt;24</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lantus</td>
<td>0.4 units/kg</td>
<td>13.5</td>
<td>median 24</td>
<td>range 10.8 to &gt;24</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toujeo</td>
<td>0.4 units/kg</td>
<td>12</td>
<td>19</td>
<td>16</td>
<td>5-8</td>
</tr>
<tr>
<td></td>
<td>0.6 units/kg</td>
<td>12</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9 units/kg</td>
<td>16</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 5. Information Regarding Special Populations

<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Pediatric Patients</th>
<th>Pregnant Women</th>
<th>Geriatric Patients</th>
<th>Renal or Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Degludec</strong> (Tresiba)</td>
<td>Approved for pediatric patients with T1DM and T2DM, 1 year of age and older</td>
<td>Human data is lacking; animal data suggest low risk to fetus per Briggs et al(^\text{27})</td>
<td>Although differences in safety and effectiveness were not evident in subgroup analyses for patients older than 65 years, older adults should be treated more conservatively when initiating and titrating doses since they may be more sensitive to insulin or may have hypoglycemia unawareness.</td>
<td>Safety and effectiveness differences were not evident in subgroup analyses for subjects with renal impairment.</td>
</tr>
<tr>
<td></td>
<td>For pediatric patients requiring less than 5 units of degludec/day, use of the U-100 vial is recommended over the pen</td>
<td>Insulin degludec is excreted into rat milk; Probably compatible during breastfeeding per Briggs et al(^\text{27})</td>
<td></td>
<td>No pharmacokinetic differences were identified in patients with renal or hepatic impairment</td>
</tr>
<tr>
<td><strong>Insulin Detemir</strong> (Levemir)</td>
<td>Has not been studied in children with T2DM or in children with T1DM who are &lt;2 years of age.</td>
<td>There is RCT evidence in pregnant women with T1DM showing no increased risk of fetal abnormalities (Pregnancy Category B; Compatible during pregnancy per Briggs et al(^\text{27}))</td>
<td>In a pharmacokinetic study in geriatric patients, exposure to insulin detemir (AUC) was increased by 35%, as subjects were found to have reduced clearance.</td>
<td>Some studies have showed increased human insulin levels in patients with renal impairment; thus, close glucose monitoring and dose adjustments of insulin may be necessary in patients with renal impairment</td>
</tr>
<tr>
<td></td>
<td>In children (6-12 years), the insulin exposure (area under the curve) and the maximum concentration were increased by 10% and 24%, respectively, compared to parameters in adults.</td>
<td>It is unknown whether detemir is excreted into human milk; however, human insulin is known to be excreted into breast milk (Compatible during breastfeeding per Briggs et al(^\text{27}))</td>
<td>Although differences in safety and effectiveness were not evident in subgroup analyses for patients older than 65 years, older adults should be treated more conservatively when initiating and titrating doses since they may be more sensitive to insulin or may have hypoglycemia unawareness.</td>
<td>Exposure to insulin may increase or decrease with hepatic insufficiency; thus, glucose levels should be closely monitored and insulin adjustments may be necessary</td>
</tr>
</tbody>
</table>

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\(^{7,10,13,27}\)
Table 5. Information Regarding Special Populations\textsuperscript{7-10,13,27}

<table>
<thead>
<tr>
<th></th>
<th>Pediatric Patients</th>
<th>Pregnant Women</th>
<th>Geriatric Patients</th>
<th>Renal or Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Glargine</strong></td>
<td>Safety and efficacy have not been established for children with T2DM or in children with T1DM and &lt;6 years of age</td>
<td>“Published studies with use of insulin glargine products during pregnancy have not reported a clear association with insulin glargine products and adverse developmental outcomes”\textsuperscript{13}</td>
<td>Labeling for Lantus notes that in controlled studies a higher incidence of cardiovascular events was seen in the older population treated with Lantus compared to the entire study population; however, since then the ORIGIN randomized controlled trial\textsuperscript{28} lasting 6 years in older adults found no increased risk of cardiovascular outcomes compared to standard of care</td>
<td>The effect of renal and hepatic impairment on insulin glargine pharmacokinetics has not been studied, but more frequent glucose monitoring and dose adjustments may be necessary</td>
</tr>
<tr>
<td>(Basaglar and Lantus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin Glargine</strong></td>
<td>Safety and effectiveness have not been established in pediatric patients</td>
<td>Insulin glargine is considered compatible during pregnancy and breastfeeding per Briggs et al\textsuperscript{27}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Toujeo)</td>
<td></td>
<td></td>
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</tbody>
</table>
Direct-Comparative Evidence for Long-Acting-Insulins

Our literature search yielded a total of 411 unique titles from which 9 systematic reviews were included. **Figure 1** displays the PRISMA flow chart for the publication screening process. The majority of SRs excluded during full-text review either did not include a systematic literature search methodology (eg, MAs of pre-selected RCTs), did not report direct meta-analysis results (ie, network MAs focusing on indirect or mixed comparisons), or missed more recently published RCTs captured in the included 2017 and 2018 systematic reviews. **Appendix C** provides a list of studies excluded in the full-text review stage. **Figure 2**, on the next page, shows the systematic reviews included and the patient population for which they apply. **Appendix D** provides a table describing the design and findings for each systematic review. **Appendix E** provides an abbreviated summary of treatment-effect differences between agents that were consistently reported among the comparative evidence.

---

**Figure 1. PRISMA Flow Diagram for Publication Screening**

- Records identified from Medline, 275
- Records identified in Embase, 345
- Unique records de-duplicated in Covidence 411

Records screened (411) ➔ Records excluded (346)

- Full-text articles assessed for eligibility (n = 65)
  - Publications included in qualitative synthesis (n = 9)

- Full-text articles excluded, with reasons
  - (n = 56)
  - Wrong comparator (9)
  - Wrong study design (30)
  - More up-to-date SR available (13)
  - Other (4)

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* See Appendix C for a list of excluded studies

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19
Adults with Type 1 Diabetes Mellitus

A. Insulin Degludec (Tresiba) Comparisons

A.1. Degludec vs. Detemir

The SR by Holmes et al reported a fair-quality, open-label RCT in adults (N=456) with T1DM that compared degludec (U-100) versus detemir (U-100), both combined with prandial insulin aspart for 26 weeks. Basal insulins were administered in the evening and patients on detemir were allowed addition of a second dose if glycemic control remained inadequate after 8 weeks of titration. At week 26, the
A reduction from baseline in the mean fasting plasma glucose (FPG) was significantly greater with degludec compared to detemir (estimated treatment difference $-1.66 \text{ mmol/L or 30 mg/dL}; 95\% \text{ CI } -2.37, -0.95, P<0.0001$).\textsuperscript{4} Yet, there was no difference between treatment groups in the change of A1c from baseline, A1c level at week 26, or the proportion of patients achieving an A1c<7%.\textsuperscript{4}

The overall rate of confirmed hypoglycemia (with blood glucose [BG]<56 mg/dL), the rate of severe hypoglycemia, and adverse-event profiles were similar between treatments. Nocturnal confirmed hypoglycemia (<56 mg/dL) was lower with degludec (4.14 vs. 5.93 episodes per patient year exposure; rate ratio of 0.66; 95% CI 0.49, 0.88, P=0.0049).\textsuperscript{4} There was a modest weight gain observed with degludec compared to detemir, about 1 kg more (mean gain 1.5 kg vs. 0.4 kg; estimated treatment difference 1.08; 95% CI 0.58, 1.57).\textsuperscript{4}

A.2. Degludec vs. Glargine

Holmes et al SR identified 4 RCTs, representing a patient sum of 1801, which compared degludec U-100 versus glargine U-100.\textsuperscript{6} The SR by Liu et al additionally identified a small cross-over study with 20 patients.\textsuperscript{5} All 5 RCTs included concomitant insulin aspart in each arm. These RCTs were rated fair- to good-quality by Holmes et al and as high-quality per Liu et al.\textsuperscript{5,6} Meta-analyses from both SRs showed no significant difference in A1c control between treatments.\textsuperscript{5,6} Liu et al meta-analysis showed that FPG was significantly lower with degludec compared to glargine (estimated treatment difference $-0.84 \text{ mmol/L or -15 mg/dL}; 95\% \text{ CI } -1.18, -0.51 \text{ mmol/L})$.\textsuperscript{5}

There was no significant difference in the risk of overall hypoglycemia events per patient year;\textsuperscript{5} however, both SRs found that events per patient year of all nocturnal hypoglycemia were significantly lower with degludec compared to glargine (Holmes et al MA rate ratio 0.68; Liu et al MA risk ratio 0.74). No other differences regarding severe hypoglycemia or weight gain were evident.\textsuperscript{5,6}

B. Insulin Detemir (Levemir) Comparisons

B.1. Detemir vs. Glargine

Between two 2018 SRs, 3 RCTs (rated fair or moderate quality) were identified for this comparison showing no difference in A1c control between treatments (either measured by the change in A1c from baseline, or A1c at endpoint).\textsuperscript{5,35} There were mixed results between the 3 RCTs with respect FPG: Heller 2009 and Renard 2011 suggest similar control in FPG between groups (Heller measured FPG at week 52, and Renard measured FPG over the last 8 weeks of each 16 week cross-over period), while Pieber 2007 found that FPG was significantly lower with once daily glargine after 26 weeks (treatment difference of $-0.7 \text{ mmol/L or -12 mg/dL}, P<0.001$).\textsuperscript{36-38}

The 3 trials were consistent in showing no difference in weight gain and overall hypoglycemic risk between treatments.\textsuperscript{36-38} Results from the 52 week RCT by Heller et al showed that the percentage of patients experiencing hypoglycemia, the rate of all hypoglycemic episodes, overall risk of hypoglycemia, and the risk of nocturnal hypoglycemia were similar between treatment groups.\textsuperscript{36} Renard et al showed that the median monthly rate of hypoglycemia and the frequency of severe symptomatic hypoglycemia was similar between groups.\textsuperscript{37} Pieber et al (N=322) showed that overall hypoglycemic episodes, confirmed hypoglycemic episodes, and severe nocturnal hypoglycemic episodes were similar between
treatment groups over the entire treatment period; although when data was analyzed only for the maintenance period (20 week period), the once daily glargine group experienced less episodes of symptomatic nocturnal hypoglycemia, all severe hypoglycemia, and all nocturnal hypoglycemia compared to the twice daily detemir group. Yet, authors did not assess whether this trend was offset by higher rates of hypoglycemia in the glargine group during the titration phase.38

C. Insulin Glargine (Basaglar, Lantus, Toujeo) Comparisons

C.1. Basaglar U-100 vs. Lantus U-100

Three 2018 SRs report outcomes from 1 RCT (ELEMENT 1, Blevins et al 2015) comparing Basaglar to Lantus for use in patients with T1DM.6,30,31,39 There were no differences in the following: reduction in A1c at 24 weeks, proportion of patients achieving an A1c <7.0% or <6.5%, all-cause mortality, hypoglycemia, or severe hypoglycaemia.31,39 For adults with T1DM, Basaglar and Lantus reduced the A1c by about 0.35% to 0.46% from baseline.30

C.2. Glargine U-300 vs. Glargine U-100

Two 2018 SRs found the same 4 RCTs regarding this comparison.6,11 Meta-analyses showed no difference between treatments with respect to A1c at 6 months6 or for the change in A1c.11 Two trials had follow-up out to month 12, both showing no significant difference in A1c at 12 months.6,40,41 Both SRs found no difference in overall risk of nocturnal hypoglycemia in patients with T1DM.6,11 Diez-Fernandez et al also assessed confirmed nocturnal hypoglycemia (< 54 mg/dL) and found a lower rate with U-300 glargine compared to U-100 (rate ratio 0.64; 95% CI 0.42, 0.97). Authors noted there was moderate between-study heterogeneity for this outcome.11 Holmes et al further concluded that these trials provided low-strength evidence showing similar risk of severe hypoglycemia and withdrawals due to adverse events.6

Pediatric Patients with Type 1 Diabetes Mellitus

a. Degludec vs. Detemir

Holmes et al SR identified a fair-quality RCT in children (N=350) with T1DM, with the main phase of the study comparing 26 weeks of degludec U-100 once daily to detemir U-100 once or twice daily (all arms also receiving concomitant prandial insulin aspart).6,42 At week 26, there was no significant difference in the change in A1c from baseline between treatment groups. Most patients in the detemir group (64%) required twice-daily administration to achieve glycemic targets and “after 52 wk of treatment, participants receiving IDeg required 30% less basal insulin, and 18% less insulin overall,”(significance not reported).42

There was more weight gain with degludec compared to detemir, about 0.11 kg, compared to a loss with detemir (treatment difference 0.17 kg, P<0.001).42 The trial authors found that cumulative rates of nocturnal confirmed hypoglycemia and rates of all hypoglycemia at week 52 did not show a difference
between treatments (authors did not report data for the 26 week time point after the main treatment phase).\textsuperscript{42}

b. Degludec vs. Glargine

One poor quality study in 18 children was identified by Holmes et al which showed that after 24 weeks there were no significant differences in the change from baseline in fasting plasma glucose or A1c between once daily glargine or detemir (in combination with unspecified rapid-acting insulin analogs).\textsuperscript{6,43} There was no difference in basal doses between groups.\textsuperscript{43} Authors report that the frequencies of overall hypoglycemia and severe hypoglycemia were similar between groups. Authors go on to conclude that results suggested degludec better reduced nocturnal hypoglycemia risk; yet, authors did not test for significance in the difference between groups at week 12 or 24 weeks, nor did they test for significance in the change from baseline between groups.\textsuperscript{43} In addition, it is unclear if the type of rapid insulin analog was balanced between groups (confounding issue) as this detail was not reported among the baseline characteristic of the populations.

c. Detemir vs. Glargine

Holmes et al identified 1 small (N=15), 12 week, cross-over RCT and rated this study as fair quality.\textsuperscript{6} Holmes et al state that this study provided insufficient evidence to compare the effects of the treatments.\textsuperscript{6} Cherubini et al report that due to detection of carry over effects from the crossover study design, analyses were limited to the first period only.\textsuperscript{44} Treatment effects did not differ with respect to changes in A1c or total daily basal dose; however, glargine was associated with a lower fasting blood glucose level compared to detemir (8.2 ± 1.7 vs. 8.1 ± 1.5 mmol/L, p = 0.01). Incidence rate of confirmed hypoglycemia and confirmed severe hypoglycemia was similar between treatment groups. Detemir was associated with a higher increase in body weight (p=0.008) and height (p=0.02) when compared with glargine.\textsuperscript{44}

Adults with Type 2 Diabetes Mellitus

A. Insulin Degludec (Tresiba) Comparisons

A.1. Degludec vs. Detemir

No studies were found for direct comparison of degludec versus detemir in patients with T2DM (Holmes SR searched up to February 2018); this is consistent with other systematic reviews.\textsuperscript{6,45}

A.2. Degludec vs. Glargine

Holmes et al identified 10 fair-quality RCTs and 1 poor quality RCT, with the total patient sum >13,000. Authors comment that based on 9 RCTs (excluding the poor-quality trial and a phase 2 fair-quality trial), there is high-strength evidence showing no difference in glycemic control between degludec and glargine (based on results from individual studies).\textsuperscript{6} In contrast, Liu et al performed an MA including the phase 2 trial, plus the 9 RCTs included by Holmes, and found a marginal significant difference in the
change of A1c from baseline in favor of glargine (treatment difference was 0.04%, P<0.05, inverse variance model); yet, the overall percentage of patients achieving an A1c <7% was no different between treatment groups and fasting plasma glucose levels were lower with degludec compared to glargine (mean difference −0.34; 95% CI −0.45, −0.23). If we consider that a non-inferiority margin of 0.4% for the change in A1c from baseline to endpoint has been used by the FDA to determine clinically meaningful differences in non-inferiority trials, then this marginal effect (a difference of change in the A1c by 0.04% between the two treatments) is unlikely to be clinically meaningful.

Most trials compared U-100 degludec vs. U-100 glargine, while 2 compared U-200 degludec versus U-100 glargine and both showed no difference in A1c control between treatments. Two of the RCTs included were the DEVOTE trial (by Marso et al 2017) and the SWITCH2 trial (by Wysham et al 2017), accounting for more than 8,000 patients together; both found no difference in A1c at the end of study between degludec and glargine treatment groups.

Additionally, Holmes et al stated that there was moderate-strength evidence showing that treatment with degludec was associated with a lower rate of severe hypoglycemia and nocturnal hypoglycemia compared to glargine: a) meta-analysis for severe hypoglycemia rate (9 RCTs): 3.3% with degludec vs. 5.1% with glargine, relative risk 0.72; 95% CI 0.54, 0.96; I² = 2.5%; b) meta-analysis of nocturnal hypoglycemia rate ratio (8 RCTs) 0.73; 95% CI 0.65, 0.82; I² = 0%. These findings are congruent with the MA findings of Liu et al where meta-analyses showed a lower overall risk in hypoglycemia (risk ratio 0.82; 95% CI 0.73, 0.92) and nocturnal hypoglycemia (risk ratio 0.74; 95% CI 0.66, 0.82) with degludec compared to glargine. There were no differences in mortality rates (low strength of evidence), cancer rates (low strength evidence), cardiovascular events (moderate-strength evidence), rates of withdrawals due to adverse event, or body weight gain between drugs.

A.3. Degludec U-100 vs. Degludec U-200

One open-label trial in 373 patients with T2DM showed that after 22 weeks of treatment there were no significant differences in glycemic control (based on A1c or fasting plasma glucose change from baseline), basal insulin dose, body weight change, confirmed hypoglycemic episodes (by the proportion of patients or the events per patient year), and nocturnal confirmed hypoglycemia.

B. Insulin Detemir (Levemir) Comparisons

B.1. Detemir vs. Glargine

Holmes et al identified 6 fair-quality RCTs and 3 poor-quality RCTs. Based on the fair-quality trials authors concluded that there was low-strength evidence of no difference between treatments with respect to control of A1c or the percentage of patients reaching an A1c<7%. There was no difference in the risk of severe hypoglycemia and nocturnal hypoglycemia based MA analysis of low-strength evidence. There was less body weight gain with detemir (treatment difference -1.2 kg [95% CI -1.5, -0.78]). There was no difference in the risk of cancer (low-strength) between each treatment.
C. Insulin Glargine (Basaglar, Lantus, Toujeo) Comparisons

C.1. Basaglar U-100 vs. Lantus U-100

Three 2018 SRs report outcomes for one RCT (Element 2) comparing Basaglar to Lantus for use in patients with T2DM. There were no differences in the following: reduction in A1c at 24 weeks, fasting plasma glucose, proportion of patients achieving an A1c <7.0% or <6.5%, all-cause mortality, hypoglycemia, or severe hypoglycaemia. For adults with DMT2, Basaglar and Lantus reduced the A1c by about 1.3% from baseline.

C.2. Glargine U-300 vs. Glargine U-100

Diez-Fernandez et al evaluated the Cohen’s d index as the effect size statistic for the difference in the change of A1c between treatments (“Cohen’s d values around 0.2 were considered to be a weak effect, values around 0.5 were a moderate effect, values around 0.8 were a strong effect, and values larger than 1.0 were a very strong effect”). Authors concluded that although results favored U-300 glargine (Effect Size, -0.08, 95% CI -0.15—0.01; 5 RCTs) the effect size seemed negligible from a clinical standpoint. Meta-analysis by Holmes et al showed that A1c at 6 months was similar between treatments; results that went beyond 6 months were mixed as 3 RCTs found no difference in A1c, and 1 trial found a difference.

Holmes et al concluded that there was moderate-strength evidence from 3 RCTs showing a lower MA-pooled rate of nocturnal hypoglycemia with glargine U-300 than with U-100 at 2-6 months (rate ratio of 0.74, 95% CI 0.66, 0.82; I² = 0%), yet not at month 12 (RR 0.78, 95% CI 0.59-1.03; I² = 49%). Diez-Fernandez et al assessed confirmed nocturnal hypoglycemia (≤70 mg/dL) and found a lower risk with U-300 only when using an inverse-variance fixed effects MA method (rate ratio 0.85, 95% CI 0.74, 0.98), however, not no difference was found with the random-effects MA method. In this case, the more conservative estimate produced by the random-effects model seems the more appropriate statistical method considering the statistical heterogeneity (I²=35%) and clinical heterogeneity (eg, patient populations, treatment duration, and concomitant antihyperglycemic agents) between included studies. Additionally, there was no difference in rates of clinically significant nocturnal hypoglycemia ≤54 mg/dL between treatments.

Pregnant Women

There were no RCTs found comparing LAIAs with one another in the population with gestational diabetes or in pregnant women with pre-existing diabetes based on 2 Cochrane reviews published in 2017.
Safety

The most common adverse reaction for the LAIAs include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain.7-10 Of these, hypoglycemia is the most common adverse effect related to insulin use; hypoglycemia risk increases with intensification of glycemic control.1,52 Symptoms can vary across individuals but generally include inability to concentrate, sweating, palpitations, and tremor. Severe hypoglycemia is life-threatening with the potential to cause seizures, coma, and death. Patients may have difficulty realizing they are hypoglycemic (ie, hypoglycemia unawareness), especially patients with longstanding diabetes, recurrent hypoglycemia, diabetic neuropathy, or those prescribed certain medications such as beta-blockers.7-10 There are many factors that can influence the potential for hypoglycemia including but not limited to a history of prior episodes of hypoglycemia, hypoglycemia unawareness, time-action profile of insulin agents (basal and prandial), intensity of insulin regimen, changes in meal pattern, medication changes, illness, or renal/hepatic insufficiency. The patient’s insulin regimen should be regularly re-assessed for potential optimization opportunities in order to meet the changing metabolic needs of patients, especially children, older adults, and pregnant/post-partum women.1,52

Based on our review of head-to-head evidence reported in systematic reviews, as explained in greater detail in the Direct-Comparative Evidence for Long-Acting Insulins section of this report, the following treatment-effect differences were found regarding safety outcomes:

- Degludec was associated with a lower rate of nocturnal hypoglycemia compared to detemir for patients with T1DM4 and compared to glargine for patients with T1DM or T2DM.5,6 Rates of severe hypoglycemia and overall hypoglycemia also appeared lower with degludec in comparison to glargine for patients with T2DM.5,6
- Body weight gain was lower with detemir compared to degludec for patients with T1DM4,42, and compared to glargine for patients with T2DM.6
- Compared to glargine U-100 in adults with T1DM, the U-300 formulation was associated with a lower rate of clinically significant-nocturnal hypoglycemia (BG<54 mg/dL); yet, products were similar with respect to nocturnal hypoglycemia (BG <70 mg/dL), any nocturnal hypoglycemia, and severe hypoglycemia in T1DM.6,11
- Compared to glargine U-100 in patients with T2DM, the U-300 formulation may have a lower rate of confirmed nocturnal hypoglycemia (<70 mg/dL); however, the difference was less clear since the statistical significance depended on the meta-analysis method used (fixed versus random-effects). Additionally, there were no differences found for confirmed nocturnal hypoglycemia (BG <54 mg/dL) or for overall nocturnal hypoglycemia at month 12 for adults with T2DM.6,11

Table 6 summarizes warnings and potential drug interactions pertaining to LAIA therapy.
**Table 6. Warnings for Long-Acting Insulin Analogs**

**Contraindicated** during episodes of hypoglycemia or if patient has hypersensitivity to the insulin analog or any of the product excipients

- Hypokalemia: All insulins can induce intracellular potassium transport, possibly resulting in hypokalemia. Monitor potassium levels in patients at risk of hypokalemia.
- Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZD) and Insulins; exercise close observation for potential signs of heart failure with concomitant TZD administration. Dosage reduction or discontinuation of TZD may be necessary.
- Hyper- or Hypoglycemia: Increase the frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairments and hypoglycemia unawareness
- Hypersensitivity reactions are possible with insulins
- Medication Errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection
- Antibody development: all insulin product can induct formation of anti-insulin antibodies, which may increase or decrease the efficacy of insulin; thus necessitating dose adjustments
- Intensification of insulin therapy or rapid improvement in glucose control has been associated with a transitory and reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy.
- Never share devices between patients, even if the needle is changed; never share or reuse needles or syringes

**WARNINGS UNIQUE TO SPECIFIC PRODUCTS**

*Toujeo (insulin glargine U-300)*: Cardiovascular Safety: although there has been a study showing cardiovascular risk neutrality with glargine U-100, it is unknown if this result is generalizable to U-300 glargine

**DRUGS THAT CAN IMPACT INSULIN NEEDS AND/OR RECognition OF HYPOGLYCEMIA SYMPTOMS**

- Drugs that increase insulin sensitivity and therefore increase potential for hypoglycemia: oral and injectable antidiabetic medications, pramlintide acetate, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.
- Drugs that reduce the effect of insulins: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (eg, epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (eg, in oral contraceptives), protease inhibitors and atypical antipsychotic medications (eg, olanzapine and clozapine).
- Drugs that may have mixed effects (increase or decrease insulin effects): Beta-blockers, clonidine, lithium salts, and alcohol
- Drugs that hide hypoglycemia signs: beta-blockers, clonidine, guanethidine, and reserpine
Summary

The LAIAs are approved for the improvement of glycemic control in adults and children with diabetes mellitus. LAIA dosing is individualized according to the patient’s metabolic needs and glycemic targets. Each LAIA (insulin degludec, detemir, and glargine) is available in a U-100 dosage form either in a vial or pen. Concentrated products include Tresiba (insulin degludec) U-200 FlexTouch and Toujeo (insulin glargine) U-300 SoloStar or Max SoloStar pens. The ADA notes that “[t]hese concentrated preparations may be more comfortable for the patient and may improve adherence for patients with insulin resistance who require large doses of insulin.”

In general, the ADA highlights the importance of individualizing therapy and frames basal insulin options in the context of patient-specific CVD co-morbidities or compelling need to lower hypoglycemia risk or cost. When choosing a basal insulin for patients with cardiovascular disease, heat failure, or chronic kidney disease, prescribers may consider that degludec and U-100 glargine have demonstrated safety in cardiovascular disease; other basal insulin products have not been studied in large prospective cardiovascular outcomes trials. The ADA considers that cost be a consideration in medication choices and when the risk of hypoglycemia is low or when A1c goals are relaxed, authors suggest that patients can be safely treated with lower cost insulins such as NPH and regular human insulin. Otherwise, when patients have a compelling need to minimize hypoglycemia, the ADA treatment algorithm specifies the following basal insulin therapies in order of lowest hypoglycemia risk (degludec/glargine U-300 < glargine U-100/detemir < NPH insulin).

Based on our review of SR evidence, the long-acting insulin analogs appeared to similarly control A1c; however, there were some treatment differences regarding safety outcomes. Degludec may be preferable for patients at higher risk of nocturnal hypoglycemia compared to detemir for patients with T1DM or compared to glargine U-100 for patients with T1DM or T2DM, due to lower nocturnal hypoglycemia event rates. Rates of severe hypoglycemia and overall hypoglycemia appear lower with degludec compared to glargine U-100 for patients with T2DM. Compared to glargine U-100, the U-300 formulation was associated with a lower risk of confirmed nocturnal hypoglycemia (<54 mg/dL) in patients with T1DM; in patients with T2DM, results tended toward a lower risk of confirmed nocturnal hypoglycemia (<70 mg/mL) with U-300 glargine but statistical significance was less clear. Body weight gain appeared lower with detemir (about 1 kg less gain) compared to degludec in adults with T1DM, and compared to glargine in adults with T2DM.
References


26. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 Units . mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units . mL-1. Diabetes Care. 2015;38(4):637-643.


47. 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. *Clinical diabetes : a publication of the American Diabetes Association.* 2017;35(2):90-95.


50. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus(R)) 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.


54. Ritzel R, Harris SB, Baron H, et al. A Randomized Controlled Trial Comparing Efficacy and Safety of Insulin Glargine 300 Units/mL Versus 100 Units/mL in Older People With Type 2 Diabetes: Results From the SENIOR Study. *Diabetes Care.* 2018;41(8):1672-1680.

Appendix A: Medline Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 24, 2018>

Search Strategy

1  insulin, long-acting/ or insulin detemir/ or insulin glargine/ (3107)
2  (((long or basal) adj2 insulin*) or (degludec or detemir or glargine)).ti,ab,kw,kf. (9208)
3  insulin/ and (long-acting or long acting or detemir or degludec or glargine or basal).ti,ab,kw,kf. (14979)
4  (tresiba or leemir or basaglar or lantus or toujeo).ti,ab,kw,kf. (243)
5  Meta-Analysis/ (95003)
6  (metaanaly$ or meta-analy$).ti,ab,kw,kf. (140402)
7  ((systematic adj3 review) or (overview adj4 review)).ti,kw,kf. (97567)
8  (cochrane$ or systematic review?).jw. (16153)
9  (or/5-8) and English.la. (210525)
10  1 or 2 or 3 or 4 (19796)
11  9 and 10 (275) [Systematic Reviews]
### Appendix B: Embase Search Strategy

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Appendix C: Excluded Studies

Wrong Comparators


Wrong Study Design


Not an SR; misses some more recently published RCTs (Lane 2017, Pan 2016, Warren 2017 known of from Liu SR)


Reports only indirect analysis data; also there additional RCTs published more recently not included, as found in Diez et al SR


Authors do not report any direct meta-analysis findings, only mixed and indirect summary estimates


Addresses other study questions (eg, insulin vs. oral therapy, lifestyle)


Study does not include head-to-head comparisons between individual agents (instead reports group summary effect differences)


Not an SR


Not an SR; missed RCT Terauchi et al.
   Not an SR; See Holmes et al SR which includes more data out to 12 months follow-up from additional extension publications of the EDITION trials


   Not an SR

   Not an SR; more recent SRs have additional RCTs not considered in this paper

   Not an SR but good background info


   Authors include some studies that do not have balanced arms with respect to concomitant rapid-acting insulin analogs (confounding issue). Also, repeats some info already captured by Liu et al 2018 SR.

   No direct GLA vs. DET studies are identified by authors, yet there are studies (see Holmes et al SR)

Other

   This is the SR protocol. The 2017 full publication was included

   This was a protocol for a review that was never completed

   This is a notice of withdrawal since the project was not completed in the allotted time frame
**More Up-to-date SR Available**

43. Swinnen SGHA, Holleman F, DeVries JH, Hoekstra JBL. Long-acting insulin analogue versus another long-acting insulin analogue for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2007(1). This is a protocol only; we considered the completed review of 2011 by Swinnen et al.


## Appendix D: Systematic Reviews

### Table 1. Systematic Reviews

<table>
<thead>
<tr>
<th>Study lead author, year</th>
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| Holmes 2018⁶ | **Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: A systematic review and meta-analysis** | **Children with T1DM**

**DEG (U-100 Pen) vs. DET (U-100 Pen)** (1 open-label RCT (Thalange 2015), N=350, study rated fair-quality):
- No differences in A1c change from baseline after 26 weeks
- There was more body weight with degludec than with detemir (gain of 0.11 kg with degludec compared to loss of 0.06 kg with detemir (estimated treatment difference of 0.17, 95% CI 0.1, 0.25).
- Holmes et al state “[t]he evidence was insufficient to compare hypoglycaemia or withdrawals because of adverse events between degludec and detemir.”

**DEG vs. GLA** (1 small randomized cross-over study (Urakami 2017), rated as poor-quality; N=18)
- No differences in A1c change or FBG change from baseline after 24 weeks of treatment
- There was no significant change in body weight or basal doses with either degludec or glargine versus baseline values.
- Study authors compared hypoglycemia rates to baseline values and report significant improvement in the DEG arm, however, not in the GLA arm. Nonetheless, authors don’t state whether rates were different between groups at week 24.
- There were no events of severe hypoglycemia or other adverse events besides mild hypoglycemia associated with the use of these agents during the study.

**DET vs. GLA** (1 small (N=15) 12 week cross-over RCT rated fair quality, Cherubini)
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**DEG (U-100 Pen) vs. DET (U-100 Pen)** (1 open-label RCT (Davies 2014), rated fair-quality; N=456):
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- There was more body weight gain with degludec than with detemir (mean gain 1.5 vs. 0.4 kg, estimated treatment difference of 1.08, 95% CI 0.58, 1.57)
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<tr>
<td><strong>Holmes 2018</strong>^5</td>
<td><strong>DEG (U-100) vs. GLA (U-100)</strong> (4 RCTs: Birkeland 2011, Heller 2012, Mathieu 2013, Lane 2017, studies rated fair or good quality, treatment for 16 to 2 years; 1801 patient sum from the 4 RCTs):**</td>
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<td><strong>A1c:</strong> Meta-analysis by Holmes et al showed no difference in A1c change from baseline (from 3 RCTs, parallel design). The single RCT with cross-over design reported no difference between groups after 32 weeks of treatment in the A1c at treatment end. Holmes et al conclude these 4 RCTs provide moderate-strength evidence that there is no difference in the effect on A1c control between treatments.**</td>
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<td></td>
<td><strong>Nocturnal hypoglycaemia:</strong> Meta-analysis of the 4 RCTs showed rates were less frequent with degludec than with glargine (pooled rate ratio 0.68; 95% CI 0.56-0.81; I² = 53%), and the difference persisted over 2 years in one trial.</td>
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<td></td>
<td><strong>Weight gain:</strong> Meta-analysis of the 4 RCTs showed no difference.</td>
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<td>“Evidence was insufficient to compare other adverse events in patients with type 1 diabetes.”</td>
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<tr>
<td><strong>DET vs. GLA</strong> (2 RCTs; Heller 2009, Pieber 2007; total patient sum of 763, with treatment from 26 to 52 weeks; rate fair-quality)</td>
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<td></td>
<td>The 2 trials each showed no difference in glycemic control between treatments (low-strength evidence)</td>
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<td></td>
<td>o Heller et al 2009 (N=443) showed no difference in A1c, change from baseline of A1c, mean FPG, or percentage of patients reaching A1c&lt;7% without major hypoglycemia at week 52. There was no difference in basal doses or weight gain at the end of the trial. Percentage of patients experiencing hypoglycemia, rate of all hypoglycemic episodes, overall risk of hypoglycemia, and the risk of nocturnal hypoglycemia were similar between groups.(^36)</td>
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<td>o Pieber 2007 (N=320) showed no difference in A1c between treatment groups after 26 weeks, however FPG was significantly lower with glargine at week 26 (treatment difference of -0.7 mmol/L, P&lt;0.001). There was no difference in weight gain, overall hypoglycemic episodes, confirmed hypoglycemic episodes, severe nocturnal hypoglycemic episodes; however, difference in favor of detemir were seen if analyzing data only for the maintenance period with respect to symptomatic nocturnal hypoglycemia, severe hypoglycemia, and all nocturnal hypoglycemia.(^38)</td>
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<tr>
<td></td>
<td>• There was no difference in adverse-event related withdrawals (thought to be due to study drug) between treatment groups, body weight gain, risk of severe hypoglycemia, or nocturnal hypoglycemia.</td>
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</tr>
</tbody>
</table>
Table 1. Systematic Reviews

<table>
<thead>
<tr>
<th>Study lead author, year</th>
<th>Title and Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes 2018⁶</td>
<td></td>
<td>• Note that authors missed Renard 2011 that was identified by Dawoud et al 2018; not sure why since it is referenced in Medline</td>
</tr>
<tr>
<td></td>
<td>GLA U-300 vs. GLA U-100 (4 fair-quality RCTs [Home 2015, Matsuhia 2016, Jinnouchi 2015, Bergenstal 2017]; patient sum of 871 with treatment up to 12 months)</td>
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<td></td>
<td></td>
<td>• No differences in glycaemic control at 6 months (MA weighted mean treatment difference in A1c at 6 months 0.02%, 95% CI −0.10, 0.15%; I² = 25.6%). Two trials with follow-up to month 12, also reported no difference.</td>
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<td></td>
<td></td>
<td>• No differences (low-strength evidence) for severe hypoglycaemia and withdrawals because of adverse events, and moderate-strength evidence for no difference in nocturnal hypoglycaemia.</td>
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<tr>
<td></td>
<td>Adults with T2DM</td>
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<td></td>
<td>DEG U-100 vs. DEG U-200: 1 study (Bode 2014) was found but authors state there was insufficient evidence to compare benefits or harms between treatments. After reviewing the full-text of Bode et al 2014, there were no efficacy or safety difference found between the treatments.⁴⁹</td>
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<tr>
<td></td>
<td>DEG vs. DET: No studies were found for degludec versus detemir in patients with T2DM. SRs searched up to February 2018.</td>
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<td></td>
<td>DEG (U-100 or U-200) vs. GLA (U-100) (10 fair quality RCTs (Garber 2012, Gough 2013, Marso 2017, Meneghini 2013, Onish 2013, Pan 2016, Zinman 2012, Zinman 2011, Wysham 2017, Warren 2017) and 1 poor quality RCT (Aso 2017); &gt;13,000 patient sum from the 10 RCTs, treatment for 16 weeks to 2 years):</td>
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<td></td>
<td>• A1c: “Nine trials provided high-strength evidence that glycaemic control did not differ between patients treated with degludec and glargine.”⁶ Six of these include the DEVOTE trial (Marso 2017) and SWITCH2 (Wysham 2017) accounting for more than 8000 together and each finding no difference in A1c between DEG and GLA treatment at the end of study.</td>
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<td></td>
<td>• Nine trials provided moderate-strength evidence that there is a lower rate of severe and nocturnal hypoglycemia with DEG.</td>
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<tr>
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<td>o Meta-analysis of severe hypoglycemia rate (9 RCTs): 3.3% with DEG vs. 5.1% with GLA, pooled RR 0.72, 95% CI 0.54-0.96; I² = 2.5%;</td>
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<tr>
<td></td>
<td>o Meta-analysis of nocturnal hypoglycemia rate: rate ratio of episodes per patient year (RR) 0.73, 95% CI 0.65-0.82;I² = 0%, in favor of DEG</td>
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</table>
Table 1. Systematic Reviews

<table>
<thead>
<tr>
<th>Study lead author, year</th>
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<tbody>
<tr>
<td>Holmes 2018⁶</td>
<td></td>
<td>• There were no difference in mortality rates (low strength of evidence), cancer rates (low strength evidence, cardiovascular events (moderate-strength evidence), rates of withdrawals due to adverse event, or body weight gain between drugs</td>
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<td></td>
<td>DET vs. GLA (9 RCTs, 6 were fair-quality and the 3 more recent studies were poor quality [Hollander 2008, Raskin 2009, Rosenstock 2008, Swinnen 2010, Fadini 2011, Meneghini 2013, Cander 2014, Elisha 2016, Makino 2016])</td>
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<td></td>
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<td>• From the 6 fair-quality trials authors concluded that there was low-strength evidence of no difference in glycemic control or the percentage of patients reaching an A1c&lt;7% between treatments</td>
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<tr>
<td></td>
<td></td>
<td>• Risk of withdrawing from study due to adverse event (authors didn’t define relation to treatment drug or for other reason) in favor of glargine per MA RR of 2.13 (95% CI 1.38,3.28)</td>
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<tr>
<td></td>
<td></td>
<td>• Risk of severe and nocturnal hypoglycemia: low-strength of evidence showing no difference between treatments based on MA of RCTs.</td>
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<tr>
<td></td>
<td></td>
<td>• Body weight gain was more less with detemir (treatment difference -1.2kg (CI -1.5,-0.78)</td>
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<tr>
<td></td>
<td></td>
<td>• Low-strength of evidence that there was no difference with respect to risk of cancer</td>
</tr>
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<td></td>
<td>GLA U-300 vs. GLA U-100 (4 fair-quality RCTs, patient sum of 2718)</td>
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<td></td>
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<td>• Note that the SR by Diez et al 2018 has a more updated literature search, resulting in an additional RCT (Ritzel 2018)⁵⁴ not captured by Holmes et al.</td>
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<tr>
<td></td>
<td></td>
<td>• The 4 RCTs provided moderate-strength evidence that both agents similarly control A1c by month 6 months based on MA (weighted mean difference in A1c at month 6: 0.04%, CI−0.05, 0.12%; I² = 0%). At month 12, results were mixed as 3 RCTs found no difference in A1c, and 1 trial found a difference.</td>
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<td></td>
<td></td>
<td>• There was moderate-strength evidence from 3 RCTs showing lower rates of nocturnal hypoglycemia with glargine U300 than with glargine U100 at 2-6 months (37% vs. 50%; pooled RR 0.74; 95% CI 0.66-0.82; I² = 0%), yet not at month 12 (RR 0.78, 95% CI 0.59-1.03; I² = 49%).</td>
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</tbody>
</table>

Notes:
• Importantly, authors kept trials comparing fixed-dose degludec/aspart 70/30 versus glargine separate from results and meta-analysis of trials comparing DEG vs. GLA where antihyperglycemic drugs were more balanced among treatment arms. |
• Liu et al 2018 SR also identified the same 4 RCTs for DEG versus GLA in T1DM adults
Table 1. Systematic Reviews

<table>
<thead>
<tr>
<th>Study lead author, year</th>
<th>Title and Methods</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Liu 2018</td>
<td><em>Efficacy and Safety of Insulin Degludec versus Insulin Glargine: A Systematic Review and Meta-Analysis of Fifteen Clinical Trials</em></td>
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<td></td>
<td>Searched PubMed, EMBASE, and Cochrane Library electronic databases were searched for studies published up to July 15, 2017</td>
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<td></td>
<td>Included RCTs of at least 12-weeks, with patients having T1DM or T2DM, comparing effect of once daily degludec versus glargine (once or twice daily)</td>
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<td></td>
<td>Exclusion studies with DEG co-formulated with other hypoglycemic agents [this is a main difference from Zhang et al 201855 SR], arms with DEG injected three times per week</td>
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<tr>
<td></td>
<td>Funding: National Clinical Key Specialty Construction Project of China and Clinical Research Center Project of the Department of Science and Technology of Guizhou Province</td>
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<tr>
<td>Adults with Type 1 DM</td>
<td><strong>DEG vs. GLA</strong> (5 RCTs, all rated high-quality per Jadad scale; Birkeland 2011, Heller 2012, Mathieu 2013, Lane 2017, Iga 2017)</td>
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<td></td>
<td>• Note: Holmes et al SR did not include Iga 2017</td>
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<td></td>
<td>There were significant differences found for the following outcomes:</td>
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<td></td>
<td>- change of fasting plasma glucose in favor of degludec (with lower levels), mean difference $-0.84 \text{ (} -1.18, -0.51)$</td>
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<td></td>
<td>- nocturnal hypoglycemia: risk ratio in favor of degludec, RR $0.74 \text{ (} 0.68, 0.81)$</td>
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<td>There were no differences based on MA for the following outcomes: A1c change from baseline, % of participants achieving A1c&lt;7%, body weight change, risk of overall hypoglycemia, odds of adverse events, odds of serious adverse events, and odds of adverse events possibly/probably due to the trial product</td>
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<td></td>
<td>There were significant differences found for the following outcomes:</td>
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<td>- <em>A1c change from baseline</em>: marginal difference in favor of glargine (mean difference $0.04, 95% \text{ CI - 0.00, 0.07, } \text{ P=0.04}$)</td>
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<td></td>
<td>- change of fasting plasma glucose in favor of degludec (with lower levels), mean difference $-0.34 \text{ (} -0.45, -0.23)$</td>
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<td></td>
<td>- overall risk of hypoglycemia: risk ratio (RR) in favor of degludec, RR $0.82 \text{ (} 0.73, 0.92)$</td>
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<td></td>
<td>- nocturnal hypoglycemia: risk ratio in favor of degludec, RR $0.74 \text{ (} 0.66, 0.82)$</td>
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<tr>
<td></td>
<td>There were no differences based on MA for the following outcomes: % of participants achieving A1c&lt;7%, body weight change, odds of adverse events, odds of serious adverse events, and odds of adverse events possibly/probably due to the trial product</td>
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Table 1. Systematic Reviews

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<thead>
<tr>
<th>Study lead author, year</th>
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</thead>
</table>
| **Dawoud 2018**         | Basal Insulin Regimens for Adults with Type1 Diabetes Mellitus: Systematic Review and Network Meta-Analysis | Note: since the literature search of this SR is more dated compared to some more recent SRs, authors miss a few more recently published studies for a few comparisons:  
  a. **DEG vs. DET** Authors do not include Davies et al 2014  
  b. **DEG vs. GLA** Authors do not include Lane et al 2017  
  c. **DET vs. GLA** Authors do not include Pieber 2007  
  Thus, for comparison a. and b., Holmes et al SR will be the focus since it is more up-to-date in these areas. However, for comparison c., 1 RCT (Renard 2011) found by Dawoud et al was not included in Holmes et al, so will be incorporated into our discussion regarding this comparison.  
  **DET vs. GLA** (2 RCTs, Renard 2011, Heller 2009; moderate quality)  
  o Heller et al 2009 (N=443) showed no difference in A1c, change from baseline of A1c, mean FPG, or percentage of patients reaching A1c<7% without major hypoglycemia at week 52. There was no difference in basal doses or weight gain at the end of the trial. Percentage of patients experiencing hypoglycemia, rate of all hypoglycemic episodes, overall risk of hypoglycemia, and the risk of nocturnal hypoglycemia were similar between groups.  
  o Renard et al 2011 (N=135) showed no significant difference in glycemic control (A1c change from baseline, FBG over the last two months of treatment), weight gain, or median monthly rate of hypoglycemia, and frequency of severe symptomatic hypoglycemia. Nocturnal hypoglycemia was not assessed separately. |
| **Tieu 2018**           | Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review | Tieu et al report outcomes from individual studies without performing a meta-analysis  
  **Efficacy**  
  **Basaglar (LY2963016) vs. Lantus**  
  • No significant difference found for the relative reduction in A1c by week 24 between treatment groups for patients with either T1DM or T2DM  
  **Adults with T1DM**: 1 RCT (Blevins 2015); The change in A1c at week 24 with Basaglar was -0.35 (SD 0.05) and with Lantus was -0.46 (SD 0.05). The mean difference between treatment groups was not significantly different.  
  **Adults with T2DM**: 1 RCT (Rosenstock, 2018); The change in A1c at week 24 with Basaglar was -1.29 (SD 0.06) and with Lantus was -1.34 (SD 0.06). The mean difference between groups was not significantly different. |
Table 1. Systematic Reviews

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<th>Study lead author, year</th>
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<tr>
<td></td>
<td>Including randomized controlled trials (RCTs) comparing safety and efficacy of any biosimilar insulin with a reference product. Excluded insulin pump studies. Participants were adults with type 1 or 2 diabetes.</td>
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<tr>
<td>Basaglar vs. Lantus</td>
<td>Searched MEDLINE, Embase, and Cochrane library to December 2017. Also searched Clinicaltrials.gov, and the databases of major diabetes conferences. Included randomized controlled studies of the biosimilar versus originator insulins. Outcomes included for the clinical efficacy primary outcome was the change in glycated haemoglobin (HbA1c) from baseline) and hypoglycemia for the safety primary outcome. Participants were adult patients (aged ≥18 years) with type 1 or type 2 diabetes.</td>
<td>Basaglar vs. Lantus No significant differences between insulin glargine biosimilar (Basaglar) and originator (Lantus), based on 2 RCTs (ELEMENT 1, Blevins 2015; and ELEMENT 2, Rosenstock 2015) in T1DM and T2DM respectively. Individual study results were provided for the difference in the treatment effect for the following outcomes: HbA1c at 24 weeks, fasting plasma glucose, hypoglycemia, severe hypoglycemia, and all cause mortality.</td>
</tr>
<tr>
<td>Study lead author, year</td>
<td>Title and Methods</td>
<td>Results</td>
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<tr>
<td>Diez-Fernandez 2018</td>
<td><em>Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1 and type 2 diabetes: a systematic review and meta-analysis</em></td>
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<td>Searched MEDLINE, EMBASE, CENTRAL, and Web of Science from their inception until July 4th, 2018</td>
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<td>Included RCTs in any stage with adults diagnosis with DM, reporting rate ratio or number of events of nocturnal hypoglycemia (from 00:00 to 05:59 h); A1c effects; comparison of Gla-300 and Gla-100; with hypoglycemia definitions by the American Diabetes Association (ADA)</td>
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<td></td>
<td>Funding: none from public, non-profit, or commercial sectors</td>
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**Adults with T1DM**

**GLA U-300 vs. GLA U-100** (4 RCTs; Bergenstall 2017, Home 2017, Matsuhisa 2016, Jinnouchi 2015) One of these was less than 12 weeks (Jinnouchi 2015)
- Rate ratio of confirmed nocturnal hypoglycemia ≤70 mg/dL (4 RCTs): MA showed no significant difference between treatments
- Rate ratio of clinically significant nocturnal hypoglycemia ≤54 mg/dL (4 RCTs): MA result was in favor of U-300, rate ratio 0.64 (95% CI 0.42, 0.97)
- Effect difference for the change in A1c (4 RCTs): MA showed no significant difference between treatments

**Adults with T2DM**

**GLA U-300 vs. GLA U-100** (5 RCTs; Ritzel 2018, Riddle 2015, Bolie 2017, Terauchi 2017, Yki-Jarvinen 2015; with 12 to 24 weeks of treatment)
- Rate ratio of confirmed nocturnal hypoglycemia ≤70 mg/dL (5 RCTs): MA showed no significant difference between treatments with DerSimonian and Laird randomi-effects method, but when using inverse-variance, fixed-effects method, there was a significant difference (RR 0.85, 95% CI 0.74, 0.98)
- Rate ratio of clinically significant nocturnal hypoglycemia ≤54 mg/dL (5 RCTs): MA results showed no significant difference
- Effect difference for the change in A1c favored U-300 (4 RCTs): (-0.08, 95% CI -0.15—0.01), however effect size was considered not clinically significant by the authors.
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<tr>
<th>Study lead author, year</th>
<th>Title and Methods</th>
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<tr>
<td>Ovalle 2017&lt;sup&gt;21&lt;/sup&gt;</td>
<td><strong>Understanding concentrated insulins: a systematic review of randomized controlled trials</strong>&lt;br&gt;Search of Medline, Embase, CENTRAL, searched Trialtrovel Pharma Intelligence, ClinicalTrials.gov from January 2000 to April 2016&lt;br&gt;Includes RCTs, published in English, of phase 1–4 clinical studies using concentrated insulins</td>
<td>Ovalle et al. shows that there are no head-to-head RCTs of concentrated insulins versus the U-100 counterpart (e.g., glargine U-100 vs glargine U-300). Double check this is correct</td>
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<tr>
<td>O’Neill, 2017&lt;sup&gt;51&lt;/sup&gt;</td>
<td><strong>Different insulin types and regimens for pregnant women with pre-existing diabetes (Review)</strong>&lt;br&gt;Search CENTRAL, MEDLINE, Embase, CINAHL, hand searched 30 journals and conference abstracts; also searched Cochrane Pregnancy and Childbirth’s Trials Register by contacting their Information Specialist. Searched literature through October 2016&lt;br&gt;Includes studies RCTs and cluster randomized trials. Excluded quasi-randomized controlled trials and those using cross-over design.</td>
<td><strong>Pregnant Women with Pre-Existing Diabetes</strong>&lt;br&gt;• No RCTs were found comparing LAIA with one another in pregnant women with pre-existing diabetes</td>
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</table>
Participants of interest included women with pre-existing diabetes (type 1 or 2), regardless of age or parity. Excluded women with GDM.

Brown 2017

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<tr>
<th>Study lead author, year</th>
<th>Title and Methods</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Brown 2017(^{34})</td>
<td><em>Insulin for the treatment of women with gestational diabetes</em></td>
<td>Gestational Diabetes Mellitus</td>
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</table>

Searched Cochrane Pregnancy and Childbirth’s Trials Register (1 May 2017; which includes reference that have been extracted from CENTRAL, MEDLINE, Embase and CINAHL), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) (1 May 2017) and reference lists of retrieved studies in 2017.

Included RCTs comparing different insulin analogues for treating women with diagnosed GDM. Excluded cross-over trials, quasi-randomized trials, and patients with pre-existing type 1 or type 2 diabetes.

Authors found no studies comparing long-acting insulin analogs with one another.

Abbreviations: A1C, glycated hemoglobin; CSII, continuous subcutaneous insulin infusion with type 1; DMT1, diabetes mellitus type 1; GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c; LAIA, long acting insulin analogs; MDI, multiple daily injections; PPG, post prandial glucose; RAIA, rapid acting insulin analog; RCT, randomized controlled trial; RHI, regular human insulin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
Appendix E: Summary of Treatment-Effect Differences

This section summarizes the outcomes for which significant differences were found consistently among RCTs and SR/MA. The section of the report, Direct-Comparative Evidence for Long-Acting Insulin Analogs, and Table 1 of Appendix D provides more detailed information regarding these studies, along with additional evidence showing agents were similar for certain outcomes or where there were mixed or inconsistent findings (some RCTs finding a difference and some finding agents to be similar for the same outcome).

Degludec vs. Detemir

- For adults with T1DM, a single RCT was found (N=456).\(^4,6\) This 26 week, parallel group, RCT reported the following significant differences between degludec U-100 and glargine U-100: a) at week 26, the reduction in mean fasting plasma glucose (FPG) from baseline was significantly greater with degludec (estimated treatment difference $-1.66$ mmol/L; 95% CI $-2.37$, $-0.95$), b) the rate of nocturnal confirmed hypoglycemia (<56 mg/dL) was lower with degludec (rate ratio of 0.66; 95% CI 0.49, 0.88), and c) a modest weight gain was observed with degludec compared to with detemir (estimated treatment difference 1.08 kg; 95% CI 0.58, 1.57).\(^4\) No differences were found between treatment groups with respect to the change in A1c from baseline, the A1c level at week 26, the proportion of patients achieving an A1c<7%, the rate of confirmed hypoglycemia, or the rate of severe hypoglycemia.\(^4\)

- In children with T1DM, after 52 weeks, there was a small but significant difference in weight gain observed with degludec compared to with detemir: about 0.11 kg gain with degludec compared to a loss with detemir (treatment difference 0.17 kg, $P<0.001$) based on a single fair-quality RCT (N=350) available for this population.\(^4,42\)

Degludec vs. Glargine

- Regarding adults with T1DM, a 2018 meta-analysis (Liu et al) of 5 RCTs showed that FPG was significantly lower with degludec compared to glargine at treatment end (treatment difference $-0.84$ mmol/L or $[-14$ mg/dL]; 95% CI $-1.18$, $-0.51$ mmol/L); although, meta-analyses from Liu et al and Holmes et al SRs both showed no difference between treatments with respect to A1c control.\(^5,6\) Both SRs also found nocturnal hypoglycemia was significantly lower with degludec compared to glargine (Holmes et al MA rate ratio (RR) 0.686; Liu et al MA RR 0.745); yet, there were no differences with respect to the rate of overall hypoglycemia or severe hypoglycemia.\(^5,6\)

- Two SRs reported mixed findings regarding whether degludec treatment results in better A1c control compared to glargine for adults with T2DM.\(^5,6\) The meta-analysis by Liu et al found a marginal significant difference in the change of A1c from baseline in favor of glargine (mean difference 0.04%, using a fixed effects model); yet, this difference is unlikely to be clinically meaningful considering a non-inferiority margin of 0.4% in the change in A1c (from baseline to endpoint) has been used by the FDA to determine clinically meaningful differences in non-inferiority trials.\(^46\) Additionally, the overall percentage of patients achieving an A1c <7% was no different between treatment groups.\(^5\)
Liu et al also found fasting plasma glucose levels were lower with degludec compared to glargine (mean treatment difference $-0.34$; 95% CI $-0.45$, $-0.23$). This differs from Holmes et al SR that reported high-level evidence showing no difference in glycemic control between the two agents (based on results from individual RCTs and not by MA). Finally, Holmes et al found moderate-strength evidence showing that treatment with degludec was associated with a lower rate of severe hypoglycemia and nocturnal hypoglycemia compared to glargine: a) meta-analysis for severe hypoglycemia (9 RCTs) relative risk 0.72; 95% CI 0.54, 0.96; b) meta-analysis of nocturnal hypoglycemia rate ratio (8 RCTs) 0.73; 95% CI 0.65, 0.82. These findings are congruent with the MA findings of Liu et al SR/MA which showed a lower overall risk in hypoglycemia (risk ratio 0.82) and nocturnal hypoglycemia (risk ratio 0.74) with degludec compared to glargine.

**Detemir vs. Glargine**

- Based on 3 RCTs found for adults with T1DM, overall rates of hypoglycemia and nocturnal hypoglycemia appear similar between treatments. Of note, the differences found in 1 RCT represents select data for the maintenance period only. Pieber et al showed that overall hypoglycemic episodes, confirmed hypoglycemic episodes, and severe nocturnal hypoglycemic episodes were similar between treatment groups over the entire treatment period. When data was analyzed only for the maintenance period, the once daily glargine group experienced less episodes of symptomatic nocturnal hypoglycemia, all severe hypoglycemia, and all nocturnal hypoglycemia compared to the twice daily detemir group; however, authors did not assess whether this is offset by higher rates of hypoglycemia in the glargine group during the titration phase.
- For adults with T2DM, Holmes et al SR/MA of 6 fair-quality RCTs found body weight gain was less with detemir compared to glargine (treatment difference -1.2 kg; 95% CI -1.5, -0.78). All three RCTs in adults with T1DM were consistent in showing no difference in weight gain for this population.

**Glargine U-300 vs. Glargine U-100**

- Diez-Fernandez et al found a lower rate of nocturnal hypoglycemia (< 54 mg/dL) with U-300 glargine compared to U-100 in adults with T1DM (rate ratio 0.64 [95% CI 0.42, 0.97] via DerSimonian and Laird method); authors note that there was moderate between-study heterogeneity for this outcome.
- Regarding adults with T2DM, Holmes et al concluded that there was moderate-strength evidence from 3 RCTs showing a lower MA-pooled rate of nocturnal hypoglycemia with glargine U-300 than with U-100 at 2-6 months (rate ratio of 0.74; 95% CI 0.66, 0.82; $I^2 = 0\%$), yet not at month 12 (RR 0.78; 95% CI 0.59, 1.03; $I^2 = 49\%$). Diez-Fernandez et al assessed confirmed nocturnal hypoglycemia ($\leq70$ mg/dL), finding a lower risk with U-300 when using inverse-variance, fixed-effects method for meta-analysis (rate ratio 0.85, 95% CI 0.74, 0.98); however, there was no difference if using the DerSimonian and Laird, random-effects method ($I^2=35\%$), a more conservative approach if the true effect varies between studies (considering clinical heterogeneity). In this case, DerSimonian seems more appropriate considering some differences in patient populations, treatment duration, and concomitant treatments between studies. Authors also concluded that although results tended to favor U-300 with respect to the change in A1c, the very small Cohen’s d effect size statistic of -0.08 seemed negligible from a clinical standpoint.