NEW BASAL INSULINS

Insulin degludec
(Tresiba®)

Insulin glargine
(Lantus®, Toujeo®, Basaglar®)

Insulin detemir
(Levemir®)
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Introduction

In the United States, 29.1 million people (9.3% of the U.S. population) have diabetes. In 2012, the estimated diabetes costs in the United States were $245 billion; direct medical costs were $176 billion, and indirect costs were $69 billion (disability, work loss, premature death).

Patients with type 1 diabetes (T1DM) require insulin treatment due to a lack of insulin. Insulin options include rapid-acting, short-acting, intermediate-acting, long-acting, and premixed insulin. In T1DM, insulin therapy regimens usually include a basal insulin with pre-meal, rapid-acting insulin injections. Type 2 diabetes mellitus (T2DM) results from reduced insulin secretion or cellular insulin resistance. Therefore, the mechanisms of action of the medications for type 2 diabetes include stimulating insulin release, decreasing absorption or hepatic production of glucose, and improving the insulin sensitivity of target organs. Oral agents become less effective as beta cell function declines and it may be necessary to add an injectable medication such as insulin (or to switch to insulin) to manage blood glucose levels. Estimates of the proportion of patients achieving a target HgbA1c (glycosolated hemoglobin) of <7% varies considerably for the different treatments, ranging from 26% with α-glucosidase inhibitors to 63% with the GLP-1 (glucagon-like peptide-1) agonist, exenatide. Basal insulins achieved target HgbA1c (A1C) in 39% of individuals and basal-bolus regimens achieved A1C target in 50% of individuals.

A1C is a predictor of diabetes complications; higher A1C levels increase the likelihood of both microvascular and macrovascular complications (including renal, ophthalmic, neurologic and cardiovascular). According to current guidelines, A1C target levels range from <6.5% to <7%, although individualized goals may be higher (based on diabetes duration, age/life expectancy, comorbid conditions, known cerebrovascular disease or microvascular complications, risk of hypoglycemia, and other individual patient considerations). Initially in T2DM, a trial of lifestyle modifications (such as medical nutrition therapy, weight loss, exercise and diabetes education) is recommended, but pharmacotherapy is often required due to persistent elevated glucose levels. Insulin and sulfonylureas have been available since the early 1920's and the 1950's respectively, and until 1995, these were the only available drug classes for patients affected by type 2 diabetes. Currently, 12 classes of medications are FDA-approved for treating type 2 diabetes, including biguanides (e.g. metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, amylin analogue, bromocriptine (dopamine agonist), alpha-glucosidase inhibitors, the bile acid sequestrant colesvelam, insulins, and the sodium-glucose co-transporter inhibitors (SGLT2).

Insulin is indicated in the treatment of type 1 diabetes, type 2 diabetes, diabetes during pregnancy (preexisting and gestational), and in some patients without diabetes (e.g. glucose control in critical care or sepsis treatment). Insulin functions to suppress hepatic glucose production, lipolysis, proteolysis, gluconeogenesis and promote glycogen synthesis and transport of glucose into adipocytes and myocytes. Basal insulin secretion accounts for 40% of the body’s daily insulin secretion. Basal insulin secretion inhibits hepatic glycogenolysis, ketogenesis and gluconeogenesis.

Early integration of insulin into the treatment of T2DM may preserve β-cell function, improve insulin sensitivity and slow disease progression. Insulin is available as recombinant human insulin...
(regular and NPH) and modified insulin analogs with rapid onset (e.g. insulin lispro, insulin aspart, insulin glulisine), short-acting (insulin regular), intermediate-action (NPH), long-acting/extended duration (e.g. insulin glargine, insulin detemir, insulin degludec) or in combination (e.g. insulin degludec + insulin [7/30], NPH + regular insulin [70/30, 50/50], insulin lispro protamine + insulin lispro [75/25, 50/50], and insulin aspart protamine + insulin aspart [70/30]).\textsuperscript{26,27} All long-acting, basal insulins are available in prefilled disposable pens.\textsuperscript{28-32} Levemir and Lantus are additionally available in 10 mL vials.\textsuperscript{30,32}

Insulin is usually administered subcutaneously (90-degree angle to skin) in the abdomen, outer thigh, back of arm, or flank/buttocks.\textsuperscript{21} Insulin may be administered with disposable plastic syringes (1.0, 0.5, and 0.3 mL sizes) or via insulin pens. Injection sites should be rotated to avoid lipo hypertropy and the needle should be left in place for 5-10 seconds after injecting to avoid leaking.\textsuperscript{21} Insulin injections in the abdominal wall are absorbed most rapidly and may be preferred for pre-meal injections while absorption from the leg or buttock occurs more slowly and may be appropriate with evening administration of intermediate-acting insulin.\textsuperscript{5} Glycemic control is affected by many factors including the type of insulin (onset, peak, activity, duration), preparation, the size of the subcutaneous depot, injection site and subcutaneous blood flow.\textsuperscript{8} Inter- and intra-patient absorption variability of 25-50\% is reported for all insulin preparations, especially for longer acting insulins.\textsuperscript{5} The safe and effective use of insulin requires patients or caregivers to have visual acuity, adequate motor skills for use of insulin syringes or pens, and cognitive ability.\textsuperscript{33,34}

Dose-taking compliance statistically differed when patients with diabetes were assigned ≥3 doses of any therapy per day.\textsuperscript{35} Using the Morisky-Green questionnaire (self-administered), the best compliance (67\%) was found in patients receiving insulin monotherapy and lowest in patients receiving combination insulin and oral antihyperglycemic medications (39\%).\textsuperscript{36} Nonadherence to any initial diabetes regimen increased the rate of hospitalization and Emergency Department (ED) visits by 13\% compared with adherent patients.\textsuperscript{37} Conversely, patients who were initially adherent and become nonadherent demonstrated a 15\% increased rate of hospital and ED utilization versus adherent patients.\textsuperscript{37} Adherence improves when patient’s emotional well being is considered and they understand the treatment regimen and benefit (especially for complex regimens), adverse effects and medication costs.\textsuperscript{38} Strategies associated with improved adherence include lessening regimen complexity to reduce the risk of hypoglycemia and adverse reactions.\textsuperscript{38} Patient compliance remains an unresolved issue for insulin administered via subcutaneous injection, thus several other delivery systems have been under investigation including buccal, oral, rectal, ocular, nasal, and transdermal routes.\textsuperscript{39,40}

- Utah Medicaid instituted a Prior Authorization (PA) for use of insulin pens on 3/1/13 which was rescinded in December 2016. The criteria had included,
  - legal blindness
  - debilitating rheumatoid or osteoarthritis of one or both arms, hands, and/or one or more fingers
  - other conditions causing severe debilitation of one or both arms, hands, and/or one or more fingers
  - reductive deformities of one or both arms, hands, and/or one or more fingers
  - Parkinsonism or essential tremor
  - mental retardation (severe intellectual disability)
any condition that necessitates that a patient, greater-than-or-equal-to the age of 19 years, have a legal guardian other than him/herself”

“Note: patient age of less-than-or-equal-to the age of 18 years is not sufficient justification for approval of insulin pens(s)”.41

The purpose of this review is to ensure appropriate use of long-acting basal insulins (insulin detemir, insulin glargine and insulin degludec). Basal insulin analogues provide peak-less basal insulin coverage with sustained glucose lowering, a low risk of hypoglycemia, possibility of alternate basal insulin dosing schedules and safety in combination with oral hypoglycemic agents. The more concentrated insulin preparations reduce the volume of each injection, limit the number of injections required per dose/day, reduce pain, discomfort, leakage, unpredictable absorption, and may improve adherence and patient satisfaction.42 The availability in pen injectors improves delivery and reduces errors associated with syringe and needle administration.42

**Insulin options**

Appendix 1 contains a product comparison table for the basal insulin analogues degludec, detemir, glargine and the traditional basal insulin, neutral protamine Hagedorn (NPH) insulin.2,3 Appendix 2 contains a pharmacokinetic comparison of the basal insulins. None of the basal analogues are available in generic formulation. Basaglar is a “biosimilar” or “follow-on” insulin of identical amino-acid sequence as insulin glargine.43 According to the FDA, “A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products.”44 Basaglar was found non-inferior to insulin glargine in A1C lowering in both T1DM and T2DM with no difference in dose, mean blood glucose or hypoglycemia.45,46

**Methodology**

A Cochrane Library literature search for systematic reviews was conducted. Medline (PubMed), Embase, UptoDate, the Agency for Healthcare Research and Quality (AHRQ), American Diabetes Association (ADA) website, the FDA website (including product labeled information), Micromedex and Lexicomp were searched for safety information, systematic reviews, clinical trials, and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence-based guidelines were searched for first.

**Clinical Practice Guidelines**

Clinical practice guidelines for treatment of diabetes are available from the American Diabetes Association47, Canadian Diabetes Association48,49, European Association for the Study of Diabetes50, American Association of Clinical Endocrinologists & American College of Endocrinology51 and National Institute for Health and Care Excellence52,53. Patient populations addressed include T1DM, T2DM, pregnancy, children and adolescents, the elderly and hospitals. Safety guidelines and recommendations are available from the Centers for Disease Control and Prevention54,55, Institute for Safe Medication Practices56,57 and National Institute for Health and Care Excellence.58 Clinical practice guidelines for use of long-acting, basal insulin products are presented in Table 1.
All guidelines recommend individualization of the target A1C goal.47,48,51,59 The American Diabetes Association suggests an A1C goal in non-pregnant adults of <7% with a more stringent goal of <6.5% in highly motivated individuals if it may be achieved without significant hypoglycemia (e.g. shorter duration of diabetes, T2DM treated with lifestyle or metformin only, long life expectancy or no significant cardiovascular disease). A less stringent goal 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.14 The Canadian breakpoints for similar patient groups are ≤7%, ≤6.5%, 7.1-8.5%.60 The American Association of Clinical Endocrinologists and American College of Endocrinology suggest two A1C breakpoints.51 A target A1C goal of ≤6.5% is recommended if it can be achieved without significant hypoglycemia or other complications. A target of >6.5-8% is recommended for those in whom the lower threshold cannot be achieved without adverse outcomes. ADA guidelines for glycemic control in the elderly define three A1C breakpoints at <7.5% for the healthy-aged, <8% for the complex/intermediately ill-aged and <8.5% for the very complex aged in poor health.61

T1DM insulin therapy includes subcutaneous insulin infusion administration (SIIA) or basal-bolus therapy. The choice of therapy involves consideration of treatment goals, age, duration of diabetes, lifestyle, diet, general health, motivation, hypoglycemia awareness status, self-management ability, socioeconomic status, financial factors and patient-, family- and provider-preferences. Basal therapy with long-acting analogues (vs NPH) may result in lower fasting plasma glucose levels and less nocturnal hypoglycemia.

In T2DM, insulin therapy is recommended initially if the A1C or blood glucose is high (guidelines differ on the threshold), if the patient has symptomatic hyperglycemia, metabolic decompensation or if diabetes is long-standing. In these instances, initiation of dual therapy may be considered. For other patients, the choice of therapy should consider the degree of hyperglycemia, cardiovascular and end-organ complications, age, patient preference, motivation, access to treatments, effectiveness, risk of hypoglycemia, effects on weight, side effects, contraindications and cost. Lifestyle management is at the core of all diabetes therapy. Metformin remains the preferred initial agent for type 2 diabetes if tolerated and not contraindicated (e.g. glomerular filtration rate above 45 mL/min or significant heart failure). If glycemic goals are not achieved in 3 months with maximally tolerated metformin or alternative non-insulin medication, therapy should advance. A second oral agent (e.g. sulfonylurea, thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonist, sodium-glucose co-transporter 2 (SGLT2) inhibitor or insulin should be added. If the target goal remains unmet, triple therapy is recommended. Most patients will require insulin therapy eventually. Basal analogues (detemir or glargine) compared with NPH may reduce the risk of nocturnal and symptomatic hypoglycemia. The addition of insulin therapy to oral therapy is preferred with a single daily dose of basal insulin. The ADA recommendations state, “people with type 2 diabetes without a history of hypoglycemia may use NPH insulin safely and at a much lower cost.”47 The National Institute for Health and Care Excellence also prefer initial insulin therapy with NPH once or twice daily. The American Association of Clinical Endocrinologist and American College of Endocrinology prefer basal insulins over NPH even though achieved glycemic control is similar. The advantages of basal therapy include long duration of action, flat serum insulin concentrations with minimal/no peak, less hypoglycemia and the availability of concentrated formulations. Varieties of medications are added to basal therapy if glycemic goals are not reached. When basal-oral therapy has not met glycemic goals,
consider the addition of a single dose of rapid acting insulin before the largest meal of the day. Overall, basal-bolus therapy is the most effective insulin regimen.

Insulin is the drug of choice for treating preexisting and gestational diabetes in pregnancy. A regimen using multiple daily injections is preferred. Insulin doses vary by trimester, high doses and concentrated insulins may be required and a high risk of post-delivery hypoglycemia occurs with a return to normal insulin sensitivity within 2-3 weeks. Alternatives include metformin and glyburide which cross the placenta and lack long-term safety data. Guidelines suggest that basal insulins, detemir and glargine, may be used in place of NPH. Levemir may be the safest choice with FDA pregnancy category designation “B”, while Basaglar, Lantus and Tresiba are assigned category “C”. Toujeo includes the new FDA narrative subsections that state fetal risk cannot be ruled out.

Children and adolescents with T1DM and T2DM are treated to the same glycemic targets. Multidisciplinary care is essential. High blood glucose, A1C or undifferentiated T1DM vs T2DM should receive insulin therapy initially. T1DM may be associated with a 2 year honeymoon period. In T1DM, basal-bolus or SIIA are equally preferred. Children with T2DM presenting with high A1C (≥9%) or severe metabolic decompensation should receive insulin therapy initially. If the A1C is above 7%, pharmacotherapy with metformin is recommended. In other youth, if lifestyle therapy fails after 3-6 months, monotherapy with metformin, glimepiride or insulin should be initiated.

In the elderly, glycemic targets are individualized. Reducing the risk of hypoglycemia is more important than glycemic control. Minimizing the number of daily insulin injections is preferred. The use of premixed insulins and prefilled insulin pens may reduce dosing errors. Glycemic control is similar with basal-bolus and premixed insulin therapy. Insulin therapy requires cognitive ability, and good visual and motor skills. Basal insulins (detemir and glargine) are associated with less hypoglycemia and dosing errors than NPH or premixed insulin and may be a good option in the elderly. Poorly controlled therapy may include SIIA.

In the hospital setting, use of insulin, hypoglycemia and self-management pathways are recommended. In critically ill patients SIIA may be preferred, while basal-bolus insulin therapy is recommended in non-critically ill patients. Sole use of sliding scale insulin is strongly discouraged.

Guidelines concerning insulin safety state that insulin pens should not be shared due to the risk of blood-borne pathogen transmission. Insulin should never be withdrawn from an insulin pen (especially with concentrated insulins). The word “units” should always be spelled out, and only insulin syringes marked in mL should be used. Hospitalized individuals should be able to self-administer insulin (via protocol) to reduce the harm of incorrect timing with respect to food.

Currently, practice guidelines do not clearly address concentrated insulin use in the setting of intercurrent illness, hemodynamic instability, diet, stress, concurrent medications (e.g. glucocorticoids) or during hospitalization.
### Table 1: Guidelines for Use of Long-acting Basal Insulins in the Treatment of Diabetes Mellitus (See guidelines for full recommendations concerning use of other therapies, including non-basal insulins)

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| Pharmacologic Approaches to Glycemic Treatment<sup>62</sup> (American Diabetes Association, 2017) | **Type 1 DM**  
• Insulin is the mainstay therapy, starting with 0.4-1 units/kg/day  
  o Multiple daily injections of basal and bolus insulin OR subcutaneous insulin infusion  
  o Insulin requirements are higher during puberty  
  o Rapid acting insulins reduce the hypoglycemia risk  
  o Balance intensive therapy with hypoglycemia risk  

**Type 2 DM**  
• Consider insulin for newly diagnosed, symptomatic, A1c ≥10% or blood glucose ≥300 mg/dL  
• Consider Dual Therapy (which may include insulin) if A1C is ≥9%  
  o Insulin may be effective when other agents are not, is effective vs severe hyperglycemia and should be considered in the presence of weight loss, ketosis, polyuria, polydipsia  
• Consider adding insulin to maximally tolerated noninsulin therapy at 3 months (one of a number of possible options)  
  o Choice of agent depends on efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, patient preference  
  o Empagliflozin/liрагlutide may be used or added to insulin especially with long-standing poorly controlled T2DM and established atherosclerotic cardiovascular disease  
• Do not delay insulin therapy if glycemic goals are not being met  
• Most patients will eventually require insulin therapy  

**Initial Basal Insulin Therapy**  
• “People with type 2 diabetes without a history of hypoglycemia may use NPH insulin safely and at much lower cost”  
• Begins with basal therapy, 10 units/day or 0.1-0.2 units/kg/day  
• Adjust twice weekly to target by 10-15% or 2-4 units  
  o Hypoglycemia without reason, decrease dose 4 units or 10-20% per day  
**Dual Insulin Therapy**  
If not at goal A1C, consider combination  
• With rapid acting insulin before largest meal OR  
• Addition of GLP-1 RA OR  
• Change to premixed insulin twice daily  
**General**  
• Patients should have an algorithm for self-titration, self-monitoring  
• In patients requiring high-dose basal therapy consider concentrated basal insulin; U300 glargine and U200 degludec  
  
• Presentations of symptomatic hyperglycemia and metabolic decompensation should receive an initial regimen containing insulin ± metformin  
• A1C <8.5% and goals not achieved with 2-3 months medication and lifestyle management, consider combination therapy with insulin an option.  
• Choice of additional pharmacological treatment should consider the degree of hyperglycemia, risk of hypoglycemia, overweight or obesity, cardiovascular disease or multiple risk factors, comorbidities (renal, congestive heart failure, hepatic, etc), patient preferences and access to treatment.  
  o In the presence of clinical cardiovascular(CV) disease choose a antihyperglycemic with demonstrated CV outcome benefit  
• When basal insulin is added to a antihyperglycemic regimen, long-acting analogues (detemir or glargine) may be used instead of NPH to reduce the risk for nocturnal or symptomatic hypoglycemia.  
• Counseling should be offered for individuals using or starting insulin about the prevention, recognition and treatment of drug-induced hypoglycemia.  

**Management of Diabetes in Pregnancy<sup>59</sup> (American Diabetes Association, 2017)**  
• In pregnancy the A1C goal is lower due to increased red blood cell turnover (<6% to <7% dependent upon hypoglycemia risk).  
• Lower rates of adverse fetal outcomes with A1C < 6-6.5%  
**Preexisting Diabete (Type 1 or Type 2)**  
• Insulin is the preferred agent. Titrate dosage with frequent self-monitoring of blood glucose  
  o T2DM insulin doses may be quite high, necessitating concentrated insulins  
• 1<sup>st</sup> trimester often require less insulin (especially in T1DM with increased risk of hypoglycemia)  
• 2<sup>nd</sup> trimester increasing glucose resistance (weekly/biweekly adjustments to glycemic target)  
  o Overall, smaller basal doses and larger bolus/prandial doses  
• Late 3<sup>rd</sup> trimester reduced insulin requirements possible  
• Following delivery insulin sensitivity increases (returns to normal over 1-2 weeks)  
**Preexisting Type 2 Diabetes**  
• Insulin is preferred medications (metformin and glyburide may be used but cross the placenta and lack long term safety data)  
  o Following delivery insulin sensitivity increases (returns to normal over 1-2 weeks)  

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<td>Diabetes and Pregnancy (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)³⁴⁶</td>
<td><strong>Gestational Diabetes (If diet and exercise are inadequate)</strong>&lt;br&gt; - Insulin is preferred medications (metformin and glyburide may be used but cross the placenta and lack long term safety data)</td>
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<td><strong>Preexisting T1DM or T2DM</strong>&lt;br&gt; - Individualized insulin regimen and glycemic targets using intensive insulin therapy (FPG &lt;95 mg/dL; 1-hour prandial &lt;140 mg/dL; 2-hour prandial &lt;120 mg/dL)&lt;br&gt;  - Individualize based on severe hypoglycemic risk&lt;br&gt;  - Basal insulin may use detemir or glargine instead of NPH&lt;br&gt;  - Monitor post-partum for high risk of hypoglycemia</td>
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<td><strong>Gestational Diabetes</strong>&lt;br&gt; - Glycemic targets same as above&lt;br&gt; - Initiate insulin if 2-weeks of nutritional therapy do not achieve glycemic targets&lt;br&gt; - Insulin therapy is preferred with multiple daily injections&lt;br&gt;  - Similar outcomes with short-acting analogues vs regular insulin&lt;br&gt;  - Patients who refuse or are nonadherent to insulin may receive off-label metformin or glyburide</td>
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<td>Older Adults³⁵ (American Diabetes Association, 2017)</td>
<td><strong>Individualized therapy to promote patient safety</strong>&lt;br&gt; - Hypoglycemia and hyperglycemia should be avoided, individually adjust glycemic targets&lt;br&gt;  - Premixed advantage: can be injected after a meal, may give better glycemic control than basal insulin&lt;br&gt;  - Premixed disadvantage: increased risk of hypoglycemia and greater weight gain&lt;br&gt;  - Glycemic control similar with basal-bolus vs premixed insulin&lt;br&gt;  - Basal-bolus regimes may be associated with greater improvements with once-daily injections of long-acting insulin.</td>
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<td><strong>Premixed disadvantage:</strong> increased risk of hypoglycemia and greater weight gain</td>
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<td><strong>Glycemic targets same as above</strong>&lt;br&gt; - Hyperglycemia increases the risk of cognitive defects and cognitive defects increase the risk of hypoglycemia&lt;br&gt; - Insulin therapy requires good visual skills, motor skills and cognitive ability (or an able caregiver)&lt;br&gt; - Glycemic targets should be individualized (e.g. HgbA1c &lt;7% to &lt;8.5%)&lt;br&gt; - Attempt to minimize the number of daily insulin doses&lt;br&gt;  - Once-daily basal injection may be a reasonable option in many older patients</td>
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<td>Diabetes in the Elderly (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)³⁵⁷</td>
<td><strong>Individualized therapy to promote patient safety</strong>&lt;br&gt; - Medication dose errors and glycemic control may be minimized with premixed insulins vs mixing insulins and prefilled insulin pens vs conventional syringes&lt;br&gt;  - Premixed advantage: can be injected after a meal, may give better glycemic control than basal insulin&lt;br&gt;  - Premixed disadvantage: increased risk of hypoglycemia and greater weight gain&lt;br&gt;  - Glycemic control similar with basal-bolus vs premixed insulin&lt;br&gt;  - Basal-bolus regimes may be associated with greater improvements with once-daily injections of long-acting insulin.</td>
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<td><strong>Poorly controlled T2DM requiring insulin may be managed with CSII or basal-bolus regimens</strong>&lt;br&gt; - Detemir and glargine are associated with lower rates of hypoglycemia than NPH or 30/70 insulin</td>
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<td>Children and Adolescents³⁸ (American Diabetes Association, 2017)</td>
<td><strong>A1c goal of &lt;7.5% across all age-groups</strong>&lt;br&gt; - Treatment goals identical for T1DM and T2DM in youth&lt;br&gt; - Multidisciplinary care is essential&lt;br&gt;  - Youth with blood glucose ≥250 mg/dL or A1c &gt;9% or undifferentiated T1 vs T2DM should receive insulin&lt;br&gt;  - T2DM treatment includes insulin and/or metformin</td>
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<td>Type 1 diabetes in children and adolescents (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)³⁹⁰</td>
<td><strong>Insulin remains the mainstay therapy</strong>&lt;br&gt; - Choice of insulin regimen depends on child’s age, duration of diabetes, family lifestyle, socioeconomic factors, and family, patient and physician preferences&lt;br&gt;  - Honeymoon period of up to 2 years associated with low (&lt;0.5 units/kg/day) insulin requirement&lt;br&gt;  - Basal-bolus or continuous subcutaneous insulin infusion administration (CSII)&lt;br&gt;  - CSII may give slightly improved metabolic control&lt;br&gt;  - Conflicting information whether basal therapy with glargine or detemir reduces A1C&lt;br&gt;  - Neither regimen is preferred to minimize non-severe hypoglycemia</td>
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<td><strong>Target A1C ≤7.0%</strong>&lt;br&gt; - Children with T2DM and A1C ≥9.0% or those with severe metabolic decompensation (e.g. DKA)&lt;br&gt;  - Initiate insulin therapy&lt;br&gt;  - May be weaned off once glycemic target achieved&lt;br&gt;  - If glycemic targets are not achieved within 3-6 months by lifestyle modification, consider monotherapy&lt;br&gt;  - Metformin&lt;br&gt;  - Glimepiride (metformin preferred over glimepiride)&lt;br&gt;  - Insulin&lt;br&gt;  - Presentation with A1C &gt;7%&lt;br&gt;  - Consider therapy upon presentation with metformin</td>
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<td>Type 2 diabetes in children and adolescents (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)³⁹¹</td>
<td><strong>Decision to start insulin therapy should consider patient’s motivation, cardiovascular and end-organ complications, age, general well-being, risk of hypoglycemia, and overall health status as well as cost considerations.</strong>&lt;br&gt; - Consider insulin if A1C is &gt;8% and/or longstanding type 2 diabetes (less likely to achieve goal with a third oral agent).&lt;br&gt;  - Although GLP-1 RA may lower glycemia, insulin will likely be required&lt;br&gt;  - Initiate insulin therapy with a single daily dose of basal insulin ADDED to the regimen.  - Adjust to target glycemic goal while avoiding hypoglycemia.</td>
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<td>Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the</td>
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| comprehensive Type 2 Diabetes Management Algorithm – 2017 Executive Summary<sup>21</sup> | - Titration can be managed by the provider or the patient  
  - Basal insulin analogues are PREFERRED OVER NPH even though no differences in achieving glycemic control  
    - Provide a flat serum insulin concentration for up to 24 hours  
    - Less hypoglycemia than NPH  
    - Concentrated and longer-acting basal analogues (glargine U300, degludec U100 and U200) yield prolonged and stable PK/PD vs glargin U100 or detemir.  
      - Glycemic control is equivalent with reduced rates of severe or confirmed hypoglycemia (especially nocturnal) vs glargine or detemir U100 (evidence is lacking for degludec vs glargine U300)  
      - Hypoglycemia is more common with premixed insulins than basal-bolus regimens, although simpler regimens may be preferred in some patients.  
  - Patients not achieving glycemic goal on basal insulin  
    - Consider the addition of GLP-1 RA, SGLT-2 inhibitor, DPP-4 inhibitor  
    - The dosage of basal insulin may require a reduction  
  - Patients not achieving glycemic control on basal ± oral therapy  
    - Consider the addition of mealtime insulin to cover postprandial hyperglycemia or when the total daily basal dose exceeds 0.5 units/kg (beyond this hypoglycemia risk is increased without significant A1c reduction)  
  - Basal-bolus regimens are the most effective insulin regimen, providing flexibility for mealtimes and meal CHO content (con: weight gain). |
| Pharmacotherapy in T1DM (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Interim Update, 2015)<sup>55</sup> | - Basal-bolus or SCI are the regimens of choice for all adults with T1DM  
  - Individualize regimens to treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status, self-management ability, and social and financial issues.  
  - Basal-bolus using rapid-acting insulin analogues may result in improved postprandial glycemic control and A1c with minimized hypoglycemia  
  - Basal-bolus using long-acting analogues detemir or glargine results in lower fasting plasma glucose levels and less nocturnal hypoglycemia compared with once- or twice-daily NPH insulin  
  **Twice daily bolus dosing**  
    - Glargine is longer acting than detemir, yet 15-30% of patients using insulin glargine will experience pre-injection hyperglycemia requiring twice-daily administration.  
    - **Twice daily detemir vs NPH in basal-bolus regimens resulted in less nocturnal hypoglycemia** |
| NICE: Type 1 diabetes in adults: diagnosis and management (NG17)<sup>52</sup> | - Insulin therapy  
  - Regimen of choice for all adults: Multiple daily basal-bolus injection regimens are preferred over twice-daily mixed insulin regimens  
  - Do not offer any newly diagnosed person a non-basal-bolus regimen  
  **Long-acting insulin**  
  - **Offer twice-daily insulin detemir as basal insulin therapy**  
  **Alternative**  
    - an existing insulin regimen achieving agreed targets  
    - **once daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person or once-daily insulin detemir is not tolerated**  
    - Consider other basal insulin regimens if targets are not achieved with consideration of patient preferences and acquisition cost |
| Pharmacologic Management of T2DM (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Interim Update, 2015)<sup>55</sup> | - Lifestyle management for 2-3 months is preferred unless the A1C is ≥8.5% (initiate therapy with 2 agents) or the patient has symptomatic hyperglycemia and metabolic decompensation (initiate insulin therapy)  
  Pharmacologic therapy choices should consider degree of hyperglycemia, comorbidities, patient preference, access to treatments, effectiveness and durationality of the agent, risk of hypoglycemia, effectiveness to reduce diabetic complications, effects on body weight, side effects and contraindications  
  - Metformin should be the initial medication used for overweight patients  
  - Combinations of medications should be used to attain target A1C within 3-6 months  
  - **The addition of basal therapy (detemir or glargine) may be preferred to NPH to reduce the risk of nocturnal and symptomatic hypoglycemia**  
  - The addition of bolus therapy may be preferred with rapid-acting analogues vs regular insulin to improve glycemic control and reduce the risk of hypoglycemia |
| Type 2 diabetes in adults: management (NG28)<sup>51</sup> | - Reinforce diet, lifestyle and drug therapy adherence  
  - Individualize HgbA1c target goal  
  - Choose drug therapy based on effectiveness, safety, tolerability, individual clinical circumstances, preferences and needs, available agents, costs  
  - Symptomatic hyperglycemia consider insulin or sulfonylurea  
  - In metformin-tolerant individuals metformin ± other therapies (not insulin) for intensification  
    - Insulin is not considered as an option (vs triple therapy) until HgbA1c reaches 7.5%  
    - When metformin is contraindicated or not tolerated other therapies are initiated and intensified  
    - **Insulin is an option at HgbA1c threshold of 7.5%**  
  Insulin-based treatment |
<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Consensus on Insulin Dose and Titration Algorithms in Ambulatory Care of Type 2 Diabetes in India⁵⁵ | • Structured program, continue metformin in tolerant individuals  
  • **Initial therapy: NPH once or twice daily**  
    o Consider NPH and short-acting insulin separately or as a pre-mixed (especially with HgbA1c ≥9.0%)  
    o Consider alternative to NPH, insulin detemir or glargine (or biosimilar), IF  
    ▪ Needs assistance to inject insulin  
    ▪ Lifestyle is restricted by recurrent symptomatic hypoglycemia  
    ▪ Requires twice-daily NPH in combination with oral hypoglycemic medications  
  • **Start basal insulin (degludec/glargine/detemir)** as 10 units once daily at bedtime  
  • Titrate to FPG of 80-130 mg/dL  
  • Adjust once weekly based on lowest/mean value of 3 most recent FPG values  
  • Reduce the dose 10-20% with hypoglycemia (<70 mg/dL)  
| Diabetes Care in the Hospital (American Diabetes Association, 2017)  | • Sole use of sliding scale insulin is strongly discouraged  
  • All institutions should have a hypoglycemia management protocol including medical record documentation  
  • When blood glucose is <70 mg/dl the treatment regimen should be reviewed and changed as necessary  
  • Use structured discharge plans for individual patients with diabetes  
| CDC Clinical Reminder: Insulin Pens Must Never Be Used for More than One Person (Centers for Disease Control and Prevention 2012)⁶⁵ | **Critically Ill Patients**  
  • Insulin therapy is started with persistent hyperglycemia (≥180 mg/dL)  
  • Target glucose range is 140-180 mg/dL (also for non-critically ill)  
  • Individualized goal of < 140 mg/dl if significant hypoglycemia can be avoided  
  • Insulin infusions (intravenous) used according to validated protocols with infusion rate adjusted based on glycemic fluctuation and dose.  
| Diabetes in India 2012  Digital Diabetes Care in the Hospital (American Diabetes Association, 2017)  | **Non-critically ill patients**  
  • Insulin therapy by basal-bolus regimen is preferred in patients with poor oral intake or NPO  
  • Recommended regimen includes basal, nutritional, correctional components in patients with good nutritional intake  
| Ongoing Concern About Insulin Pen Reuse Shows Hospitals Need to Consider Transitioning Away from Them (ISMP 2013)²⁲ | **T1DM**  
  • Pre-meal glucose monitoring only is insufficient (risk hypoglycemia, hyperglycemia, diabetic ketoacidosis  
| Draft Guidelines for the Safe Use of Subcutaneous Insulin Across the Continuum of Care (ISMP 2016)⁹⁶ | **Transitioning from Intravenous to Subcutaneous Insulin**  
  • First basal insulin dose 1-2 hours before discontinuing intravenous insulin.  
  • Administer 60-80% of the total daily insulin infusion dose as basal insulin  
| Safer insulin prescribing (NICE KTT20)⁵⁶ | **Self-Management**  
  • Acceptable for patients performing self-management at home, with adequate oral intake, cognitive skills, physical skills, be proficient in carbohydrate estimation, use multiple daily insulin injections or a subcutaneous insulin infusion pump, stable insulin requirements an understand sick day management.  
  • Documentation of self-management should include a protocol approved by the patient, nursing staff and physician.  
| CDC Clinical Reminder: Insulin Pens Must Never Be Used for More than One Person (Centers for Disease Control and Prevention 2012)⁶⁵ | **Insulin pen:**  
  • Insulin pens with multiple doses are for use by a single patient only  
  • Insulin pens should be clearly labeled with the patient’s name and identifying information  
  • Hospitals and facilities should educate their staff about safe use of insulin pens  
  • Persons exposed to reuse of an insulin pen should be notified and have appropriate blood-borne pathogen testing  
| Ongoing Concern About Insulin Pen Reuse Shows Hospitals Need to Consider Transitioning Away from Them (ISMP 2013)²⁲ | **Ongoing issues with insulin pens – Transition away from insulin pens for routine inpatient use**  
  o **Use of pen on multiple patients**  
    ▪ Disease transmission  
| Draft Guidelines for the Safe Use of Subcutaneous Insulin Across the Continuum of Care (ISMP 2016)⁹⁶ | **Specialist consultation for complex insulin needs**  
  • Develop protocols, order sets and decision support capabilities for institutional administration and self-management  
  • Use of tall man lettering, entire name of fixed combination insulins  
  • Sliding scale should not be the only method to control hyperglycemia  
  • Insulin pens dispensed for a single patient only  
| Safer insulin prescribing (NICE KTT20)⁵⁶ | • People with diabetes  
  o should receive information about awareness and management of hypoglycemia  
    ▪ A fast-acting source of glucose should always be available  
    ▪ Severe hypoglycemia with reduced level of consciousness may require glucagon administered by another person  
  o must notify the Driver and Vehicle Licensing Agency, if they drive  
  o should receive ‘sick-day’ awareness and rules  

Insulin degludec is a recombinant, modified, human insulin that forms multihexamers at the injection site.\textsuperscript{79,80} The multihexamers slowly separate and are absorbed. Degludec is a long-acting basal insulin analogue with a half-life of approximately 25 hours and long duration of activity (>42 hours) in
T1DM. Steady state is achieved after 2-3 days of once daily subcutaneous injection. Compared to other basal insulins, insulin degludec produces 4-times less intra-subject variability than glargine, as well as other basal insulins. The package insert states insulin degludec may not be mixed with other insulins, however, a manufacturer premix of insulin degludec and insulin aspart is approved (but not yet marketed) in the United States.

Clamp studies in T1DM are the source of most PK/PD information. Insulin glargine and insulin detemir have flatter activity profiles than NPH insulin. Neither agent is truly peakless. Both demonstrate a gentle increase and decrease in activity with a 24 hour duration of activity. Detemir is associated with lower within-subject variability than glargine or NPH. Once-daily administration of glargine and detemir is possible, although twice daily dosing is required in some patients. Due to the 24-hour duration of activity, glargine and detemir require administration at the same time each day. Pharmacokinetic and pharmacodynamic studies with glargine U300 show a flatter, more consistent glucose-lowering effect over a 24-hour period with a duration of activity exceeding 24 hours, low within-day variability, and high between day reproducibility. Insulin degludec also has a smooth, stable pharmacokinetic profile with a longer half-life (25 hours) and duration of action (42 hours) allowing for dosing without regard to meals. Insulin degludec provides less inter-individual variability in day-to-day glycemic control than glargine U100. Degludec U100 and U200 formulations are bioequivalent in individuals with T2DM. The pharmacokinetics of the basal insulins are presented in Table 2.

Table 2: Basal Insulin Pharmacokinetics

<table>
<thead>
<tr>
<th>Generic Name*</th>
<th>Trade Name</th>
<th>Form</th>
<th>Onset (hours)</th>
<th>Peak (hours)</th>
<th>Active Metabolite</th>
<th>Half-Life (hours)</th>
<th>Duration (hours)</th>
<th>RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate Acting</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Humulin® N Novolin® N</td>
<td>Human</td>
<td>2 to 4</td>
<td>6-10</td>
<td>No</td>
<td>4.4</td>
<td>14 to 24</td>
<td>No</td>
</tr>
<tr>
<td>Long Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insulin detemir</td>
<td>Levermir®</td>
<td>Analog</td>
<td>1 to 3</td>
<td>No peak</td>
<td>No</td>
<td>5 to 7</td>
<td>18 to 20 (6 to 23; dose dependent)</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus®</td>
<td>Analog</td>
<td>2 to 4</td>
<td>No peak</td>
<td>M1 &amp; M2 metabolites</td>
<td>12.5</td>
<td>20 to 24 (10.8 to &gt; 24)</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Basaglar® Follow-on biologic</td>
<td>2 to 4</td>
<td>No peak</td>
<td>M1 &amp; M2 metabolites</td>
<td>12.5</td>
<td>24</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ultra-Long Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Insulin glargine U300</td>
<td>Toujeo®</td>
<td>Analog</td>
<td>6</td>
<td>No peak</td>
<td>M1 &amp; M2 metabolites</td>
<td>19</td>
<td>36</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin degludec (U100 and U200)</td>
<td>Tresiba®</td>
<td>Analog</td>
<td>~1</td>
<td>No peak</td>
<td>No</td>
<td>25</td>
<td>42</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Key: *U-100 unless otherwise noted
Special Populations

Ethnic Groups

No difference in pharmacokinetics were noted between African Americans, Hispanics/Latinos or Caucasians for detemir or degludec. Dose-response relationships and time-action profiles were similar across ethnic groups.

Elderly

No differences in safety or efficacy have been observed in patients ≥65 years in key clinical trials of glargine or detemir.

Children and Adolescents

Tresiba® is labeled for use in T1DM and T2DM in pediatrics. Basaglar®, Lantus® and Levemir® are labeled for use in T1DM while use of concentrated insulin glargine, Toujeo® is not established in pediatrics. The newer basal insulins afford less interpatient and intrapatient pharmacokinetic variability across and within age groups compared with NPH. This may reduce the risk of hypoglycemia in children and adolescents. Where approved, dosing and titration in pediatrics is similar to adults. In the treatment of T1DM, NPH, glargine and detemir produced similar A1C reductions while the insulin analogues resulted in significantly lower FPG. Most trials found comparable hypoglycemia risk with NPH and insulin glargine, although one trial found hypoglycemia more frequent with glargine use.

Pregnancy

In pregnant women with T2DM or gestational diabetes in which hyperglycemia remains uncontrolled with diet and lifestyle modifications insulin remains the gold standard treatment. Detemir is indicated in pregnancy (pregnancy category B) while use of other basal insulin requires assessment of risk and benefit. In gestational diabetes, no insulin or insulin regimen has proven superior.

Renal and Hepatic Dysfunction

Renal and hepatic dysfunction are risk factors for hypoglycemia. The basal insulin analogues are not well studied in this setting, however, professional prescribing information for all basal insulin analogues except Tresiba® report increased circulating levels of insulin associated with renal dysfunction. Use of any of these agents should include careful monitoring and dosage adjustment in patients with renal or hepatic dysfunction.

Clinical Efficacy

Trials were excluded if regarding acute care/hospital care/critically ill; regarding glucose monitoring; regarding insulin pumps/continuous infusion; regarding pen devices vs vial and syringe; not FDA-approved routes of administration (i.e. oral/buccal); combination therapies of DPP4 inhibitors or GLP1 analogues with insulin; use for non-diabetes indications or when full-text of the trial was unavailable for review. Appendix 3 includes the identified systematic reviews, meta-analyses, pooled-evidence and network analysis concerning clinical use of basal insulins in the treatment of type 1 and type 2 diabetes mellitus. Trials are arbitrarily grouped by predominant population and include basal insulin use in T1DM insulin-naive T2DM, basal-oral therapy in T2DM, basal or basal/bolus
Long-acting insulin analogues versus NPH insulin: Three meta-analysis and a Cochrane review compared grouped long-acting analogues (LAA) to NPH. Two were performed in T1DM and two in T2DM patients. In T1DM, both analyses found LAA statistically superior to NPH in reducing A1C values, nocturnal and severe hypoglycemia. The Cochrane review additionally reported superiority of LAA in reduced weight gain and FPG. In T2DM, both analyses agree that LAA significantly reduce nocturnal hypoglycemia without significant effect on severe hypoglycemia. In analyses defining the specific LAA, detemir statistically reduced weight gain vs NPH in T1DM and T2DM. The evidence suggests LAA may afford reductions in anytime or nocturnal hypoglycemia and aid in blood glucose control. Detemir use is associated with less weight gain.

Detemir versus NPH: A total of 9 meta-analysis, network meta-analysis, pooled-post hoc analysis, and Cochrane review evaluated the use of detemir with NPH in T1DM and T2DM. Detemir use resulted in a statistically significant reduction in weight gain. Detemir demonstrated A1C lowering effects at least as effective as NPH with three analyses finding detemir significantly superior. Evidence is inconclusive for FPG effects and insulin dosage. In T1DM, the incidence of any hypoglycemia with detemir did not differ from NPH although symptomatric, nocturnal and severe hypoglycemia were significantly lower with detemir in one report. One analysis reported on adverse outcomes. More withdrawals due to adverse events occurred with detemir while more withdrawals due to a lack of efficacy were found with NPH. Overall, detemir use resulted in similar glycemic effects, lower weight gain and lower rates of overall and nocturnal hypoglycemia.

Detemir versus glargine: Detemir was compared with glargine in 6 meta-analysis or Cochrane reviews. Detemir consistently and statistically reduced weight gain associated with insulin therapy. A1C levels were similar with use of daily detemir or glargine, however, when detemir was dosed twice daily it resulted in superior A1C reductions versus daily glargine. Two reports included information concerning FPG and insulin doses. Results were similar in the meta-analysis, while the Cochrane review found glargine superior in reducing FPG at lower insulin dosage requirements. The incidence of hypoglycemia was similar between agents for overall, nocturnal and severe classifications. Detemir ± oral therapy was associated with more withdrawals due to adverse events and more injection site reactions than glargine ± oral therapy. Treatment of T1DM and T2DM with detemir vs glargine required 38% higher detemir dosages in a systematic review of 7 large RCTs (range 8-77.2%). Twice daily dosing of detemir may be required in T1DM patients, at doses ≤0.4 units/kg/day, and when glucose control appears to decline after 12 hours. Swinnen et al. reported detemir was dosed twice-daily in 13-57% of subjects. Treatment satisfaction was higher with glargine therapy. Overall, glucose control and hypoglycemia risk were similar in T2DM treated with detemir or glargine. In T1DM, detemir was associated with a lower incidence of severe and nocturnal hypoglycemia although detemir patients were less likely to have achieved glycemic control and more patients required twice daily dosing. Overall, detemir may reduce weight gain but often requires twice daily dosing.

Glargine versus NPH: A total of 14 meta-analysis, meta-regression analysis, pooled analysis and Cochrane review compared glargine to NPH in T1DM, T2DM and pooled T1DM/T2DM. A significant reduction in weight gain was found more commonly with NPH than
Glargine use resulted in lower A1C levels than NPH in 5 or 11 reports with the remaining trials finding no difference. Of note, A1C reductions were more common with glargine monotherapy in T2DM in people with a longer duration of diabetes. Glargine and NPH doses were similar, with two trials reporting significantly lower NPH doses. Glargine use was associated with significant reductions in nocturnal hypoglycemia, severe nocturnal hypoglycemia and symptomatic hypoglycemia. Reports differed with 50% reporting glargine superior in reducing overall hypoglycemia. Severe hypoglycemia was significantly lower with glargine compared with NPH in 4 of 10 analyses. Reports of injection site pain were 4-times more frequent with glargine than NPH (2.7% vs. 0.7%). Patient satisfaction was higher with glargine + oral medications compared with NPH + oral medications. Overall, glargine is associated with less hypoglycemia than NPH insulin.

**Degludec versus glargine:** Comparison of degludec and glargine was performed in 6 meta-analysis. Degludec was found noninferior to glargine for measures of A1C. Degludec was found superior to glargine in reducing FPG levels. In the single analysis that presented insulin dosage information, degludec doses were significantly less than glargine in T1DM, T2DM and type 2 insulin naïve patients. Degludec consistently and significantly reduced the risk of hypoglycemia (overall, nocturnal and severe) compared with glargine in trials of T1DM, T2DM, insulin naïve T2DM, basal-bolus therapy and during both trial and maintenance periods. Two quality of life meta-analysis evaluated therapy with degludec or glargine. These analysis found that degludec therapy was associated with a statistically significant improvement in both mental and physical health status as well a significant, modest improvement in health utility. It is likely that the extended duration of action of degludec producing more consistent glycemic control contributes to the efficacy and safety outcome superiority over glargine.

**Degludec versus detemir:** Evidence comparing degludec with detemir comes from two randomized, controlled trials in T1DM. Degludec resulted in a significantly lower risk of nocturnal hypoglycemia and greater weight gain than detemir.

**Degludec versus other LAAs:** Two meta-analysis provide information concerning degludec versus other LAA, one performed in T1DM and another in T1DM/T2DM. Degludec produced similar weight and A1C changes. One of the trials found degludec statistically superior to LAA in reducing FPG and anytime hypoglycemia. Both analyses found degludec superior in reducing nocturnal hypoglycemia. In T1DM, a statistically lower degludec dose was required, whereas in combined T1DM/T2DM a higher degludec dose was required. This may reflect the prevalence of insulin resistance in T2DM.

Degludec trials must be interpreted with caution. Most trials targeted a FPG of <90 mg/dL and may not be generalizable to real-world practice. Degludec was administered with the evening meal while glargine was administered any time of the day. The definitions of hypoglycemia and severe hypoglycemia did not match the ADA criteria, although statistical significance remained in most trials after reanalysis using ADA criteria.

**Concentrated Insulins**

**Glargine U300 (Toujeo®) versus U100:** In the treatment of T2DM, meta-analysis comparing glargine U300 to glargine U100 found the concentrated U300 preparation to significantly reduce weight gain while providing similar A1C and FPG effects. The dose of U300 was 12% higher than U100.
Glargine U300 was statistically superior to U100 in producing less hypoglycemic episodes, symptomatic hypoglycemia, nocturnal hypoglycemia and severe hypoglycemia.\textsuperscript{120} The NNT to prevent one case of severe or confirmed hypoglycemia was 16.\textsuperscript{120} Randomized trials found nocturnal or any-time hypoglycemia occurred similarly with glargine U300 and U100 in T1DM.\textsuperscript{163,164} Nocturnal hypoglycemia was reduced during the first 8-weeks of treatment (when hypoglycemia is more common).\textsuperscript{163} Meta-analysis found a reduction in nocturnal hypoglycemia in T2DM trials.\textsuperscript{165-167} An extension trial found no difference in anytime hypoglycemia between U300 and U100 glargine.\textsuperscript{167} Nocturnal or any-time hypoglycemia occurred similarly with glargine U300 and U100 in T1DM.\textsuperscript{163,168} Nocturnal hypoglycemia was reduced during the first 8-weeks of treatment.\textsuperscript{163} A reduction in nocturnal hypoglycemia was also found in T2DM trials.\textsuperscript{165-167} No difference was reported for anytime hypoglycemia between U300 and U100 glargine, but U300 glargine use resulted in a reduction in nocturnal hypoglycemia.\textsuperscript{169} Use of glargine U300 versus U100 resulted in significantly less hypoglycemia, especially nocturnal.\textsuperscript{77,170}

\textbf{Glargine U300 versus detemir or degludec:} In meta-analysis comparing glargine U300 to degludec or detemir, most trials involved basal-oral therapy.\textsuperscript{115,136} No differences were reported between U300 and detemir or degludec for weight change, insulin dose or development of any or nocturnal hypoglycemia. Detemir trials found a significant reduction in A1C with U300 glargine use.\textsuperscript{115}

\section*{Special Populations}

\textbf{Gestational Diabetes:} Evidence included 3 systematic review/meta-analyses and a randomized controlled trial evaluating diabetes in pregnancy and maternal and fetal safety. Evaluated agents included glargine, NPH, and detemir.\textsuperscript{131-134} Overall, no differences were found between basal insulins for glycemic efficacy, hypoglycemia and maternal or fetal outcomes.\textsuperscript{131-134} Use of detemir-BB vs NPH-BB in a RCT did find detemir superior in reducing FPG at 24- and 36-gestational weeks.\textsuperscript{133}

\textbf{Elderly:} A meta-analysis and a pooled-analysis evaluated the use of basal insulin in the elderly.\textsuperscript{135} The meta-analysis of 7 trials comparing degludec with glargine included 917 adults age >65 years.\textsuperscript{135} The proportion of patients with confirmed hypoglycemia did not differ among T1DM or T2DM patients although the proportion with hypoglycemia was higher in T1DM patients (T1DM 94.1%-97.7% vs T2DM 58.7% for both agents).\textsuperscript{135} In T2DM, treatment with degludec resulted in significantly less overall confirmed and nocturnal confirmed hypoglycemia. In T1DM, degludec use resulted in significantly fewer cases of nocturnal confirmed hypoglycemia. Over the maintenance period of the included trials, the agents performed similarly.\textsuperscript{135} All trials were funded by Pharma and patients were excluded with hypoglycemic unawareness, serious comorbidity or a history of more than one episode of severe hypoglycemia. The pooled data analysis comparing detemir with NPH in the elderly, found detemir significantly reduced all and symptomatic hypoglycemic episodes while nocturnal episodes did not differ.\textsuperscript{114} Detemir use significantly reduced weight gain. Mean insulin dosages were similar.\textsuperscript{114}

\section*{Safety Monitoring}\textsuperscript{2,171}

Monitoring of insulin therapy includes periodic determination of A1C levels. Achieving glycemic control (A1C targets) is indicative of efficacy. Monitoring is similar with insulin degludec, insulin detemir and insulin glargine. In patients meeting A1C goals, monitor twice yearly. In patients not meeting A1C
goals or during therapy changes, monitor A1C every 3 months or more often, as indicated. Self-monitoring of blood glucose should be performed as needed for patients receiving a single daily injection of basal insulin therapy, to meet goals. Patient’s receiving multiple daily injections (or pump therapy) should monitor blood glucose at least 3 times a day; prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise/critical tasks, upon suspicion of hypoglycemia and if hypoglycemic, until normoglycemic. Additional blood glucose monitoring may be required in pediatric, pregnant, renally/hepatically impaired patients, during times of stress, illness, changes in therapy (including insulin dosage, manufacturer or method of administration), with co-administration of interacting medications, changes in meal patterns and in patients at higher risk of hypoglycemia or reduced awareness of hypoglycemia. Monitoring potassium levels in patients at risk of hypokalemia is recommended for insulin degludec and insulin glargine. Monitoring for signs and symptoms of heart failure is recommended for patients receiving insulin glargine and a thiazolidinedione.

**Adverse Events**

The most common adverse event reported with use of basal insulin analogues is hypoglycemia. Use of any insulin may be associated with hypersensitivity and allergic reactions (which may include anaphylaxis), injection site reactions, lipodystrophy, development of immunogenicity (anti-insulin antibodies), peripheral edema and weight gain. Overall, no significant differences in non-hypoglycemic adverse events are noted among the basal insulin analogues. Table 4 compares the adverse event profiles of the basal insulin analogues.

**Table 3: Comparison of Long-acting Basal Insulin Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Event Rates &gt;10%</th>
<th>Adverse Event Rates 1 to 10 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basaglar® Insulin glargine</strong></td>
<td><strong>Cardiovascular:</strong> Hypertension (20%), peripheral edema (20%)&lt;br&gt;Central nervous system: Depression (11%)&lt;br&gt;Endocrine &amp; metabolic: Hypoglycemia (Type I on combination regimens: ≤69%; Type II on combination regimens: ≤8%; monotherapy in adults ≥50 years old: 6% [ORIGIN trial])&lt;br&gt;Gastrointestinal: Diarrhea (11%)&lt;br&gt;Genitourinary: Urinary tract infection (11%)&lt;br&gt;Immunologic: Antibody development (20% to 44%; effect on therapy not reported)&lt;br&gt;Infection: Influenza (19%), infection (9% to 14%)&lt;br&gt;Neuromuscular &amp; skeletal: Arthralgia (14%), back pain (13%), limb pain (13%)&lt;br&gt;Ophthalmic: Cataract (18%), retinopathy (14%)&lt;br&gt;Respiratory: Upper respiratory tract infection (adults: 6% to 29%; children &amp; adolescents: 14%), sinusitis (19%), bronchitis (15%), nasopharyngitis (7% to 13%), cough (12%)&lt;br&gt;Local: Pain at injection site (3%)&lt;br&gt;Respiratory: Pharyngitis (children &amp; adolescents: 8%), rhinitis (children &amp; adolescents: 5%)&lt;br&gt;Miscellaneous: Accidental injury (6%)&lt;br&gt;Frequency not defined: Endocrine &amp; metabolic: Sodium retention&lt;br&gt;Local: Erythema at injection site, itching at injection site, localized edema, swelling at injection site&lt;br&gt;&lt;1%, postmarketing, and/or case reports: Anaphylaxis, angioedema, bronchospasm, hyperglycemia, hypersensitivity reaction, hypertrophy at injection site, hypokalemia, hypotension, injection site reaction (including urticaria and inflammation), lipoatrophy at injection site, lipoatrophy at injection site, shock, skin rash, weight gain</td>
</tr>
<tr>
<td><strong>Lantus® Insulin glargine</strong></td>
<td><strong>Cardiovascular:</strong> Hypertension (20%), peripheral edema (20%)&lt;br&gt;Central nervous system: Depression (11%)&lt;br&gt;Endocrine &amp; metabolic: Hypoglycemia (Type I on combination regimens: ≤69%; Type II on combination regimens: ≤8%; monotherapy in adults ≥50 years old: 6% [ORIGIN trial])&lt;br&gt;Gastrointestinal: Diarrhea (11%)&lt;br&gt;Genitourinary: Urinary tract infection (11%)&lt;br&gt;Immunologic: Antibody development (20% to 44%; effect on therapy not reported)&lt;br&gt;Infection: Influenza (19%), infection (9% to 14%)&lt;br&gt;Neuromuscular &amp; skeletal: Arthralgia (14%), back pain (13%), limb pain (13%)&lt;br&gt;Ophthalmic: Cataract (18%), retinopathy (14%)&lt;br&gt;Respiratory: Upper respiratory tract infection (adults: 6% to 29%; children &amp; adolescents: 14%), sinusitis (19%), bronchitis (15%), nasopharyngitis (7% to 13%), cough (12%)&lt;br&gt;Cardiovascular: Retinal vascular disease (6%)&lt;br&gt;Central nervous system: Headache (6% to 10%)&lt;br&gt;Local: Pain at injection site (3%)&lt;br&gt;Respiratory: Pharyngitis (children &amp; adolescents: 8%), rhinitis (children &amp; adolescents: 5%)&lt;br&gt;Miscellaneous: Accidental injury (6%)&lt;br&gt;Frequency not defined: Endocrine &amp; metabolic: Sodium retention&lt;br&gt;Local: Erythema at injection site, itching at injection site, localized edema, swelling at injection site&lt;br&gt;&lt;1%, postmarketing, and/or case reports: Anaphylaxis, angioedema, bronchospasm, hyperglycemia, hypersensitivity reaction, hypertrophy at injection site, hypokalemia, hypotension, injection site reaction (including urticaria and inflammation), lipoatrophy at injection site, lipoatrophy at injection site, shock, skin rash, weight gain</td>
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<td><strong>Endocrine &amp; metabolic</strong>: Hypoglycemia (Type I combination regimens: children &amp; adolescents: 93% to 95%, adults: 82% to 88%; Type 2 combination regimens: adults: 9% to 41%), severe hypoglycemia (Type 1 combination regimens: children &amp; adolescents: 2% to 16%; adults 5% to 9%; Type 2 combination regimens: adults: ≤2%)</td>
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<td><strong>Respiratory</strong>: Upper respiratory tract infection (13% to 26%; children &amp; adolescents: 36%), pharyngitis (10%; children &amp; adolescents: 17%), flu-like symptoms (8%; children &amp; adolescents: 14%)</td>
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</tbody>
</table>

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**Toujeo® Insulin glargine**

**Cardiovascular**: Hypertension (20%), peripheral edema (20%)

**Central nervous system**: Depression (11%)

**Endocrine & metabolic**: Hypoglycemia (Type I on combination regimens: ≤69%; Type II on combination regimens: ≤8%; monotherapy in adults ≥50 years old: 6% [ORIGIN trial])

**Gastrointestinal**: Diarrhea (11%)

**Genitourinary**: Urinary tract infection (11%)

**Immunologic**: Antibody development (20% to 44%; effect on therapy not reported)

**Infection**: Influenza (19%), infection (9% to 14%)

**Neuromuscular & skeletal**: Arthralgia (14%), back pain (13%), limb pain (13%)

**Ophthalmic**: Cataract (18%), retinopathy (14%)

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**Cardiovascular**: Retinal vascular disease (6%)

**Central nervous system**: Headache (6% to 10%)

**Local**: Pain at injection site (3%)

**Respiratory**: Pharyngitis (children & adolescents: 8%), rhinitis (children & adolescents: 5%)

**Miscellaneous**: Accidental injury (6%)

**Frequency not defined**: **Endocrine & metabolic**: Sodium retention

**Local**: Erythema at injection site, itching at injection site, localized edema, swelling at injection site

<1%, postmarketing, and/or case reports: Anaphylaxis, angioedema, bronchospasm, hyperglycemia, hypersensitivity reaction, hypertrophy at injection site, hypokalemia, hypotension, injection site reaction (including urticaria and inflammation), lipoatrophy at injection site, shock, skin rash, weight gain

**Levemir® Insulin detemir**

**Central nervous system**: Headache (adults: 7% to 23%, children: 31%)

**Endocrine & metabolic**: Hypoglycemia (Type 1 combination regimens: children & adolescents: 93% to 95%, adults: 82% to 88%; Type 2 combination regimens: adults: 9% to 41%), severe hypoglycemia (Type 1 combination regimens: children & adolescents: 2% to 16%; adults 5% to 9%; Type 2 combination regimens: adults: ≤2%)

**Gastrointestinal**: Gastroenteritis (children & adolescents: 17%), abdominal pain (6%; children & adolescents: 13%)

**Respiratory**: Upper respiratory tract infection (13% to 26%; children & adolescents: 36%), pharyngitis (10%; children & adolescents: 17%), flu-like symptoms (8%; children & adolescents: 14%)

**Gastrointestinal**: Nausea (children & adolescents: 7%), vomiting (children & adolescents: 7%)

**Infection**: Viral infection (children & adolescents: 7%)

**Respiratory**: Cough (children & adolescents: 8%), rhinitis (children & adolescents: 7%)

**Miscellaneous**: Fever (children & adolescents: 10%)

<1%, postmarketing, and/or case reports: Pain at injection site
Adverse Event Rates >10% | Adverse Event Rates 1 to 10%
---|---
**Tresiba® Insulin degludec**
- **Frequency not always defined.**
- **Cardiovascular:** Peripheral edema (1% to 3%)
- **Central nervous system:** Headache (9% to 12%)
- **Endocrine & metabolic:** Severe hypoglycemia (10% to 13%, type 1 diabetics on combination therapy; ≤5%, type 2 diabetics on combination therapy), antibody development, hypoglycemia, hypokalemia, weight gain
- **Gastrointestinal:** Diarrhea (6%, type 2 diabetes), gastroenteritis (5%, type 1 diabetes)
- **Local:** Injection site reaction (4%; including hematoma, pain, hemorrhage, erythema, warmth, swelling, mass, nodules, and discoloration), hypertrophy at injection site, lipoatrophy at injection site
- **Respiratory:** Nasopharyngitis (13% to 24%), upper respiratory tract infection (8% to 12%), sinusitis (5%, type 1 diabetes)

<1%, postmarketing and/or case reports: Hypersensitivity reaction

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**Hypoglycemia**

Hypoglycemia (blood glucose<50 mg/dL) is reported at least annually in 7% to 15% of insulin-treated patients, with 1-2% reporting severe hypoglycemia. On average, patients with T1DM experience two symptomatic hypoglycemic episodes weekly and one severe, temporarily incapacitating episode yearly. In T2DM, the incidence is lower initially, but as disease duration increases and beta-cell function fails, the incidence approaches that of T1DM.

Hypoglycemia is defined by 1) the development of neurogenic/autonomic symptoms (trembling, shakiness, palpitations, sweating, anxiety, hunger, nausea, tingling) or neuroglycopenic symptoms (difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness); 2) a plasma glucose level below or 72 mg/dL in the presence of insulin or insulin secretagogue therapy; and 3) symptoms responsive to carbohydrate administration. Clinical manifestations define the severity of hypoglycemia, *mild:* autonomic symptoms in a patient able to self-treat; *moderate:* autonomic and neuroglycopenic symptoms in a patient able to self-treat; *severe:* the individual may be unconscious, requires the assistance of another person and is often associated with plasma glucose levels below 54 mg/dL. Hypoglycemia may affect work or driving over the short-term and produce neurological symptoms with prolonged coma over the intermediate-time. Long-term and severe hypoglycemia may lead to mild and permanent cognitive and neurologic sequelae. Recurrent hypoglycemia impairs the ability to sense future episodes. Some evidence suggests frequent, severe hypoglycemia is associated with small (but perhaps clinically meaningful) decreases in intellectual performance. Hypoglycemia in T2DM is associated with a 2 to 4-times higher death rate.

Meta-analysis suggest that microvascular complications and not hypoglycemia, *per se,* are responsible for the cognitive changes in patients with type 1 diabetes. In contrast, evidence suggests T2DM patients with severe hypoglycemia requiring hospital care have an increased risk for developing dementia. Symptomatic hypoglycemia is associated with an increased mortality rate in T2DM patients.
with established or very high risk for cardiovascular disease. The mechanism remains ill-defined but may include hypoglycemia-induced inflammation or cardiac conduction effects. Overall, it is believed sympathetic effects and not glycemic effects are responsible for the cognitive changes associated with hypoglycemia.\textsuperscript{14,49,99}

Individuals with diabetes receiving insulin therapy develop hypoglycemia for a variety of reasons. No currently available insulin product or insulin dosage regimen perfectly matches normal human insulin secretion and hypoglycemia (as well as hyperglycemia) may result.\textsuperscript{24,69,176,177} Caloric intake may be inadequate for the insulin dose due to reduced intake, increased exercise, catabolic stress (e.g. infection, myocardial infarction), decreased gluconeogenesis, reduced insulin elimination via impaired renal function in chronic kidney disease, end-stage kidney disease or acute kidney injury, increased insulin dose, unintentional medical error or intentional error (e.g. self-harm, homicide)\textsuperscript{175,178}

Risk factors for hypoglycemia in T1DM, include prior episode(s) of severe hypoglycemia, low A1C (<6%) levels, hypoglycemia unawareness, longer duration of diabetes, autonomic neuropathy, adolescence and preschool age children unable to detect or self-treat hypoglycemia.\textsuperscript{14,49,174,175} Risk factors for hypoglycemia in T2DM, include older age, severe cognitive impairment, poor health literacy, food insecurity, increased A1C, hypoglycemia unawareness, duration of insulin therapy, renal impairment and neuropathy. Hypoglycemia risk in T2DM is also increased in women with established CV disease, or age >54 years with two cardiovascular disease (CVD) risk factors. Risk factors for severe hypoglycemia, include prior hypoglycemic episode, A1C <6%, hypoglycemia unawareness, long-duration of insulin therapy, autonomic neuropathy, low socioeconomic status, food insecurity, low health literacy, cognitive impairment, adolescence and preschool age children unable to detect or self-treat mild hypoglycemia.\textsuperscript{14,49,174,175} The elderly with diabetes are at particular risk of hypoglycemia.\textsuperscript{51,179,180} Geriatric risk factors include renal insufficiency, preexisting and progressing cognitive deficits that may affect self-care and contribute to administration issues.\textsuperscript{61,180} Targeted glycemic control in the elderly depends upon clinical and cognitive factors, social difficulties, functional dependency, living situation and life expectancy. A1C targets may range from <7.5% in healthy elderly with long(er) life expectancy to <8.5% for complex patients with limited life expectancy.\textsuperscript{61,180}

For any individual with a case of clinically significant hypoglycemia, glycemic targets should be raised for at least several weeks to reverse hypoglycemia unawareness and reduce the risk of future episodes.\textsuperscript{14}

Meta-analysis of A1C treats-to-target trials found that long-acting basal insulin analogues are associated with lower rates of nocturnal and symptomatic hypoglycemia. The risk of hypoglycemia is lower with use of insulin degludec than insulin glargine or insulin detemir.\textsuperscript{101,124,127,130,157,158,161,181} One meta-analysis found no difference in the incidence of any-time, or nocturnal hypoglycemia with insulin glargine concentrations U-300 or U-100.\textsuperscript{120}

The treatment of individuals with diabetes requires the balancing of glycemic control with the avoidance of hypoglycemia. For this reason, A1C targets should be individualized, based on diabetes duration, age/life expectancy, comorbid conditions, known cerebrovascular disease or microvascular complications, risk of hypoglycemia, adverse consequences of hypoglycemia, patient motivation and adherence.\textsuperscript{15,16}
**Cardiovascular Safety**

Insulin receptors line the vascular walls. Insulin acts to produce vasodilation via intrinsic kinase activity, endothelial nitric oxide synthase, reductions in vascular tone and smooth muscle proliferation, reduced adhesion of inflammatory cells and platelet aggregation, and less production of reactive oxygen molecules. Insulin can also result in vasoconstriction by activating the mitogen-activated protein kinase (MAPK) cascade and induce endothelial cell growth. In individuals without diabetes, insulins acts to produce vasodilation; while in the setting of insulin resistance, vasoconstrictive properties predominate.

Epidemiological studies in T2DM found a higher risk of cardiovascular events in patients treated with insulin compared with other therapies. Patients treated with insulin tend to be older, with longer duration of diabetes and more comorbidities and complications. If patients who use insulin have more severe disease, the observational data is no longer valid as statistical analysis cannot account for severity of disease.

Overall, the cardiovascular risk associated with use of human or analogue insulin remains ill-defined. The available evidence must be interpreted with caution. In the DIGAMI 1 (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction) trial, insulin reduced mortality, but it is unclear whether this reflects the effect of improved glucose control or a glucose-independent action. The DIGAMI 2 trial was intended to evaluate cardiovascular outcomes stratified by different glycemic endpoints but all patients showed similar glucose control in spite of different glycemic targets. A trial evaluated insulin-sensitizing therapy (metformin ± thiazolidinedione) vs insulin-providing therapy (insulin ± sulfonylurea) in T2DM patients with ischemic heart disease. Five year cardiovascular mortality and myocardial infarction rates did not differ significantly although interpretation is confounded because each of the additional drugs carries its own effects on cardiovascular risk (metformin reduces risk, sulfonylureas and thiazolidinediones may increase risk). The UK Prospective Diabetes Study was underpowered to assess the cardiovascular effects of insulin during the core phase. Cardiovascular morbidity and mortality of insulin therapy was higher than metformin and lower than sulfonylureas. Followup at 10-years identified a significant reduction in myocardial infarction and cardiovascular mortality with insulin therapy. The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial found no difference in cardiovascular outcomes in patients with recent onset diabetes given glargine vs no therapy or oral therapy. As with all other trials, this trial must be interpreted cautiously as glargine was not compared to NPH or other basal insulin and the mean dose of glargine was very low, 0.4 U/kg. The effects of more commonly used, higher dosages, remains unknown. Evidence suggests that hypoglycemia itself is associated with poor cardiovascular outcomes, perhaps from adrenergic mediated QT prolongation, abnormal myocardial repolarization, ventricular arrhythmias or myocardial ischemia. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial targeting aggressive blood glucose control resulted in a high incidence of severe hypoglycemia and cardiovascular mortality. A systematic review summarizing the literature concerning cardiovascular morbidity and mortality associated with insulin therapy in T2DM included 8 trials of over 100,000 persons. Significant heterogeneity prevented a quantitative synthesis of the data. No difference in cardiovascular risk was found between fixed versus variable insulin regimens, or prandial vs basal regimens. Confidence intervals were wide with increased and decreased cardiovascular risk reported.
**Basal Insulin Analogues**: Insulin receptor binding affinity varies among the basal insulin analogues. Glargine and its metabolite bind at 80%, detemir at 46%, and degludec at 14%. Mitogen-activated protein kinase (MAPK) phosphorylation and intracellular signaling properties also differ among the analogues. Meta-analysis found the risk of severe hypoglycemia compared to NPH insulin is 30% lower with glargine and 50% lower with determir. If hypoglycemia translates to an increased risk of cardiovascular morbidity and mortality, the newer basal insulins should have a favorable cardiovascular risk profile. The ORIGIN trial suggests that glargine is safe at low doses.

Degludec produces the lowest rate of hypoglycemia among the basal insulins. Data submitted to the FDA revealed an increased risk of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina with degludec vs comparators (estimated hazard ratio 1.29, 95% confidence interval 0.88-1.88). The FDA further analyzed the data, omitting patients with unstable angina pectoris (USA) and found a higher rate of cardiovascular risk (incidence rates 1.41 per 100 events per patient per year for degludec or degludec/aspart compared with 0.90 per 100 events per patient year with the comparator). Data was further analyzed excluding USA and including outcome data for 30 days after degludec discontinued and prior therapy (usually glargine) initiated. This analysis yielded a hazard ratio of 1.61 (95% CI 0.99-2.6) for degludec regimens vs comparators. The reason(s) for these various analyses which differ from the predefined analysis plan for approval of diabetes drugs is unclear.

An unanswered question concerning insulin degludec is the effects of overinsulinization and long-term cardiovascular effects. Whereas insulin glargine or NPH administration yield plasma insulin levels of 50-200 pmol/L, insulin degludec yields total plasma concentrations of 6000 pmol/L in patients with type 2 diabetes. A 38-month trial comparing cardiovascular outcomes with degludec vs glargine in T2DM was completed September 2016 and results are expected in the next few years.

**Mitogenicity**

Relationships exists between cancer and exogenous insulin use, diabetes, obesity, insulin resistance and hyperinsulinemia although studies report conflicting results with respect to the cancer risk of long-acting insulin analogues. Binding to human insulin-like growth factor receptor (hIGF-IR) is associated with mitogenic potency. Glargine binding potency to hIGF-IR is 6.5 x greater than human insulin but each binds with the same residence time. Glargine is quickly transformed to its M1& M2 metabolite, which have lower affinity for hIGF-IR than either glargine or human insulin. Detemir and degludec bind to hIGF-IR with less potency than glargine. Detemir and degludec have not exhibited increased mitogenic activity.

Various studies suggest the use of glargine is associated with a greater risk than human insulin for the development of cancer. Increased incidence of breast, pancreas, prostate and any cancer were reported in meta-analyses. These analyses also found a reduction in colorectal cancers with glargine use. The duration of the studies were often too short to determine if the cancer was caused by glargine or if glargine may increase the growth of a preexistent cancer. A recent study in Finland examining all-cause and cause-specific mortality in 23,751 individuals with diabetes found lower rates of cancer with detemir and glargine than NPH insulin use. With NPH as the reference, the adjusted harms ratio (HR) for detemir was 0.23 (95% CI, 0.14 to 0.40), and for glargine 0.35 (95% CI, 0.22 to 0.54). Compared to glargine, the HR for detemir was 0.67 (95% CI, 0.38 to 1.18).
The American Diabetes Association (ADA)\textsuperscript{205} American Association of Clinical Endocrinologists (AACE)\textsuperscript{206} and European Association for the Study of Diabetes (EASD) suggest that the current evidence is unclear.\textsuperscript{207} The ADA encourages patients to continue to take their insulin and discuss concerns with their providers.\textsuperscript{205} The AACE commented on the contradictory findings among generally short-term trials of non-comparable populations, and recommends no change to a patients insulin therapy.\textsuperscript{206} EASD also recommends a continuation of insulin therapy until the results of the current studies are confirmed or refuted. Overall, the evidence concerning glargine is fraught with methodological and statistical issues. Nonetheless, the benefit of insulin use in individuals with diabetes remains greater than the risk for cancer. More sound scientific evidence is required.

\textit{Tolerability}

Patient bulletin boards, suggest injection with Levemir\textsuperscript{®} stings less than Lantus\textsuperscript{®}208,209. Higher rates of stinging/injection site reactions with Lantus\textsuperscript{®} may occur because of the difference in pH between Lantus\textsuperscript{®} (pH 4.0) and Levemir\textsuperscript{®} (pH neutral). Conversely, injection site reactions were more common with insulin detemir than insulin glargine (4.5% vs 1.4%) and more adverse events and withdrawals from therapy occurred with detemir than glargine.\textsuperscript{149} A trial in pediatric patients reported no difference in pain associated with the injection of NPH or insulin glargine.\textsuperscript{210}

\textit{Weight Gain}

Insulin therapy is often associated with a weight gain of 8.8-11.0 pounds.\textsuperscript{211} Weight gain may affect tolerance, adherence and compliance with therapy.\textsuperscript{78} In clinical trials, detemir is associated with a weight-sparing effect. The mechanism of reduced weight gain with detemir remains unknown. Findings from meta-analyses found significantly less weight gain with detemir than NPH in T1DM\textsuperscript{69,103,106,107} and T2DM\textsuperscript{114}. In T2DM, detemir weight gain was less than glargine\textsuperscript{122,123} with a single network meta-analysis finding glargine superior to detemir in reduced weight gain.\textsuperscript{107} Glargine was associated with significantly less weight gain than NPH in T1DM\textsuperscript{107}, while NPH weight gain was reported lower than glargine in two meta-analyses in T2DM\textsuperscript{110,112}. Weight gain associated with the use of glargine U300 was statistically less than with glargine U100 in T2DM.\textsuperscript{110} Randomized, controlled trials report similar or less weight gain with concentrated basal insulins than to U100. Insulin degludec U200 increased weight nonstatistically vs U100. In T1DM insulin glargine U300 resulted in less weight gain than U100.\textsuperscript{163} Likewise in T2DM, glargine U300 and U100 produced similar weight gain over 12 months of treatment.\textsuperscript{166} Weight gain with insulin is common and detemir has the most favorable effect in limiting weight gain.

\textit{Injection Fears}

Each of the basal insulins is available in a disposable pen for administration. Compared with the use of vials and insulin syringes, pens are more portable, easier to use, and do not require resuspension (as NPH).\textsuperscript{78} The currently available basal insulins are more commonly administered once daily than NPH, offering a less complex insulin regimen. Use of insulin pens may increase patient acceptance improving patient satisfaction and adherence to treatment.\textsuperscript{78}

\textit{Adherence}

An improvement in adherence reduced the risk of hospitalization or emergency department (ED) visits by 13% in 135,649 patients with prescriptions for diabetes treatment compared with nonadherent patients.\textsuperscript{37} Those who were initially adherent and became nonadherent were found to
have a 15% increased risk of hospitalization or ED visit compared to continuing adherent patients. Pooled data from 3 retrospective, observational trails evaluated persistence of insulin therapy in 4084 persons with T2DM where therapy advanced from oral medications to the inclusion of a basal insulin (glargine or detemir) and reported persistence at 1-year followup of 65.0%. Higher persistence was associated with older age, initiation of glargine using vial/syringe or disposable pens, or baseline exenatide or sitagliptin use. Persistence resulted in lower A1C values, A1C reductions from baseline and lower health care utilization at follow-up.

Adherence is improved when patients emotional well-being is considered and they understand the treatment regimen and benefit (especially for complex regiments), adverse events and medication costs. Adherence may be improved by lessening regimen complexity, hypoglycemia risk and adverse reactions. Adherence may be improved when the fear of hypoglycemia and incidence of hypoglycemia are reduced. This also allows for insulin dosages to be increased to achieve target A1C goals with improved long-term outcomes.

Simplification of insulin regimens with reductions in the number of daily injections increases adherence. In this regard, use of detemir may be considered less preferred as it is the only basal insulin analogue with prescribing information for once- or twice-daily dosing. Trials submitted to the FDA for approval in T1DM compared twice-daily detemir to daily glargine, daily detemir to daily NPH and twice-daily detemir to twice-daily NPH. In T2DM, twice-daily detemir was compared with twice-daily NPH and in a second trial once- or twice-daily detemir was compared to once- or twice-daily NPH. In all trials, comparable reductions in A1C and fasting plasma glucose (FPG) were noted. Twice daily dosing of glargine was reported in 32.9% with T1DM and 13% with T2DM compared with detemir, 62.5% in T1DM and 48% in T2DM. In contrast, some practitioners suggest that once-daily dosing of detemir should be the preferred regimen based on clinical evidence.

**Duplication of Therapy**

There is currently no indication for the use of combined basal insulin analogues.

**Misuse**

Insulin has been misused as a performance-enhancing agent. Psychiatric misuse of insulin, includes attempted and completed suicides, factitious hypoglycemia, Munchausen syndrome by proxy, and illicit use by substance abusers. Patients, particularly young women with T1DM may omit doses of insulin to lose weight.

**Medication Errors**

Insulin glargine U300 and U100 by Sanofi Aventis (Toujeo® and Lantus®) are available in similar pens with the U300 glargine pen white and green, with the concentration highlighted in orange to distinguish it from U100 glargine. No conversion in dosing is needed. Both U300 and U100 pens are marked in units. An individual need only dial the prescribed dose. Should an error occur and a full pen dose be injected, Tresiba® U200 will administer 160 units while all other pens will administer 80 units. Pen needles should never be used on more than one patient even if the needle is changed.
A number of medication errors are associated with the use of needle and syringe administration of insulin from vials:

- Misinterpretation of U-100 on a vial to mean the vial includes 100 units of insulin. Availability in 10 mL vials makes large dose errors possible. In institutions, stocking the smallest vial size may be preferred.
- Measuring the dose in units incorrectly in a non-insulin syringe as mL (e.g. 4 units = 4mL)
- Confusion in using concentrated insulin and calculating conversions for use in syringes marked in units.
- In an institutional setting, manufacturer vials may look similar
- Use of the same syringe to administer insulin products that should not be mixed

**Drug Interactions**

Drug interaction potential among the basal insulins is similar in producing hyperglycemia, hypoglycemia, variable glycemic response, or masking/blunting the signs or symptoms of hypoglycemia. Detemir exhibits strong, reversible binding to albumin but does not interact with other highly bound medications (e.g. warfarin, ibuprofen, diazepam, valproate). All basal insulins interact to increase blood glucose levels in combination with glucocorticoids, typical antipsychotics, oral contraceptives, protease inhibitors, diuretics, phenytoin and sympathomimetics. A decrease in blood glucose may be associated with use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and high-dose salicylates. Combination with alcohol may increase or decrease blood glucose levels.

**Storage**

All basal insulin are available in pens for administration. Lantus and Levemir are also available in vials. Table 3 presents the basal insulin storage requirements. Unopened, storage at room temperature is longest with degludec (56 days), followed by detemir (42 days), followed by glargine products (28 days). Once opened, only vials may be stored in the refrigerator. Expirations for in-use pens are longest for Tresiba® (56 days), followed by Levemir® and Toujeo® (42 days), followed by Lantus® and Basaglar® (28 days).

**Table 4: Long-acting, Basal Insulin Storage Requirements**

<table>
<thead>
<tr>
<th>Product</th>
<th>Package</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lantus®</td>
<td>10 mL vial, 100 units/mL Single vials</td>
<td>Until expiration date</td>
</tr>
<tr>
<td></td>
<td>3 mL SoloStar® PFP (100 units/mL) Package of 5 pens</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>Toujeo®</td>
<td>1.5 mL SoloStar® PFP (300 units/mL) Package of 3 or 5 pens</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>Product</td>
<td>Package</td>
<td>Storage</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>Basaglar®</td>
<td>3 mL KwikPen PFP Package of 5 pens</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>10 mL vial, 100 units/mL Single vials</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>Levemir®</td>
<td>3 mL FlexTouch® PFP (100 units/mL) Package of 5 pens</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>3 mL FlexTouch® PFP (100 units/mL) Package of 5 pens</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>Tresiba®</td>
<td>3 mL FlexTouch® PFP (200 units/mL) Package of 3 pens</td>
<td>Until expiration date</td>
</tr>
</tbody>
</table>

Key: § Keep products away from direct heat and light; ‡ No basal insulin is approved for mixing with other products, however degludec is manufactured as a 70/30 mixture with insulin aspart (Ryzodeg®) and in combination with liraglutide (Xultophy®).
**Utah Medicaid Utilization Data**

Utah Medicaid claims data from 2013 to 2016 was used to answer the following questions.

1. What long-acting insulin products are used?

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016*</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tresiba Flex Inj 100 Unit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tresiba Flex Inj 200 Unit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Levemir Inj</td>
<td>13,120</td>
<td>1,460</td>
<td>1,950</td>
<td>705</td>
<td>52,095</td>
</tr>
<tr>
<td>Levemir Inj Flexpen</td>
<td>105</td>
<td>3</td>
<td>12</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Levemir Inj Flextocuc</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Basaglar Inj 100 Unit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lantus Inj 100/ML</td>
<td>107,747</td>
<td>1,259</td>
<td>1,340</td>
<td>86,886</td>
<td>1,182</td>
</tr>
<tr>
<td>Lantus Inj SoloStar</td>
<td>678</td>
<td>19</td>
<td>37</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>Lantus For Inj Opticlik</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Toujeo Solo Inj 300/ML</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TOTAL** 121,650 7,319 1,417 123,626 7,466 1,624 101,840 6,299 1,367 81,993 5,196 1,097 428,109 26,250 3,252

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016*</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tresiba Flex Inj 100 Unit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tresiba Flex Inj 200 Unit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Levemir Inj</td>
<td>100</td>
<td>15</td>
<td>21</td>
<td>6</td>
<td>530</td>
</tr>
<tr>
<td>Levemir Inj Flexpen</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Levemir Inj Flextocuc</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>168</td>
</tr>
<tr>
<td>Basaglar Inj 100 Unit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lantus Inj 100/ML</td>
<td>5,160</td>
<td>101</td>
<td>138</td>
<td>5,202</td>
<td>133</td>
</tr>
<tr>
<td>Lantus Inj SoloStar</td>
<td>165</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Lantus For Inj Opticlik</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Toujeo Solo Inj 300/ML</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TOTAL** 5,425 488 105 6,090 561 146 5,440 489 139 3,733 339 90 20,688 1,877 324

- The Utah Medicaid Preferred Drug List (PDL) includes Lantus® and Levemir® vials as preferred agents. Use patterns reflect these preferences.
  - Less than 3% of patients received insulin pens versus vials for these products through the end of 2016.
- For both all, and pediatrics, Lantus® use is significantly higher than Levemir®.
• Use of longer-acting/concentrated agents.
  o A single adult patient filled a single claim of 15 mL for Tresiba® (degludec U100) in 2016.
  o A total of six adult patients filled 39 claims for Toujeo® (glargine U300) in 2016.
  o Each of these products is associated with more consistent glycemic control and less hypoglycemia, especially nocturnal.

• Epidemiological evidence (e.g. Centers for Disease Control, CDC) suggests the incidence of diabetes is increasing and guidelines consider the additional of long-acting basal insulin therapy appropriate in most patients. Utah Medicaid claim data suggests that the use of these agents has declined. In 2013, 105 patients had claims submitted for a long-acting insulin, but in 2016 only 90 patients had submitted a claim for long-acting insulin. This may reflect fewer fee-for-service patients with a diagnosis of diabetes, increased use of NPH insulin products for basal insulin coverage or other unknown factors.
  o A review of NPH insulin use, (data not presented) did not demonstrate an increase. Usage of most NPH containing products was consistent from 2013 to 2016, however, use of Novolin NPH had declined by >50% although usage was low (from 68 patients in 2013 to 27 patients in 2016
2. Who is being prescribed the long-acting basal insulin products?

- More women than men use long-acting insulin products.
- At age <18 years, the distribution between males and females is similar. T1DM is more common than T2DM in young people and these results are consistent with epidemiologic evidence suggesting equal gender distribution in T1DM.
- The number of patients using long-acting insulin products drops at age 18, and may reflect the loss of childhood Medicaid benefits for some individuals.
- Use is highest between ages 35 to 64 and likely reflects the adult-onset population with T2DM.
3. Who is prescribing the long-acting insulin products?

<table>
<thead>
<tr>
<th>Prescriber Type</th>
<th>TOTAL CLAIMS 2013-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse Midwife</td>
<td>47 0.18%</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>2,757 10.50%</td>
</tr>
<tr>
<td>Osteopath</td>
<td>3,008 11.46%</td>
</tr>
<tr>
<td>Physician</td>
<td>20,438 77.86%</td>
</tr>
<tr>
<td><strong>TOTAL CLAIMS</strong></td>
<td><strong>26,250</strong></td>
</tr>
</tbody>
</table>

Prescribing specialties match expected prescribing practices.
4. What patients receiving long-acting insulins have experienced at least one documented episode of hypoglycemia?

- Younger patients, likely with T1DM and receiving intensive insulin therapy, have a higher incidence of reported hypoglycemia than young adults.
- The incidence of hypoglycemia reporting increases in older adults but appears to decrease significantly in the elderly. It is unclear if this reflects a true reduction in frequency, reduced reporting, lower intensity of insulin therapy or other factors.
- Overall, Utah Medicaid patients receiving insulin therapy for T1DM, T2DM, gestational diabetes or any diabetes (includes patients with coding for both T1DM and T2DM) have an incidence of reported hypoglycemia similar to epidemiologic evidence (7-15%).
5. Do differences exist in the reporting of at least a single case of hypoglycemia with respect to classification of diabetes or use of any long-acting insulin product?

<table>
<thead>
<tr>
<th>GENERIC</th>
<th>BRAND</th>
<th>CLAIMS</th>
<th>PATIENTS</th>
<th>DX TYPE 1 DM</th>
<th>DX TYPE 2 DM</th>
<th>DX GEST DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Degludec</td>
<td>Tresiba 100 UNIT/ML</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Insulin Detemir</td>
<td>Levemir 100 UNIT/ML</td>
<td>730</td>
<td>168 (23%)</td>
<td>44 (6%)</td>
<td>140 (19%)</td>
<td>1</td>
</tr>
<tr>
<td>Insulin Glargine</td>
<td>Lantus 100 UNIT/ML</td>
<td>4,426</td>
<td>944 (21%)</td>
<td>284 (6%)</td>
<td>731 (17%)</td>
<td>21</td>
</tr>
<tr>
<td>Insulin Glargine</td>
<td>Tejoe 300 UNIT/ML</td>
<td>39</td>
<td>6 (15%)</td>
<td>2 (5%)</td>
<td>4 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>5,196</td>
<td>1,097</td>
<td>323</td>
<td>856</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AGE</th>
<th>Patients with Hypoglycemia DX</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>10</td>
<td>0.91%</td>
</tr>
<tr>
<td>18-24</td>
<td>6</td>
<td>0.55%</td>
</tr>
<tr>
<td>25-34</td>
<td>9</td>
<td>0.82%</td>
</tr>
<tr>
<td>35-44</td>
<td>9</td>
<td>0.82%</td>
</tr>
<tr>
<td>45-54</td>
<td>19</td>
<td>1.73%</td>
</tr>
<tr>
<td>55-64</td>
<td>25</td>
<td>2.28%</td>
</tr>
<tr>
<td>&gt;64</td>
<td>1</td>
<td>0.09%</td>
</tr>
<tr>
<td>TOTAL PATIENTS</td>
<td></td>
<td>1097</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Patients with Hypoglycemia DX</th>
<th>Total Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE 1</td>
<td>46</td>
<td>323</td>
<td>14.24%</td>
</tr>
<tr>
<td>TYPE 2</td>
<td>70</td>
<td>856</td>
<td>8.18%</td>
</tr>
<tr>
<td>GESTATIONAL</td>
<td>2</td>
<td>22</td>
<td>9.09%</td>
</tr>
<tr>
<td>ANY DIABETES DX</td>
<td>79</td>
<td>971</td>
<td>8.14%</td>
</tr>
</tbody>
</table>

- The incidence of hypoglycemia is similar with Levemir® and Lantus® use for All, T1DM and T2DM patients.
- Fewer patients with gestational diabetes had documented hypoglycemia while receiving Levemir® than Lantus®.
- Hypoglycemia is most common in adults age 45-64.
- Of the 79 patients who developed hypoglycemia while receiving a long-acting insulin in 2016, a larger percentage were diagnosed with T1DM, consistent with a greater likelihood of hypoglycemia in patients prescribed more intensive insulin regimens.

_Utilization conclusions:_ No issues associated with utilization of the long-acting insulins in the Utah Medicaid population were noted.
Conclusion:

Use of insulin in the treatment of diabetes mellitus improves glycemic control, and in T2DM may preserve β-cell function, improve insulin sensitivity and slow disease progression. Guidelines encourage incorporation of insulin into treatment regimens when lifestyle changes and/or oral therapy fail to achieve glycemic targets, or initial A1C levels are high.

The most common complication of insulin therapy is hypoglycemia. The long-acting, basal insulins offer an extended, peakless activity profile with reduced inter- and intrapatient variability. Compared with NPH insulin, the long-acting basal insulins reduce symptomatic and nocturnal hypoglycemia risk. Some guidelines (e.g. American Diabetes Association) suggest that patients at low risk of hypoglycemia may be cost-effectively managed with NPH, while others prefer the pharmacokinetic and pharmacodynamic advantages of the long-acting basal insulins and prefer these first-line (e.g. American Association of Clinical Endocrinologists). Overall, patients requiring basal insulin with a high(er) risk of hypoglycemia or established episodes of hypoglycemia may benefit from the long-acting basal insulin therapy.

A safety review of the long-acting basal insulin products reveals the agents have similar adverse event profiles. The incidence of hypoglycemia is reduced with use of basal insulins compared with NPH. The longer-acting (Tresiba®) and more concentrated product (Toujeo®) may afford even greater ability to reduce hypoglycemia. Cardiovascular safety remains a possible concern with these agents, although the ORIGIN trial supports glargine safety and results from a trial comparing cardiovascular outcomes with degludec and glargine are expected in the near future. Similarly, the risk of cancer with insulin therapy remains ill defined and multiple associations and organizations consider the benefit of insulin therapy to outweigh cancer risk based on current evidence. Weight gain is associated with insulin therapy and detemir is clearly associated with the lowest weight gain of any basal insulin.

Although the long-acting basal insulins have an improved activity profile, glycemic control is similar to NPH. The advantage of these products is in reduction in hypoglycemia risk, reduction in the number of daily insulin injections, positive effects on weight gain with detemir, and increased dosing flexibility with degludec.
Utah Medicaid Prior Authorization Considerations

Current Quantity Limit:

- Currently the long-acting insulin products are associated with quantity limits. Prescriptions are limited to 60 mL monthly. Ultimately, insulin dosing is individualized.
  - The maximally recommended dosage of long-acting insulins for use in pubescent children and adolescents is 2.0 units/kg/day. The maximally recommended dosage in adults is 1.2 units/kg/day.
   - A quantity of 60 mL U100 long-acting insulin would adequately supply a 100 kg young person (dosed at 2.0 units/kg/day) for 30 days.
   - A quantity of 60 mL U100 long-acting insulin would adequately supply a 167 kg adult dosed at 1.2 units/kg/day for 30 days.

  ❖ Consider: Prior Authorization override: If an adult weight > 167 kg, or a child > 100 kg, and the physician writes the patient weight on the prescription, no Prior Authorization is required for dispensed quantities > 60 mL/30 days.

- Should a change be made to reduce quantity limits to the next lowest, commercially available volume (45 mL/month) the impact would be as such:
  - A quantity limit of 45 mL/month would provide a 75 kg young person (2.0 units/kg/day) a 30-day supply
  - A quantity limit of 45 mL/month would provide a 125 kg adult (1.2 units/kg/day) a 30-day supply

Additional Considerations

➢ Consider placing a restriction on insulin pen use in facilities where insulin is administered by staff and not by individual patients.
  - This will prevent multiple-patient use of pens and the potential transmission of blood borne pathogens.
  - The advantages of pens are established for patient use (see below). Professional staff are highly trained, visually and physically unimpaired, and able to manage vial and syringe manipulations

➢ Consider placing no restriction on access to insulin pens for outpatient administration. Insulin pens offer a number of safety advantages
  - Insulin administration with pen requires fewer steps than with a vial and syringe
  - Pens allow for administration of odd-number dosages. Although rounding doses is not likely a problem with doses above 60 units/day, at lower dosages the difference may be clinically relevant
  - Pens are larger, easier to handle, make a click that can be felt and may be preferred for patients with impaired vision or dexterity
    - Exception: patients with arthritis may have more trouble pushing the plunger and patient and prescriber must assess the best mode of insulin administration
Should a limitation to use of long-acting insulin pens be considered, criteria may include:

- Clinical diagnosis of T1DM or T2DM with documented labs/tests and prior medication usage (if on prior therapy) in the patient’s medical record
- Must be able to monitor blood glucose
- Has limitations to syringe/vial insulin administration, including:
  - unable to draw up insulin in a syringe or self-administer, due to mechanical, physical or environmental factors
  - visual impairment
  - requires 1 or more injections during work/school period (this should be uncommon with long-acting insulin use)
- Lack of capable assistance from a person living with them
- Has severe phobia to traditional needle/syringe administration (true needle phobia is extremely rare)
- Patient is NOT in an institutional facility
- Cognitive impairment (requiring definition)
- History of failure, contraindication or intolerance to preferred agent(s) available in vial(s)
- Clinical rationale supporting a therapeutic advantage
  - Compared to vial
  - Compared to preferred insulin preparation

**Agent Specific Use Limitations**

- Concentrated and Ultra-long Acting Insulins (Toujeo®, insulin glargine 300 units/mL; Tresiba®, degludec U100 and U200)
  - Hypoglycemia risk:
    - Consider the use of concentrated, long-acting insulins (Toujeo or Tresiba U200) in persons at highest risk of hypoglycemia;
      - Patients with multiple prior episodes of hypoglycemia or single episode of severe hypoglycemia
      - Patients with hypoglycemia unawareness
      - Persons unable to detect or self-treat hypoglycemia
      - The elderly with significant renal insufficiency (GFR < 30 mL/min); dosing individualization will be required
      - Presence of preexisting and progressing cognitive deficits that may affect self-care and contribute to administration issues.

- Tresiba® criteria
  - Due to the flexibility in timing of administration, Tresiba may be preferred for people in which there are significant barriers to standardized administration requiring extreme flexibility in dose timing.
    - elderly patients
    - patients with learning difficulties
    - patients who have to rely on health-care professionals for their daily insulin injection
- people whose work/travel/life-style significantly impairs their ability to administer insulin regularly

- Patients requiring > 160 units of insulin per dose and having difficulty with 2-injections per dose of other insulin(s).
  - Tresiba® U200 allows for injection of ≤160 units in a single injection.

- **Storage/Stability/Waste**
  - The Preferred Drug List currently includes Levemir® with a long in-use expiration dating. Use of this product, where appropriate, may be particularly useful in poorly adherent patients to minimize waste (particularly if once-daily dosing is possible). Agents with longer expiration dating, once opened, include
    - Tresiba® (56 days), Levemir® (42 days), Toujeo® (42 days)

- **Authorization Duration:** 12 months

---

References


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64. 1: S1-S212 CDACPGECDCDACPGHrPaMoDiCCJDS.


Steintraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. Diabetes Obes Metab. 2014;16(9):873-876.


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169. Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab. 2015;17(9):835-842.


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display.cfm?article_id=4932 AAoCE-cArtigcraID-thmaca.

webcast.easd.org/press/glargine/glargine.html EAFtSoDESUi-saplwcwrfih.


## Appendix 1: Long-acting, Basal Insulin Product Comparison

<table>
<thead>
<tr>
<th>Product</th>
<th>RX</th>
<th>Available Oral Formulations</th>
<th>Labeled Indication</th>
<th>Oral Dose Range, Adults</th>
<th>Oral Dose Range, Pediatrics</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (Human)</td>
<td>No</td>
<td>HumuLIN N (NPH) Kwikpen Subcutaneous Suspension: 100 U/1 ML</td>
<td>T1DM T2DM</td>
<td>T1DM • SUBQ once or twice daily; individualized</td>
<td>T1DM • administer SUBQ once or twice daily; individualized dosing</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2DM • SUBQ: 0.1 to 0.2 units/kg/day once or twice daily o with severe hyperglycemia 0.3 to 0.4 units/kg/day SUBQ once or twice daily may be required; may be used in combination with 1 or 2 noninsulin agents (guideline dosing) [2]</td>
<td>T2DM • age 10 to 18 years: Individualized dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HumuLIN N (NPH) Subcutaneous Suspension: 100 U/1 ML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NovoLIN N (NPH) Subcutaneous Suspension: 100 U/1 ML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Acting</td>
<td>Yes</td>
<td>Le vemir® FlexPen (phasing out) Subcutaneous Solution: 100 U/1 ML</td>
<td>T1DM T2DM</td>
<td>General Dosage Information • Maximal 80 units per single injection • Unit-to-unit conversion for from insulin glargine or NPH insulin • Other insulin therapies may require adjustment of timing and dose of insulin detemir T1DM • Initial: approximately 1/3 total daily insulin requirement administered SUBQ; use in combination with rapid- or short-acting insulin • Maintenance: SUBQ: individualized dose administered once daily with the evening meal or at bedtime OR twice daily in the morning and with the evening meal, at bedtime, or 12 hours after the morning dose; use in combination with rapid- or short-acting insulin T2DM</td>
<td>Caution: Safety and efficacy not established in children with type 2 diabetes nor in children younger than 2 years with type 1 diabetes T1DM Age ≥2 years • Initial: Approximately 1/3 of total daily insulin dosage SUBQ; use in combination with rapid- or short-acting insulin • Maintenance: individualized dosing SUBQ once or twice daily; once daily administration should be with the evening meal or at bedtime; twice daily administration should be in the morning and with the evening meal, at bedtime, or 12 hours after the morning dose; use in combination with rapid- or short-acting insulin</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Le vemir® FlexTouch Subcutaneous Solution: 100 U/1 ML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Le vemir® Subcutaneous Solution: 100 U/1 ML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product</td>
<td>RX</td>
<td>Available Oral Formulations</td>
<td>Labeled Indication</td>
<td>Oral Dose Range, Adults</td>
<td>Oral Dose Range, Pediatrics</td>
<td>Generic</td>
</tr>
<tr>
<td>-------------------</td>
<td>----</td>
<td>-----------------------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Basaglar*</td>
<td>Subcutaneous Solution: 100 U/1 ML</td>
<td>T1DM T2DM</td>
<td>• Maintenance: Individualized SUBQ dose administered once or twice daily; once daily administration should be with the evening meal or at bedtime; twice daily administration would be in the morning and with the evening meal, at bedtime, or 12 hours after the morning dose</td>
<td></td>
<td>No (Basaglar is a Biosimilar)</td>
</tr>
<tr>
<td></td>
<td>Lantus® SoloStar</td>
<td>Subcutaneous Solution: 100 U/1 ML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lantus®</td>
<td>Subcutaneous Solution: 100 U/1 ML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300 (analog)</td>
<td>Toujeo®</td>
<td></td>
<td></td>
<td></td>
<td>Not established in pediatrics</td>
<td>No</td>
</tr>
</tbody>
</table>

**Ultra-Long Acting**

**Insulin glargine U-300 (analog)**

**General Dosage Information**

- Maximal 80 units per single injection
- Unit-to-unit conversion for Lantus® to Basaglar®. Time of administration should be evaluated
- Toujeo® to Lantus®: Initiate at 80% of the Toujeo dose
- Once-daily long- or intermediate-acting insulin (eg, NPH insulin) to once-daily Lantus®: Initiate at same dose. A dosage adjustment of the basal insulin may be necessary. Once-daily long- or intermediate-acting insulin (other than another insulin glargine 100 units/mL product) to Basaglar® 100 units/mL: A change in dose may be required. The timing and amount of shorter-acting insulins and doses of other antidiabetic agents may need to be adjusted
- Twice-daily NPH insulin to once-daily insulin glargine (Basaglar®, Lantus®) Initiate at 80% of the NPH insulin dose

**Type 1 diabetes mellitus**

Basaglar®, Lantus®

- Insulin-naive: Initial: approximately 1/3 of total daily insulin requirement administered subQ once daily at the same time every day; adjust dose according to clinical response. Use in combination with short- or rapid-acting, premeal insulin

**Type 2 diabetes mellitus**

Basaglar®, Lantus®

- Insulin-naive: Initial, up to 10 units (or 0.2 units/kg) subQ once daily at the same time every day. Adjust according to individual metabolic needs, blood glucose measurements, and goals of treatment

**General Dosage Information**

- Unit-to-unit conversion for Lantus® to Basaglar®. Time of administration should be evaluated
- Once-daily long- or intermediate-acting insulin (eg, NPH insulin) to once-daily Lantus®: Initiate at same dose; a dosage adjustment of the basal insulin may be necessary.
- Once-daily long- or intermediate-acting insulin (other than another insulin glargine 100 units/mL product) to Basaglar® 100 units/mL: A change in dose may be required. The timing and amount of shorter-acting insulins and doses of other antidiabetic agents may require adjustment.
- Twice-daily NPH insulin to once-daily Basaglar® or Lantus®: Initiate at 80% of the NPH insulin dose

**Type 1 diabetes mellitus**

Basaglar®, Lantus®

- (6 years or older) Insulin-naive: Initial, approximately one-third of total daily insulin requirement administered subQ once daily at the same time every day. Adjust dose according to clinical response. Use in combination with short- or rapid-acting, premeal insulin
<table>
<thead>
<tr>
<th>Product</th>
<th>RX</th>
<th>Available Oral Formulations</th>
<th>Labeled Indication</th>
<th>Oral Dose Range, Adults</th>
<th>Oral Dose Range, Pediatrics</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insuline degludec (U-100 and U-200)</td>
<td>Yes</td>
<td>Tresiba®</td>
<td>T1DM T2DM</td>
<td><strong>General Dosage Information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Maximal 80 units per single injection of U100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Maximal 160 units per single injection of U200</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 1 diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Insulin-naive</strong>: Initial dose, 1/3 to 1/2 the total daily insulin dose (general rule for total daily dose, 0.2 to 0.4 units/kg subQ; remainder of total daily dose given as a short-acting insulin and divided between each daily meal) Initiate with same unit dose as the total daily long or intermediate-acting insulin unit dose Maintenance dose: give subQ once daily at any time of the day; titrate to clinical effect with dose increases every 3 to 4 days as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 2 diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Insulin-naive</strong>: Initial dose, 10 units subQ once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(1 year or older) Insulin-naive</strong></td>
<td></td>
<td></td>
<td></td>
<td>(1 year or older) Insulin-naive: Initial dose, one-third to one-half the total daily insulin dose (general rule for total daily dose, 0.2 to 0.4 units/kg subQ; remainder of total daily dose given as a short-acting insulin and divided between each daily meal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(1 year or older) Insulin-experienced</strong>: Initiate at 80% of the total daily long or intermediate-acting insulin unit dose, give subQ once daily at the same time each day</td>
<td></td>
<td></td>
<td></td>
<td>Dosage titration: Individualize dose based on patient needs and titrate to clinical effect with dose increases every 3 to 4 days as needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Subcutaneous Solution: 300 U/1 ML
- 17.5% higher than Lantus® requirements in clinical studies
- Once-daily long- or intermediate-acting insulin (eg, NPH insulin) to once-daily Toujeo®: Initiate at same dose. A dosage adjustment of the basal insulin may be necessary.
- Twice-daily NPH insulin to once-daily Toujeo®: Initiate at 80% of the NPH insulin dose

**Type 1 diabetes mellitus**
- **Insulin-naive**: Initial: 1/3 to 1/2 of total daily insulin requirement administered subQ once daily at the same time every day; usual dosage, 1 to 80 units per injection; use in combination with short-acting insulin; total daily insulin dose is generally 0.2 to 0.4 units/kg/day; adjust dose no more often than every 3 to 4 days based on blood glucose measurements and goals of therapy; maximum effect may take 5 days

**Type 2 diabetes mellitus**
- **Insulin-naive**: Initial, 0.2 units/kg subQ once daily; usual dosage, 1 to 80 units per injection; adjust dose no more often than every 3 to 4 days based on blood glucose measurements and goals of therapy; maximum glucose lowering effect may take 5 days
- **Insulin-experienced**: Initiate with same unit dose as the total daily long or intermediate-acting insulin unit dose
- **Maintenance dose**: give subQ once daily at any time of the day; titrate to clinical effect with dose increases every 3 to 4 days as needed

### Appendix 2: Evidence

**Systematic Reviews and Meta-analysis of Basal Insulins in Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Author</th>
<th>Agents</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain (↓=less)</th>
<th>HgbA1c %</th>
<th>FPS mg/dL</th>
<th>Insulin Dosage</th>
<th>Any Hypoglycemia</th>
<th>Daytime Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Severe Hypoglycemia</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dzygato K°°° 2015</td>
<td>degludec vs LAA</td>
<td>12-weeks</td>
<td>N/A</td>
<td>NS</td>
<td></td>
<td>degludec ↓ basal dose MΔ= -0.042; p=0.0010</td>
<td>N/A</td>
<td>N/A</td>
<td>degludec ↓ RR 0.697 p&lt;0.000</td>
<td>N/A</td>
<td>N/A</td>
<td>NS</td>
</tr>
<tr>
<td>Heller S°°° 2016</td>
<td>degludec, glargine</td>
<td>≥26 or 52 weeks</td>
<td>N/A</td>
<td>NS</td>
<td></td>
<td>degludec ↓ total daily dose MΔ= -0.07; p=0.002</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Marra L°°°, 2016</td>
<td>Glargine rDNA insulins (NPH)</td>
<td>&gt;6 months</td>
<td>NS</td>
<td>Adults only glargine ↓ MΔ= -0.26; p=0.002</td>
<td>N/A</td>
<td>NS</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>45% Pharma sponsored trial</td>
</tr>
<tr>
<td>Monami M°°° 2009</td>
<td>LAA, NPH</td>
<td>≥12-weeks</td>
<td>N/A</td>
<td>detemir ↓ 0.26 kg/m² p=0.012</td>
<td>LAA ↓ -0.07%; p=0.026</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>LAA ↓ OR=0.69; p&lt;0.01</td>
<td>LAA ↓ OR=0.73; p&lt;0.01</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sanches AC°°° 2011</td>
<td>Detemir, Glargine NPH</td>
<td>4 weeks</td>
<td>N/A</td>
<td>Daily glargine=daily detemir=NPH Twice daily detemir ↓ vs daily glargine ↓ -0.14% [0.21 to 0.08]</td>
<td>N/A</td>
<td>N/A</td>
<td>Glargine=NPH Detemir=NPH</td>
<td>N/A</td>
<td></td>
<td>Glargine=NPH Detemir=NPH</td>
<td>N/A</td>
<td>Withdrewal due to AEs detemir 2.9% vs NPH 0.6%; p&lt;0.001</td>
</tr>
</tbody>
</table>

Key: FDA=Food & Drug Administration; SubQ=subcutaneous injection
<table>
<thead>
<tr>
<th>Author</th>
<th>Trials</th>
<th>N</th>
<th>Agents</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain (↓=less)</th>
<th>HgbA1c %</th>
<th>FPG mg/dL</th>
<th>Insulin Dosage</th>
<th>Any Hypoglycemia</th>
<th>Daytime Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Severe Hypoglycemia</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanches AC**</td>
<td>2013</td>
<td>35</td>
<td>(extracted info for basal insulins) N=4206 SR NMA</td>
<td>Long-acting analogues Short-acting analogues NPH</td>
<td>4 weeks</td>
<td>N/A</td>
<td>Daily glargine=daily detemir Daily glargine or detemir=NPH Twice daily detemir ↓ vs NPH -0.14 p&lt;0.0001</td>
<td>N/A</td>
<td>N/A</td>
<td>Glargine=detemir Detemir=NPH Glargine=NPH</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>detemir 0.4% vs NPH 1.2%; p=0.02 Glargine=detemir Few clinical advantages w/ long-acting analogues</td>
</tr>
<tr>
<td>Szypoweska A*</td>
<td>2011</td>
<td>10</td>
<td>N=3825</td>
<td>detemir NPH</td>
<td>12-weeks</td>
<td>detemir ↓ WMD=0.779 [-0.992 to -0.567]</td>
<td>detemir ↓ WMD=0.073 p=0.021</td>
<td>detemir ↓ RR=0.978 [0.961 to 0.996]</td>
<td>detemir ↓ WMD=0.977 p&lt;0.001</td>
<td>detemir ↓ RR=0.977 [0.816 to 0.942]</td>
<td>detemir ↓ RR=0.665 [0.547 to 0.810]</td>
<td>N/A</td>
<td>N/A</td>
<td>detemir ↓ WMD=0.073 p=0.021 Glargine=NPH</td>
</tr>
<tr>
<td>Tricco AC*</td>
<td>2013</td>
<td>39</td>
<td>N=7496</td>
<td>glargine daily detemir 1-2x/day NPH 1-2x daily</td>
<td>N/A</td>
<td>glargine daily vs NPH MD=0.04 [0.06 to 0.02] detemir 1-2x/day vs NPH daily MD=-5.51 [-6.56 to -4.46] glargine daily vs NPH daily MD=5.14 [-6.07 to -4.21]</td>
<td>glargine daily vs NPH MD=0.39% [-0.59 to -0.19%] detemir daily vs NPH MD=0.26% [-0.48% to -0.03%] detemir 1-2x/day vs NPH MD=0.36% [-0.65% to -0.08%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Overall, detemir once or twice daily was associated with the least weight gain; all-cause mortality did not differ between twice daily detemir or NPH. No differences in incident cancer over 16-26 weeks; QOL was similar with glargine daily vs NPH twice daily</td>
</tr>
</tbody>
</table>
### Systematic Reviews, Pooled Analysis and Meta-analysis of Basal Insulins in Insulin Naïve Type 2 Diabetes

<table>
<thead>
<tr>
<th>Author #Trials N</th>
<th>Agents</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain Kg (↓=less)</th>
<th>HgbA1c %</th>
<th>FBS mg/dL</th>
<th>Insulin Dosage</th>
<th>Any Hypoglycemia</th>
<th>Daytime Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Severe Hypoglycemia</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vardi M* 2008 23 trials N=6787 Cochrane Review</td>
<td>LAA NPH</td>
<td>4-weeks</td>
<td>LAA ↓ WMD=0.67 [-0.87 to -0.45]</td>
<td>LAA ↓ WMD=0.08 [-0.12 to -0.04]</td>
<td>LAA ↓ WMD=0.63 [-0.86 to -0.40]</td>
<td>LAA ↓ OR=0.93 [0.8 to 1.08]</td>
<td>NS</td>
<td>N/A</td>
<td>LAA ↓ OR=0.70 [0.63 to 0.79]</td>
<td>LAA ↓ OR=0.73 [0.61 to 0.87]</td>
<td>NS</td>
<td>Modest clinical benefit on nocturnal glucose levels. Effect on overall diabetes control is clinically unremarkable</td>
</tr>
<tr>
<td>Dailey GE* 2013 4 trials N=2330 PA</td>
<td>Glargine NPH</td>
<td>24-weeks</td>
<td>NPH ↓ Dd ≤5.8 yr NPH ↓ Dd 9.2-14 yr</td>
<td>Glargine ↓ in higher Dd groups, SS</td>
<td>NPH ↓ vs glargine in lowest and highest Dd groups, SS</td>
<td>NPH ↑ vs glargine for all Dd; each SS</td>
<td>NS</td>
<td>N/A</td>
<td>N/A</td>
<td>Degludec ↓ 12a-6a RR=0.64 [0.48 to 0.86] 10p-6a RR=0.60 [0.45 to 0.80]</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Heller S* 2016 6 Trials N=2070 (including extension trials) SR MA</td>
<td>Degludec glargine</td>
<td>26 or 52 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Degludec ↓ 12a-6a RR=0.64 [0.48 to 0.86] 10p-6a RR=0.60 [0.45 to 0.80]</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owens DR 2017 4 trials N=2091 MA</td>
<td>Glargine NPH</td>
<td>24 weeks</td>
<td>NPH ↓ 2.7 vs 2.23 P=0.009</td>
<td>NS</td>
<td>Glargine ↑ 0.42 U/kg vs 0.39 U/kg P=0.03</td>
<td>Glargine ↓ Rr=0.93 P=0.041</td>
<td>N/A</td>
<td>Glargine ↓ Rr=0.73 [0.65 to 0.83] NNH with NPH vs glargine PG=70 mg/dL=12 PG=56 mg/Cl=18</td>
<td>NS</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: [ ] = 95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate ratio; Rr=relative risk; QOL=quality of life; SR=systematic review; SS=statistically significant; T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference
<table>
<thead>
<tr>
<th>Author</th>
<th>#Trials</th>
<th>Agents</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain Kg (↓=less)</th>
<th>HgbA1c %</th>
<th>FBS mg/dL</th>
<th>Insulin Dosage</th>
<th>Any Hypoglycemia</th>
<th>Daytime Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Severe Hypoglycemia</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratner RE: 2013</td>
<td>7 trials N=4330 (extracted from trial) MA</td>
<td>I degludec vs glargine</td>
<td>26 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>insulin naïve degludec ↓ ERR=0.83 [0.70 to 0.98]</td>
<td>N/A</td>
<td>insulin naïve degludec ↓ ERR=0.64 [0.48 to 0.86]</td>
<td>N/A</td>
<td>Excluded recurrent severe hypoglycemia; reduction in hypoglycemia was more pronounced in maintenance phase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numbed needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate ratio; Rr=relative risk; QOL=quality of life; SR=systematic review; SS=statistically significant; T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

**Systematic Reviews, Pooled Analysis and Meta-analysis of Basal Insulin with Oral Therapy in Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Author</th>
<th>#Trials</th>
<th>Comparators</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain Kg (↓=less)</th>
<th>HgbA1c %</th>
<th>FBS mg/dL</th>
<th>Insulin Dosage</th>
<th>Any Hypoglycemia</th>
<th>Daytime Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Severe Hypoglycemia</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rym HS: 2015</td>
<td>28 trials N=12,669 SR MA</td>
<td>Glargin Detemir NPH (extracted)</td>
<td>12 weeks</td>
<td>With OADs Glargine=NPH Detemir ↓ vs Glargine WMD=0.77 [0.44 to 1.11]</td>
<td>N/A</td>
<td>N/A</td>
<td>Any hypoglycemia Trend favors glargine over NPH rr=0.92 [0.84 to 1.001]</td>
<td>Glargine/OAD ↓ vs NPH/OAD rr=0.63 [0.51 to 0.77]</td>
<td>Glargine/OAD=NPH/OAD</td>
<td>N/A</td>
<td>Withdrawal due to AE Detemir/OAD ↑ vs glargine/OAD rr=0.40 [0.24 to 0.69]</td>
<td>Injection site reactions Glargine/OAD ↓ vs detemir/OAD rr=0.22 [0.07 to 0.55]</td>
<td>Treatment satisfaction favored</td>
</tr>
</tbody>
</table>

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; MNC=mean net change; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numbed needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate ratio; Rr=relative risk; QOL=quality of life; SR=systematic review; SS=statistically significant; T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference
<table>
<thead>
<tr>
<th>Author</th>
<th>Trials</th>
<th>Agents</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain Kg (↓=less)</th>
<th>HgbA1c %</th>
<th>FBS mg/dL</th>
<th>Insulin Dosage</th>
<th>Any Hypoglycemia</th>
<th>Symptomatic Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Severe</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Bazzano LA</td>
<td>12 trials</td>
<td>Glargine vs NPH</td>
<td>4-weeks</td>
<td>NPH↓; MNC=0.33 [-0.61 to -0.06]</td>
<td>NS</td>
<td>NS</td>
<td>similar</td>
<td>glargine↓ p&lt;0.0003</td>
<td>glargine↓ p&lt;0.0001</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Bi X</td>
<td>22 trials</td>
<td>Long-acting analogues (LAA) NPH</td>
<td>34 weeks (median)</td>
<td>LAA=NPH</td>
<td>LAA↓ vs NPH WMD=0.20 P=0.03</td>
<td>LAA↓ vs NPH WMD=0.07 U/kg/day [0.14 to 0.00] with high heterogeneity</td>
<td>LAA↓ vs NPH OR=0.57 P&lt;0.00001</td>
<td>N/A</td>
<td>LAA↓ vs NPH OR=0.46 P&lt;0.0001</td>
<td>NS</td>
<td>No differences in AEs, treatment related AEs or withdrawals</td>
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<tr>
<td>Garber AJ</td>
<td>3 trials</td>
<td>Insulin detemir vs NPH</td>
<td>22 weeks</td>
<td>detemir↓ older -1.02 [1.61 to -0.42] younger -1.13 [1.58 to -0.69]</td>
<td>Similar</td>
<td>similar</td>
<td>detemir↓ Older Rr=0.59 p=0.002 Younger Rr=0.75 p=0.02</td>
<td>Detemir↓ in younger (p&lt;0.001) but not older group</td>
<td>uncommon</td>
<td>NS</td>
<td>Pooled analysis of phase 3 trials</td>
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<tr>
<td>Freemantle N</td>
<td>41 trials (25 included oral therapy)</td>
<td>Glargine U300 vs other insulin therapies</td>
<td>Not defined</td>
<td>U300=detemir U300=degludec</td>
<td>N/A</td>
<td>U300=detemir U300=NPH</td>
<td>none significant</td>
<td>U300↓ vs NPH RR 0.18 [0.05 to 0.55] U300=detemir U300=degludec</td>
<td>N/A</td>
<td>N/A</td>
<td>Sensitivity analysis supports robustness</td>
<td></td>
<td></td>
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<tr>
<td>Home PD</td>
<td>5 trials</td>
<td>Evening glargine vs evening NPH; morning glargine vs evening NPH</td>
<td>24 weeks</td>
<td>N/A</td>
<td>No differences</td>
<td>No differences</td>
<td>Glargine evening↓ P&lt;0.001</td>
<td>Glargine morning↓ p&lt;0.001</td>
<td>Glargine evening↓ p&lt;0.001</td>
<td>Severe nocturnal Glargine morning↓ p&lt;0.001</td>
<td>Glargine evening↓ P&lt;0.001</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td>Author</td>
<td>N</td>
<td>Agents</td>
<td>Minimum Trial Duration</td>
<td>Weight Gain Kg (↓=less)</td>
<td>HgbA1c %</td>
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<td>Insulin Dosage</td>
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<tr>
<td>Horvath K* 2007 6 trials glargine vs NPH each N=2293 on glargine or detemir Cochrane</td>
<td>117 2007</td>
<td>Glargine and Detemir vs NPH</td>
<td>24 weeks</td>
<td>N/A</td>
<td>NS</td>
<td>similar</td>
<td>N/A</td>
<td>Compared to NPH Glargine NS detemir ↓ Rr=0.82; p&lt;0.0001</td>
<td>Compared to NPH glargine- ↓ Rr=0.84 p=0.005 detemir ↓ Rr=0.56, p&lt;0.001</td>
<td>Compared to NPH glargine ↓ Rr=0.66, p&lt;0.0001 detemir ↓ Rr=0.63, p&lt;0.0001</td>
<td>Detemir=NPH Glargine=NPH</td>
<td>Clinically similar</td>
<td>Methodologic quality of trials was rated low. If at all, only a minor clinical benefit of treatment with long-acting insulin analogues (LAA) for patients with diabetes mellitus type 2 treated with &quot;basal&quot; insulin regarding symptomatic, nocturnal hypoglycaemic events. Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with insulin glargine or detemir.</td>
</tr>
<tr>
<td>Monami M** 2008 14 trials; N=3188 MA</td>
<td>NPH LAA</td>
<td>12 weeks</td>
<td>Detemir ↓ vs NPH detemir ↓ vs glargine p=0.048</td>
<td>NS</td>
<td>NPH=LAA NPH ↓ 0.1% vs detemir</td>
<td>N/A</td>
<td>Detemir=NPH Glargine=NPH LAA ↓ vs NPH OR=0.69 [0.60–0.80]</td>
<td>LAA ↓ vs NPH OR=0.46 [0.39–0.55]</td>
<td>similar</td>
<td>N/A</td>
<td>most were sponsored trial different hypoglycaemia definitions</td>
<td></td>
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<tr>
<td>Pontiroli AE*** 2011 46 trials N=14,250 SR MA</td>
<td>Intensive insulin treatment regimens: newer analogues vs older basal vs within prandial vs twice daily</td>
<td>12 weeks</td>
<td>Weight increase was lower with basal regimens vs twice-daily regimens vs prandial regimens</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Body weight increase during 1st year of insulin treatment depends on insulin regimen final A1C, change in A1C, insulin regimen</td>
<td></td>
</tr>
<tr>
<td>Ritzel R**** 2015 3 Trials N=2406 MA</td>
<td>Glargine U300 vs Glargine U100</td>
<td>2 weeks</td>
<td>glargine U300 ↓ p=0.039</td>
<td>similar</td>
<td>similar</td>
<td>Mean Dose 12% higher with U300 U300=0.85 U/kg/day U100=0.76 U/kg/day</td>
<td>glargine U300 ↓SS U300 ↓SS</td>
<td>U300 ↓ RR=0.69 [0.57–0.84]</td>
<td>U300 ↓ RR=0.86 [0.77–0.97]</td>
<td>No differences</td>
<td>Hypoglycaemia benefit with U300 was noted in the initial maintenance period; hypoglycaemia rates similar between younger and older persons; NNT to prevent 1 case of severe or confirmed hypoglycaemia with U300 vs 16</td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>#Trials</td>
<td>N</td>
<td>Agents</td>
<td>Minimum Trial Duration</td>
<td>Weight Gain Kg (↓=less)</td>
<td>HgbA1c %</td>
<td>FBS mg/dL</td>
<td>Insulin Dosage</td>
<td>Any Hypoglycemia</td>
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<tr>
<td>Rosenstock J* 2005 4 trials 2304 MA</td>
<td>Glargine NPH</td>
<td>24 weeks</td>
<td>NA</td>
<td>similar</td>
<td>glargine↓ p=0.0344</td>
<td>similar</td>
<td>N/A</td>
<td>glargine ↓ rr=11% p=0.0006</td>
<td>glargine ↓ rr=26% p&lt;0.0001 severe glargine ↓ rr=59% p=0.0231</td>
<td>glargine ↓ rr=46% p=0.0442</td>
<td>N/A</td>
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<tr>
<td>Swinnen SG 2011 4 trials N=2250 Cochrane</td>
<td>Detemir glargine</td>
<td>12 weeks</td>
<td>detemir ↓ MD=0.91 [-1.21 to -0.61]</td>
<td>similar</td>
<td>glargine ↓ MD=0.34 mmol/L [0.01 to 0.67]</td>
<td>glargine ↓ MD=0.26 U/kg [0.11 to 0.41]</td>
<td>similar</td>
<td>N/A</td>
<td>similar</td>
<td>similar</td>
<td>N/A</td>
<td>similar</td>
<td>Detemir dosing was twice daily in 13.6% to 57.2% of subjects; high risk of bias; substantial heterogeneity; clinically relevant difference in efficacy or safety</td>
</tr>
<tr>
<td>Zhuang YG 2013 13 trials N=1668 MA</td>
<td>Glargine Detemir</td>
<td>24 weeks</td>
<td>detemir ↓ p&lt;0.00001</td>
<td>similar</td>
<td>similar</td>
<td>detemir ↑ p&lt;0.00001</td>
<td>secondary outcome not well defined; no difference in prevalence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
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</tr>
</tbody>
</table>

Key: [ ] =95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; ERR=estimated rate ratio; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; MNC=mean net change; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=number needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate/risk ratio; Rr=relative risk; rr=risk reduction; QOL=quality of life; SR=systematic review; SS=statistically significant; T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

**Systematic Reviews, Meta-Analysis of Basal Insulin in Combined Assessments of T1DM and T2DM**

<table>
<thead>
<tr>
<th>Author</th>
<th>#Trials</th>
<th>Comparators</th>
<th>Minimum Trial Duration</th>
<th>Weight Gain (↓=less)</th>
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<th>Adverse Events</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Einhorn D* 2015 7 trials N=2044 (extracted from meta-analysis) MA</td>
<td>Degludec vs Glargine*</td>
<td>26 weeks</td>
<td>N/A</td>
<td>Degludec was non-inferior to glargine</td>
<td>N/A</td>
<td>N/A</td>
<td>Maintenance phase Degludec ↓ ERR=0.79 [0.68 to 0.92]</td>
<td>N/A</td>
<td>degludec ↓ ERR=0.63 [0.52 to 0.77]</td>
<td>Severe requiring assistance: degludec ↓ ERR=0.86 [0.76 to 0.98]</td>
<td>N/A</td>
<td>*Study assessed hypoglycemia associated with HgbA1c &lt;7% with Degludec vs Glargi statistically lower hypoglycemia rates with degludec more pronounced in the maintenance period</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Trials</td>
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</tr>
<tr>
<td>Monami M&lt;sup&gt;15&lt;/sup&gt; 2013 5 trials N=2105 MA</td>
<td>Degludec vs LAA</td>
<td>16 weeks</td>
<td>similar</td>
<td>similar</td>
<td>degludec ↓ SS in T2DM</td>
<td>degludec ↑ SS in T2DM</td>
<td>N/A</td>
<td>degludec ↓ SS in T1DM</td>
<td>N/A</td>
<td>Fewer with degludec</td>
<td>Basal with oral or prandial insulin</td>
<td></td>
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<tr>
<td>Mullins P&lt;sup&gt;16&lt;/sup&gt; 2007 11 trials N=5074 MRA</td>
<td>Glargine vs NPH</td>
<td>not stated</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>glargine ↓ in T1DM and T2DM p&lt;0.05 sustained when adjusted for end-point A1C</td>
<td>N/A</td>
<td>glargine ↓ in T1DM, p&lt;0.05 symptomatic glargine ↓ in T1DM/T2DM p&lt;0.05</td>
<td>N/A</td>
<td>N/A</td>
<td>Negative binomial meta-regression; sponsored trials; hypoglycemia rates increased at lower HgbA1c values; severe hypoglycemia rates reduced 16%-46.8% with glargine; low overall rates of hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Ratner RE&lt;sup&gt;17&lt;/sup&gt; 2013 7 trials N=4330 MA</td>
<td>Degludec vs glargine</td>
<td>26 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>T2DM degludec ↓ ERR 0.83 [0.74 to 0.94]</td>
<td>N/A</td>
<td>T2DM degludec ↓ ERR 0.68 [0.57 to 0.82] T1DM degludec ↓ during maintenance ERR 0.75 [0.60 to 0.94]</td>
<td>T2DM degludec ↓ SS</td>
<td>N/A</td>
<td>Excluded recurrent, severe hypoglycemia reduction in hypoglycemia was more pronounced in maintenance phase</td>
<td></td>
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<tr>
<td>Russell-Jones D&lt;sup&gt;18&lt;/sup&gt; 2015 7 trials N=4317 MA</td>
<td>Degludec vs glargine</td>
<td>26 weeks</td>
<td>N/A</td>
<td>degludec non-inferior to glargine</td>
<td>degludec ↓ T2DM p=0.05 T1DM p=0.05 T1DM degludec ↓ for titration period p=0.05 for end of trial p=0.05</td>
<td>N/A</td>
<td>N/A</td>
<td>T1DM maintenance period Degludec ↓ RR=0.74 [0.60 to 0.94] T2DM Degludec ↓ End of trial RR 0.68 [0.57 to 0.82] Maintenance period RR=0.62 [0.49 to 0.78] T1DM and T2DM Degludec ↓ End of trial RR=0.75 [0.65 to 0.85] Titration period RR=0.86 [0.74 to 1.00] Maintenance period RR=0.68 [0.58 to 0.80]</td>
<td>N/A</td>
<td>N/A</td>
<td>nocturnal confirmed hypoglycemia was lower with degludec T2DM SS Pooled T1&amp;T2DM SS</td>
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<tr>
<td>Author #Trials N</td>
<td>Comparators</td>
<td>Minimum Trial Duration</td>
<td>Weight Gain (↓=less)</td>
<td>HgbA1c %</td>
<td>FBS mg/dL</td>
<td>Insulin Dosage</td>
<td>Any Hypoglycemia</td>
<td>Daytime Hypoglycemia</td>
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<tr>
<td>Singh SR 2009 49 trials N&gt;6000 MA</td>
<td>Glargine detemir NPH</td>
<td>not stated</td>
<td>similar</td>
<td>T1DM glargine ↓ vs NPH WMD=0.11 [-0.21 to -0.02] Detemir=NPH Detemir=glargine T2DM Glargine ↓ vs NPH without OAD WMD=0.28 [0.07 to 0.49] Detemir ↓ vs NPH With OAD WMD=0.13 [0.03 to 0.22] Detemir-BB ↓ vs glargine-BB WMD=0.20 [0.10 to 0.30]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>T1DM Adults detemir ↓ vs NPH RR=0.92 [0.85 to 0.98] Children &amp; Adolescents detemir ↓ vs NPH RR=0.85 [0.77 to 0.94] T2DM Adults Glargine ↓ vs NPH with OAD RR=0.56 [0.47 to 0.68] Glargine ↓ vs NPH without OAD RR=0.78 [0.62 to 0.98] Detemir ↓ vs NPH with OAD RR=0.53 [0.31 to 0.91]</td>
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<tr>
<td>Vora J 2014 7 trials N=4740 MA</td>
<td>Degludec vs glargine</td>
<td>26 weeks</td>
<td>N/A</td>
<td>degludec non-inferior to glargine in T1DM-BB or T2DM or T2DM insulin naive</td>
<td>degludec ↓ T1DM-BB MD=0.61 [-1.13 to -0.10] T2DM insulin-naive MD=0.34 [-0.54 to -0.15]</td>
<td>degludec ↓ T1DM-BB ETR=0.88 [0.85 to 0.92] T2DM insulin-naive ETR=0.90 [0.85 to 0.96]</td>
<td>Degludec ↓ T2DM-BB ERR=0.83 [0.69 to 0.99]</td>
<td></td>
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<td></td>
<td></td>
<td>Similar; evidence suggests little benefit vs conventional insulins for glycemic control or reduced hypoglycemia</td>
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</tbody>
</table>

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; ERR=estimated rate ratio; ETR=estimated treatment ratio; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; MNC=mean net change; MRA=meta-regression analysis; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numbed needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate/risk ratio; Rr=relative risk; rr=risk reduction; QOL=quality of life; SR=systematic review; SS=statistically significant; T2BB=type 2 basal bolus; T2IN=type 2 insulin naive; WMD=weighted mean difference
<table>
<thead>
<tr>
<th>Study details</th>
<th>Author</th>
<th>Trials N</th>
<th>Comparison Group</th>
<th>Glycemic Efficacy</th>
<th>Maternal Outcomes</th>
<th>Fetal Outcomes</th>
<th>Hypoglycemia</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational, pregestational diabetes</td>
<td>Lepercq J**</td>
<td>8 trials N=702</td>
<td>Glargine NPH</td>
<td>No differences</td>
<td>Maternal outcomes NS</td>
<td>No differences</td>
<td>No differences</td>
<td>No significant efficacy or safety-related outcome issues</td>
</tr>
<tr>
<td>Diabetes in pregnancy</td>
<td>Lv S***</td>
<td>8 glargine trials N=708 2 detemir trials N=326 (extracted data)</td>
<td>Glargine detemir NPH</td>
<td>N/A</td>
<td>Glargine=NPH; Detemir=NPH</td>
<td>Glargine=NPH; Detemir=NPH</td>
<td>Glargine=NPH; Detemir=NPH</td>
<td>Safe treatment options in pregnancy without maternal or fetal complications</td>
</tr>
<tr>
<td>Glycemic control and maternal hypoglycemia</td>
<td>Mathiesen ER</td>
<td>8 trials N=310 Single RCT</td>
<td>Detemir-BB vs NPH-BB</td>
<td>A1C target noninferior to NPH-BB FPG Detemir-BB ↓ vs NPH-BB @24 GWs, p=0.012 @36 GWs, p=0.017</td>
<td>Serious adverse events were more common in the detemir group (40 vs 31%, N5) similar deterioration of retinopathy similar weight gain and insulin doses</td>
<td>N/A</td>
<td>N/A</td>
<td>No differences between all/diurnal/nocturnal major and minor hypoglycemia</td>
</tr>
<tr>
<td>Fetal safety in pregestational and gestational diabetes</td>
<td>Pollex E</td>
<td>8 trials N=702</td>
<td>Glargine NPH</td>
<td>N/A</td>
<td>N/A</td>
<td>No differences</td>
<td>N/A</td>
<td>Data from cohort studies may not be reliable</td>
</tr>
<tr>
<td>Elderly Age 65+ T1DM &amp; T2DM</td>
<td>Sorli C**</td>
<td>7 trials N=917</td>
<td>degludec vs glargine</td>
<td>N/A</td>
<td>Proportion of patients with confirmed hypoglycemia was similar between treatment groups T1DM 97.7% degludec, 94.1% glargine T2DM 58.7% both degludec and glargine T2DM Overall confirmed hypoglycemia over treatment period ERR=0.76 [0.61 to 0.95] Nocturnal confirmed hypoglycemia ERR 0.64 [0.43 to 0.95] T1DM</td>
<td>Excluded hypoglycemic unawareness, episode of severe hypoglycemia, serious comorbidity</td>
<td>All trials funded by Pharma</td>
<td></td>
</tr>
</tbody>
</table>
### Systematic Review and Meta-Analysis Comparing Long-Acting Basal Insulins Effects on Quality of Life

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Author</th>
<th>Trials N</th>
<th>Comparators</th>
<th>Minimum Trial Duration</th>
<th>Glycemic Control</th>
<th>FBS</th>
<th>Overall Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Health Status Improvement (Overall)</th>
<th>Health Status Improvement (Mental)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-related QOL (health utility)</td>
<td>Freemantle N°199 2013 6 trials N=4001</td>
<td>Insulin degludec vs insulin glargine</td>
<td>26 weeks</td>
<td>Degludec non-inferior</td>
<td>No difference</td>
<td>degludec ↓ NS</td>
<td>degludec ↓ SS</td>
<td>degludec ↑ modest but SS</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Health-related QOL (SF-36)</td>
<td>Freemantle N°199 2013 3 trials N=1922</td>
<td>Insulin degludec vs insulin glargine, each with oral anti-diabetic drugs in insulin naïve</td>
<td>26 weeks</td>
<td>A1C degludec non-inferior</td>
<td>Degludec ↓ (2/3 trials SS, trend favoring in 1 trial)</td>
<td>degludec ↓ SS</td>
<td>degludec ↓ SS</td>
<td>degludec ↑ SS</td>
<td>degludec ↑ SS</td>
<td></td>
</tr>
</tbody>
</table>

Key: A1C=hemoglobin A1c; NS=non-statistically significant; QOL=quality of life; SF-36=health-related quality of life 36-item Short Form; SS=statistically significant

### Systematic Reviews, Meta-Analysis, Expert Opinion on Cancer Risk and Basal Analogue Insulin Use

<table>
<thead>
<tr>
<th>Author</th>
<th>Insulin type</th>
<th>Cancer type</th>
<th>Cancer incidence increased</th>
<th>Cancer incidence decreased</th>
<th>Cancer incidence unchanged</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronsved HK 197 16 in vitro; 5 animal; 2 in vivo human; 29 epidemiologic Number not given</td>
<td>glargine vs non-glargine</td>
<td>Breast</td>
<td>glargine ↑ In vivo breast cancer cell lines (epidemiologic studies do not show an increased risk)</td>
<td>glargine ↑ In vivo breast cancer cell lines (epidemiologic studies do not show an increased risk)</td>
<td>glargine ↑ In vivo breast cancer cell lines (epidemiologic studies do not show an increased risk)</td>
<td>No compelling evidence that any insulin analogue is associated with increased breast cancer risk; studies underpowered, methodological limitations</td>
</tr>
</tbody>
</table>

Key: ERR=estimated rate ratio; N/A=no evidence presented in study; GWs=gestation weeks; NPH=neutral protamine Hagedorn insulin; NS=non-statistically significant; Rr=relative risk; SS=statistically significant; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus
<table>
<thead>
<tr>
<th>Author</th>
<th>Trials</th>
<th>N</th>
<th>Insulin type</th>
<th>Cancer type</th>
<th>Cancer incidence increased</th>
<th>Cancer incidence decreased</th>
<th>Cancer incidence unchanged</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen YB</td>
<td>11 trials</td>
<td>N=205,528 males N=7053 prostate cancer cases</td>
<td>insulin vs other glucose-lowering agents glargine vs non-glargine</td>
<td>Prostate</td>
<td></td>
<td>Insulin vs other glucose-lowering agents glargine vs other insulin</td>
<td>There was no substantial evidence for an increased risk of prostate cancer with insulin glargine vs non-glargine insulin use</td>
<td></td>
</tr>
<tr>
<td>Kolmers IN</td>
<td>19 trials</td>
<td>N=1,332,120 With N=41,947 cancers</td>
<td>Insulins glargine</td>
<td>Various</td>
<td>Pancreatic ↑ (new insulin or new glargine use) Prostate ↑ with glargine</td>
<td>Colorectal ↓ with glargine</td>
<td></td>
<td>Pancreatic cancer risk increased with insulin use, perhaps due to reverse causality.</td>
</tr>
<tr>
<td>Dejgaard A</td>
<td>16 trials; N=6644 (detemir vs NPH) 5 trials; N=2049 (detemir vs glargine)</td>
<td>detemir glargine NPH</td>
<td>Various</td>
<td>NPH ↑ any cancer risk vs detemir glargine ↑ vs detemir, NS</td>
<td>detemir vs glargine</td>
<td></td>
<td>Company sponsored(All Novo Nordisk-sponsored RCT in T1DM or T2DM)</td>
<td></td>
</tr>
<tr>
<td>Du X</td>
<td>7-cohort studies Number not provided</td>
<td>glargine vs non-glargine</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td>Overall and for breast, prostate, pancreatic and gastrointestinal cancers</td>
<td></td>
</tr>
<tr>
<td>Karlstad O</td>
<td>42 trials</td>
<td>Number not provided</td>
<td>glargine vs non-glargin</td>
<td>Various</td>
<td>Glargine ↑ breast</td>
<td>Glargine ↓ colon</td>
<td></td>
<td>methodological limitations and confounders</td>
</tr>
<tr>
<td>Tang X</td>
<td>11 trials</td>
<td>N=448,028 (N=19,128 with cancer)</td>
<td>glargine vs non-glargin</td>
<td>Various</td>
<td>Glargine ↓ vs non-glargin</td>
<td>Breast, prostate pancreas, respiratory tract</td>
<td>RCT and observational studies; low quality evidence</td>
<td></td>
</tr>
<tr>
<td>Edwards KL</td>
<td>Opinion Statement of the Endocrine and Metabolism Practice and Research Network of the American College of Clinical Pharmacy</td>
<td>glargin</td>
<td>Various</td>
<td></td>
<td>tenuous relationship</td>
<td></td>
<td>should not affect choice of initial insulin therapy pending additional information</td>
<td></td>
</tr>
</tbody>
</table>

**Key:** NS=non-statistically significant; RCT=randomized, controlled trials; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

### Systematic Review of Cardiovascular Morbidity and Mortality Associated With Different Insulin Regimens in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Author</th>
<th>#trials</th>
<th>N</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price H</td>
<td>2015</td>
<td>N=109,910</td>
<td>Primary outcomes: cardiovascular morbidity and mortality including fatal and non-fatal myocardial infarction, fatal and/or non-fatal stroke, major adverse cardiac events and cardiovascular death. Secondary outcome: All-cause mortality</td>
<td>&quot;Quantitative synthesis of the results from included studies was not possible due to a large amount of clinical heterogeneity. Each study evaluated cardiovascular outcomes across different insulin-exposure contrasts. RCTs did not identify any difference in cardiovascular risks among a fixed versus variable insulin regimen, or a prandial versus basal regimen, albeit clinically important risk and benefits cannot be ruled out due to wide CIs. Findings from cohort studies were variable with an increased and decreased risk of cardiovascular events and all-cause mortality being reported.”</td>
</tr>
</tbody>
</table>

**Key:** OAD=oral antidiabetic drugs; G=glargin; D=detemir; N/A=no evidence presented in study; SS=statistically significant; NS=non-statistically significant; BB=basal/bolus