Initiating and Intensifying Insulin Therapy in Patients With Type 2 Diabetes
Initiation and Intensification of Insulin Therapy in Patients With Type 2 Diabetes – An Overview

This presentation will discuss:

• Insulin evolution over the last century
• Strategies to select and initiate insulin treatment in patients with T2D
• Current treatment algorithms and the benefits of early insulinization
• The profiles of available basal and prandial insulin formulations
• Insulin delivery routes and formulations, including emerging options
• Therapeutic inertia and treatment intensification
• Using insulin therapy in combination with other antihyperglycemic agents
• Insulin safety, including cardiovascular safety and hypoglycemia risk

T2D, type 2 diabetes.
Celebrating 100 Years of Insulin Development: 1921-2021
A Century of Insulin Development and Evolution

- Insulin discovered (1921)
- Protamine and protamine zinc insulins (1936)
- NPH insulin (1946)
- Lente (zinc) insulin (1952) + Concentrated U-500 bovine insulin (1952)
- Lente (zinc) insulin (1952)
- Synthetic human insulin (1965)
- Recombinant human insulin (1979)
- Insulin pen developed (1981)
- Insulin detemir approved in US (2005)
- Insulin aspart and insulin glargine approved in US (2000)
- Insulin degludec approved in US (2015)
- Inhaled insulin approved in US (2014)
- Insulin lispro approved in US (1996)
- Inhaled insulin approved in US (2014)
- Insulin detemir approved in US (2005)
- Insulin aspart and insulin glargine approved in US (2000)
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- Insulin aspart and insulin glargine approved in US (2000)
- Insulin degludec approved in US (2015)


NPH, neutral protamine Hagedorn; US, United States.

A Timeline of Diabetes Technology

Adapted from: Kovatchev B. Bioelectronic Medicine. 2018;4(14).
Selecting Insulin vs Non-insulin Therapy in Patients With T2D

- Insulin is the most potent antihyperglycemic agent.¹
- Many factors must be considered when choosing to initiate insulin therapy vs other antihyperglycemic agents.¹
- Therapeutic selection for patients with T2D should be individualized based on patient and medication attributes.¹,²
  - **Patient attributes**: Initial A1C level, diabetes duration, obesity status, age, hypoglycemia risk, and other comorbidities.
  - **Medication attributes**: Efficacy, mechanism of action, hypoglycemia risk, risk of weight gain, adverse events, tolerability, ease of use, likely adherence, and cost.
- With the goals of safety and risk reduction, select therapy that reflects the patient’s cardiac, cerebrovascular, and renal status.¹,²


T2D, type 2 diabetes.
AACE Glycemic Control Algorithm: When to Consider Insulin Therapy in Patients With T2D

**A1C >9.0% and/or symptomatic hyperglycemia; with or without other antihyperglycemic agents**

**In combination with 1-2 other antihyperglycemic agents when A1C is ≥7.5%-9.0%**

**Added to monotherapy or dual therapy when A1C goals are not met after 3 months**

- Patients taking 2 oral agents with A1C >8.0% and/or long-standing T2D are less likely to reach target A1C with a 3rd non-insulin agent.
- Adding a 3rd non-insulin agent may successfully reduce glycemia in some patients, but many will eventually require insulin.

**Choice of treatment depends on patient and medication**

AACE Glycemic Control Algorithm

AGi, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; GLN, glinides; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HFrEF, heart failure with reduced ejection fraction; LA, long-acting; MET, metformin; QR, quick-release; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

ADA Overall Approach to Glucose-Lowering Medication: When to Consider Insulin Therapy in Patients With T2D

- The early introduction of insulin should be considered in the setting of ongoing catabolism (weight loss, hypertriglyceridemia, ketosis), symptoms of hyperglycemia, A1C levels >10%, and/or blood glucose levels ≥300 mg/dL.
- Insulin can be added to metformin (first-line therapy) if the A1C target is not achieved after 3 months.
- Due to the progressive nature of T2D, many patients eventually require and benefit from insulin therapy.

Agents other than insulin may be preferred; choice of treatment depends on patient and medication attributes.

ADA, American Diabetes Association; T2D, type 2 diabetes.
Achievement of A1C <7% With Basal Insulin Regimen in T2D

- Systematic review (29 RCTs, N=17,588 patients) evaluating the effectiveness of insulin analog regimens
- A1C <7% achieved in 41.4% (95% CI: 35.6%, 47.4%)
- Predictors of response: first insulin treatment; lower insulin dose; use of 2 OADs
- Over 30 days, mean/median hypoglycemia with basal insulin was 0.50/0.39 events/patient
- Weight gain: 1.8 kg (95% CI: 1.2, 2.1)

### Basal Insulin Proportion of patients with A1C <7%

<table>
<thead>
<tr>
<th>Study (First author, year)</th>
<th>Pooled estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riddle, 2003</td>
<td>41.4% (35.6%-47.4%)</td>
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<tr>
<td>Malone, 2004</td>
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<tr>
<td>Raskin, 2005</td>
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<tr>
<td>Heine, 2005</td>
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<td>Janka, 2005</td>
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<td>Malone, 2005</td>
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<td>Davies, 2005</td>
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<td>Davies, 2005</td>
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<td>Kann, 2006</td>
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<td>Jacober, 2006</td>
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<td>Kazda, 2006</td>
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<td>Kennedy, 2006</td>
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<td>Kennedy, 2006</td>
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<td>Kennedy, 2006</td>
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<td>Kennedy, 2006</td>
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<td>Hermansen, 2006</td>
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<td>Rosenstock, 2006</td>
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<td>Gernstein, 2006</td>
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<td>Standl, 2006</td>
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<td>Standl, 2006</td>
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<td>Holman, 2007</td>
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<td>Robbins, 2007</td>
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<td>Barnett, 2007</td>
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<td>Esposito, 2008</td>
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<td>Esposito, 2008</td>
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<td>Bretzel, 2008</td>
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<td>Rosenstock, 2008</td>
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<td>Rosenstock, 2008</td>
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<tr>
<td>Buse, 2009</td>
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<td>Raz, 2009</td>
<td></td>
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<td>Russell-jones, 2009</td>
<td></td>
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<td>Bickle, 2009</td>
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<td>Blonde, 2009</td>
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<td>Blonde, 2009</td>
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<td>Blonde, 2009</td>
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<td>Rosenstock, 2009</td>
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<td>Strojek, 2009</td>
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<td>Fogelfeld, 2010</td>
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<tr>
<td>Fogelfeld, 2010</td>
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</tbody>
</table>

Cl, confidence interval; OAD, oral antidiabetic drug; RCT, randomized controlled trial.
Very Early Insulinization in T2D

- Evidence suggests that early, short-term insulin treatment can improve glycemic control and preserve beta-cell function in patients with newly diagnosed T2D and severe, symptomatic hyperglycemia.1-3

- By treating patients with insulin before diabetes has progressed (typically for 2 weeks to 3 months), glucolipotoxicity is rapidly reversed, and beta-cells are given the chance to “rest.”1-3

- Several controlled and uncontrolled studies have shown that intensive, early, short-term insulin therapy can lead to sustained normoglycemia for up to 12 months in ~31%-51% of patients.1,4-9

- This treatment approach may also preserve residual beta-cell function, enabling the effective, future use of non-insulin antihyperglycemic agents.1,6,7

T2D, type 2 diabetes.

Patients With Ketosis-Prone T2D Require Early Insulinization

- Ketosis-prone T2D is characterized by the new, acute onset of hyperglycemia with ketoacidosis, requiring hospitalization.\(^1\)
- Patients often have a family history of T2D and are predominantly:\(^1-4\)
  - Black or Latino
  - Middle-aged (but can be younger)
  - Overweight and/or obese
  - Male
- Patients present with impaired insulin secretion and action;\(^3\) the clinical course resembles T2D.\(^1\)
- Treatment requires intensive, initial insulin for several weeks to months.\(^1,3\)
- Following insulin discontinuation, metabolic abnormalities typically improve, and a proportion of patients enter a period of near-normoglycemic remission.\(^1,3\)

T2D, type 2 diabetes.

Early Insulinization in Patients With Ketosis-Prone T2D: 40.5% Remained in Remission at 10 Years’ Follow-up

- Cohort study of 111 hospitalized patients with KP T2D (both insulin-dependent and nondependent) of Sub-Saharan African descent
- With early treatment, a majority (75.7%) achieved remission from insulin dependence:
  - Mean time to remission, 14.3 weeks
  - Mean duration of remission, 40.5 ± 23.2 months
- At 10 years of follow-up, 40.5% of patients remained in remission
- Study also included patients with T1D, T2D, and controls (see Figure)


Ten-year beta-cell secretory reserve following early intensive insulin therapy, with T1D or T2D (with or without KP in T2D) and controls

ID, insulin-dependent; KP, ketosis-prone; NID, non-insulin dependent; T1D, type 1 diabetes; T2D, type 2 diabetes.
Characteristics of Basal Insulins

- Typically administered as a single daily dose, they can be added to oral agents.\(^1,2\)
- They restrain hepatic glucose production and limit between-meal and overnight hyperglycemia.\(^1\)
- Basal insulin analogs are preferred over NPH insulin because a single basal analog dose provides a relatively flat serum insulin concentration for $\geq 24$ hours.\(^2\)
- Long-acting basal analogs (glargine U100 or detemir) have been shown to reduce the risk of symptomatic and nocturnal hypoglycemia vs NPH insulin.\(^1,2\)
- The newest ultralong-acting basal insulin formulations (glargine U300, degludec U100, and U200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U100 and detemir.\(^2\)
  - They may confer lower hypoglycemia risk.\(^1,2\)
  - Degludec U200 and glargine U300 are more concentrated than their U100 formulations, allowing for higher doses of basal insulin administration per volume injected.\(^1\)
- Regular U-500 insulin has delayed onset and a longer duration of action; it functions similarly to an intermediate-acting (NPH) insulin and can be used as 2 or 3 daily injections.\(^1\)

NPH, neutral protamine Hagedorn; T2D, type 2 diabetes.

### Available Basal Insulins

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>NPH Insulin(^1-2)</th>
<th>Insulin Glargine(^*,1,3-4)</th>
<th>Insulin Detemir(^5-6)</th>
<th>Glargine U300(^7-8)</th>
<th>Insulin Degludec U100 and U200(^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>1-2 hours</td>
<td>1.5 hours</td>
<td>3-4 hours</td>
<td>6 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td>Peak</td>
<td>4-10 hours</td>
<td>Flat</td>
<td>Relatively flat</td>
<td>Flat</td>
<td>Flat</td>
</tr>
<tr>
<td>Effective duration</td>
<td>14+ hours</td>
<td>≤24 hours</td>
<td>≤24 hours</td>
<td>≤36 hours</td>
<td>≤42 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>Unknown</td>
<td>12.5 hours</td>
<td>5-7 hours</td>
<td>17-19 hours</td>
<td>~25 hours</td>
</tr>
<tr>
<td>Steady state</td>
<td>Unknown</td>
<td>2-4 days</td>
<td>2 days</td>
<td>3-4 days</td>
<td>3-4 days</td>
</tr>
</tbody>
</table>

* Pharmacodynamic properties of biosimilar insulin glargine are similar to that of insulin glargine.

Basal Insulin Action Profiles

H, hour; NPH, neutral protamine Hagedorn.
Median Cost of Insulin Products in the US

### Average Wholesale Price per 1,000 Units of Specified Dosage Form/Product

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dosage form/product</th>
<th>AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro follow-on product</td>
<td>U-100 vial</td>
<td>$157</td>
</tr>
<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$202</td>
</tr>
<tr>
<td>Lispro</td>
<td>U-100 3 mL cartridges</td>
<td>$408</td>
</tr>
<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$424</td>
</tr>
<tr>
<td>Glulisine</td>
<td>U-100 vial</td>
<td>$314</td>
</tr>
<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$439</td>
</tr>
<tr>
<td>Aspart (original and faster-acting)</td>
<td>U-100 vial</td>
<td>$347</td>
</tr>
<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$437</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>U-100 vial</td>
<td>$165</td>
</tr>
<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$377</td>
</tr>
<tr>
<td>Human regular</td>
<td>U-100 vial</td>
<td>$165</td>
</tr>
<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$377</td>
</tr>
<tr>
<td>U-500 human regular insulin</td>
<td>U-500 vial</td>
<td>$178</td>
</tr>
<tr>
<td></td>
<td>U-500 prefilled pen</td>
<td>$230</td>
</tr>
<tr>
<td>Glargine follow-on</td>
<td>U-100 prefilled pen</td>
<td>$261</td>
</tr>
<tr>
<td></td>
<td>U-100 vial; U-100 prefilled pen</td>
<td>$340</td>
</tr>
<tr>
<td></td>
<td>U-300 prefilled pen</td>
<td>$346</td>
</tr>
<tr>
<td></td>
<td>U-100 vial; U-100 prefilled pen</td>
<td>$370</td>
</tr>
<tr>
<td></td>
<td>U-200 prefilled pen</td>
<td>$407</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-100 prefilled pen</td>
<td>$261</td>
</tr>
<tr>
<td>Detemir</td>
<td>U-100 vial; U-100 prefilled pen</td>
<td>$340</td>
</tr>
<tr>
<td></td>
<td>U-300 prefilled pen</td>
<td>$346</td>
</tr>
<tr>
<td></td>
<td>U-100 vial; U-100 prefilled pen</td>
<td>$370</td>
</tr>
<tr>
<td></td>
<td>U-200 prefilled pen</td>
<td>$407</td>
</tr>
<tr>
<td>Degludec</td>
<td>Glargine/lixisenatide</td>
<td>$565</td>
</tr>
<tr>
<td></td>
<td>Degludec/liraglutide</td>
<td>$832</td>
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<tr>
<td></td>
<td>Glargine/lixisenatide</td>
<td>$565</td>
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<tr>
<td></td>
<td>Degludec/liraglutide</td>
<td>$832</td>
</tr>
<tr>
<td></td>
<td>100/33 prefilled pen</td>
<td>$565</td>
</tr>
<tr>
<td></td>
<td>100/3.6 prefilled pen</td>
<td>$832</td>
</tr>
</tbody>
</table>

- Insulin cost has steadily risen over past 2 decades, burdening patients and contributing to nonadherence.\(^1\)
- Some PAPs provide low/no-cost insulin products.\(^2\)
- Human insulins are available for ~$25/vial at Walmart and Sam's Club.\(^3\)
- Some prices are temporarily lowered due to COVID-19.\(^4\)

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Adding/Intensifying Insulin in Patients With T2D

- When insulin becomes necessary, add a single daily dose of basal insulin to the regimen.
- Adjust dosage at regular and initially short intervals, measured in days, to achieve targeted glycemic goal while avoiding hypoglycemia.

BG, blood glucose; FBG, fasting blood glucose; NPH, neutral protamine Hagedorn; TDD, total daily dose.

Avoiding Therapeutic Inertia During Treatment Intensification

Clinical or therapeutic inertia occurs when treatment is not initiated or intensified, despite a patient not achieving their A1C goal.¹

- All patients should be educated on the progressive nature of T2D.²,³
- Avoid using insulin as a threat or sign of personal failure or punishment.²,⁴
- Do not delay intensification if treatment is not meeting goals; timely glycemic control has a beneficial effect on patient outcomes.²,⁴
- Reevaluate regimen every 3-6 months and adjust/intensify as needed.²,⁵
- If goals not met with OADs, it is recommended to intensify treatment to injectable agent (GLP-1 RA or insulin).²,⁵

GLP-1 RA, glucagon-like peptide-1 receptor agonist; OADs, oral antidiabetic drugs; T2D, type 2 diabetes.

Rates of Treatment Intensification and Non-intensification in Patients With T2D

Treatment intensification rates (by A1C) in the 6-month period following A1C ≥7%

- Retrospective electronic health records analysis of Cleveland Clinic patients (N=7389; 2005-2016)
- Overall, 63% did not receive therapeutic intensification in the 6 months following an elevated A1C measurement

<table>
<thead>
<tr>
<th>A1C Range</th>
<th>Intensification</th>
<th>No intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0%-7.9% (n=4577)</td>
<td>28.4%</td>
<td>71.6%</td>
</tr>
<tr>
<td>8.0%-8.9% (n=1364)</td>
<td>46.7%</td>
<td>53.3%</td>
</tr>
<tr>
<td>≥9.0% (n=1448)</td>
<td>59.6%</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

T2D, type 2 diabetes.
Patient-Related Factors for Delaying Insulin Therapy

- Misconceptions
  - Progression to insulin signifies failure to control disease
  - Insulin is toxic, may lead to amputations, blindness, or other complications\(^1,2\)
- Fear of needles/injections, weight gain, hypoglycemia\(^1,2\)
- Lack of information, experience, and/or support managing insulin regimens\(^1,2\)
- Inconvenient, time-consuming\(^1\)
- Concerns about potential permanence of therapy\(^2\)
- Complexity of regimen\(^2\)
- Cost\(^1,2\)

Real-World Choices Depend on the Patient

- Key variables, factors to consider\(^1,2\)
  - Patient preference for simpler regimen
  - Frequency of self-monitoring of blood glucose
  - Lifestyle variability, including meal timing and carbohydrate intake
  - Presence of postprandial hyperglycemia
  - Patient’s ability to follow the prescribed regimen
  - Educational and emotional support available to patient
  - Patient dexterity issues, age, visual impairment
  - Cost barriers, insurance coverage

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Barriers to Insulin Therapy and Strategies to Overcome Them


DSME, Diabetes self-management education.
Available Delivery Routes for Insulin Administration

**Subcutaneous**
- Syringes
- Pens
- Disposable pods (basal/bolus)
  - V-Go® (1/day)
  - OmniPod DASH™ (2-3/day)
- Insulin pumps (basal/bolus)

**Other methods**
- Inhaled (Afrezza®)
- Intravenous (hospital use)
# Insulin Pens: One Strategy to Overcome Therapeutic Inertia

## Advantages\(^1,^2\)
- Convenience; syringe and vial combined in 1 device
- Improved patient satisfaction and adherence
- Greater dosing accuracy
- Ease of use
- Greater portability
- Mealtime flexibility
- Less reported pain
- Social acceptability and improved quality of life

## Barriers\(^3\)
- Potentially higher costs than insulin vials
- Insurance coverage

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Basal Insulin in Combination With Non-insulins to Cover Postprandial Glucose Excursions

- A GLP-1 RA, SGLT2i, or DPP4i can be added to basal insulin to achieve glucose targets.\(^1\)
- When added to insulin, incretins and SGLT2 inhibitors enhance glucose reductions.\(^1\)
- Incretins and SGLT2 inhibitors may promote weight loss without increasing hypoglycemia risk.\(^1\)
  - Insulin dose reductions may be necessary to reduce hypoglycemia risk; monitor and adjust as appropriate.\(^2,3\)
- Incretins also increase endogenous insulin secretion in response to meals, reducing postprandial hyperglycemia.\(^1\)
- Basal insulin + a GLP-1 RA may offer greater efficacy than oral agents; fixed-ratio combinations are available.\(^1,4\)
  - Basal insulin dose may need to be reduced to avoid hypoglycemia.\(^1\)

DPP4i, dipetyld peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
Basal Insulin Plus Incretin Therapy in T2D: DPP-4 Inhibitors

- Systematic review of 5 RCTs evaluating DPP4i (ALO, SAXA, SITA, VILDA) combined with basal insulin in patients with T2D (N=1502)

- The combination of DPP4i with insulin improved glycemic control without excess hypoglycemia and with less weight gain than non-incretin-based therapies

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<tbody>
<tr>
<td>Intervention</td>
<td>VILDA + INS vs INS + PBO</td>
<td>ALO (12.5 mg) + INS ± MET vs ALO (25 mg) + INS ± MET vs PBO + INS ± MET</td>
<td>GLA + MET + EXE vs GLA + MET + SITA vs GLA + MET</td>
<td>SITA + INS ± MET vs INS ± MET + PBO</td>
<td>SAXA + INS ± OAD vs INS ± OAD + PBO in patients with CKD</td>
</tr>
<tr>
<td>All hypoglycemic episodes (major)</td>
<td>113 vs 185 (0 vs 6)</td>
<td>35 vs 35 vs 31* (0 vs 1 vs 6)</td>
<td>47 vs 12 vs 10 (0 vs 0 vs 0)</td>
<td>155 vs 76 (2 vs 1)</td>
<td>17 vs 19 (0 vs 2)</td>
</tr>
</tbody>
</table>

* Number of patients reporting ≥1 event

ALO, alogliptin; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase 4 inhibitor; EXE, exenatide; GLA, glargine; INS, insulin; MET, metformin; OAD, oral antidiabetic drug; PBO, placebo; RCT, randomized controlled trial; T2D, type 2 diabetes; SAXA, saxagliptin; SITA, sitagliptin; VILDA, vildagliptin.

Basal Insulin Plus SGLT2 Inhibitors in T2D

CANA RCT (N=2072, 18 weeks); patients inadequately controlled on insulin ± OADs
- A1C change with CANA 100 and 300 mg vs PBO: -0.6% and -0.7%; (P<0.001 for both)¹

EMPA RCT (N=563, 52 weeks); patients inadequately controlled on insulin ± MET
- A1C change with EMPA 10 and 25 mg vs PBO: -0.4% and -0.5%; (P<0.001 for both)²

DAPA RCT (N=808, 104 weeks); patients inadequately controlled on insulin ± OADs
- A1C change with DAPA 5mg/10mg and 10 mg vs PBO: -0.4% and -0.5%; (P<0.001 for both)³

In the CANA and EMPA studies, patients treated with SGLT2i had statistically significant weight loss vs PBO¹,²

\[ \Delta A1C, \% \text{ from BL} \]

- CANA 300 mg¹,a
  -0.7
  -1.3

- EMPA 25 mg²,b
  -0.8

- DAPA 10 mg³,c
  -0.8

- PBO
  -0.4

\[ P<0.05 \text{ vs placebo for all SGLT2 inhibitors} \]

¹ 18 weeks; BL A1C 8.3% (mean); basal, bolus, or basal-bolus; =60% to 65% on basal-bolus; ² 52 weeks; BL A1C 8.29%-8.39%; multiple daily insulin (basal-bolus) injections, insulin titrated weeks 19 to 40; ³ 104 weeks; BL A1C 8.46%-8.62%; 17% on basal only, 83% on bolus or basal-bolus (=48% basal-bolus, =35% bolus only).

BL, baseline; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; MET, metformin; OAD, oral antidiabetic drug; PBO, placebo; RCT, randomized controlled trial; SLGT2i, sodium-glucose cotransporter-2 inhibitor.

Basal Insulin Plus Incretin Therapy in T2D: GLP-1 RAs

Systematic review (RCTs and real-world studies), representing ~5000 patients with T2D

- Review analyzed the safety and efficacy of insulin + GLP-1 RA combination therapy.
- Combination therapy improved glycemic control without increased weight gain or hypoglycemia.
- Relative treatment benefit was influenced by insulin titration patterns.
  - Aggressive insulin titration to optimize glycemic control yielded less weight loss benefit.
  - Insulin sparing was associated with greater weight loss but more modest glycemic control.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; RCT, randomized controlled trial; T2D, type 2 diabetes.
Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

• iGlarLixi 100/33
  • Insulin glargine and lixisenatide injection
  • Approved by FDA November 2016
  • Indication: Adults with T2D inadequately controlled on basal insulin (<60 units daily) or lixisenatide
  • 1 unit contains:
    • 1 U insulin glargine and
    • 0.33 mcg lixisenatide
  • Administered SC once daily
  • Starting dose: 15 or 30 units (15 or 30 U insulin glargine and 5 or 10 mcg lixisenatide)
  • SoloStar® pen

• iDegLira 100/3.6
  • Insulin degludec and liraglutide injection
  • Approved by FDA November 2016
  • Indication: Adults with T2D inadequately controlled on basal insulin (<50 units daily) or liraglutide
  • 1 unit contains:
    • 1 U insulin degludec and
    • 0.036 mg liraglutide
  • Administered SC once daily
  • Starting dose: 16 units (16 U insulin degludec and 0.58 mg liraglutide)
  • FlexTouch® pen

FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iDegLira, insulin degludec and liraglutide; iGlarLixi, insulin glargine and lixisenatide; SC, subcutaneous; T2D, type 2 diabetes.

Soliqua™ 100/33 (insulin glargine and lixisenatide injection) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US. November 2016.

Xultophy® 100/3.6 (insulin degludec and liraglutide injection) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2016.
Glucose Control With Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

Phase 3 RCTs in patients with T2D showed improved glycemic control with fixed-ratio basal insulin and GLP-1 RA combination compared with individual components administered alone.

### Table: Baseline and Change in A1C (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Add-on to OAs, Insulin-Naive 26 Weeks</strong></td>
<td></td>
<td>8.3</td>
<td>-1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lira</td>
<td>1663</td>
<td>8.3</td>
<td>-1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iDeg</td>
<td>8.3</td>
<td>-1.4</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>iDegLira</td>
<td></td>
<td>-1.9</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td><strong>Add-on to Basal Insulin ± OAs 26 Weeks</strong></td>
<td></td>
<td>8.8</td>
<td>-0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iDeg</td>
<td>413</td>
<td>8.7</td>
<td>-1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iDegLira</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Add-on to OAs, Insulin-Naive 30 Weeks</strong></td>
<td></td>
<td>8.1</td>
<td>-1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lixi</td>
<td>1170</td>
<td>8.1</td>
<td>-1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iGlar</td>
<td>8.1</td>
<td>-1.1</td>
<td>S</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iGlarLixi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Add-on to Basal Insulin ± OAs 30 Weeks</strong></td>
<td></td>
<td>8.1</td>
<td>-0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iGlar</td>
<td>736</td>
<td>8.1</td>
<td>-1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iGlarLixi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Per protocol maximum dose: 50 units/day (no maximum dose of degludec alone was specified in the insulin naïve trial). * Per protocol maximum dose: 60 units/day.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; iDeg, insulin degludec; iDegLira, insulin degludec and lixisenatide; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lira, liraglutide; Lixi, lixisenatide; NI, noninferior; OA, oral agent; S, superior; T2D, type 2 diabetes.

When Basal Insulin Is Not Enough to Control Glycemia

- Patients whose glycemia remains uncontrolled while receiving basal insulin in combination with oral agents or GLP-1 RAs may require mealtime insulin to cover postprandial hyperglycemia.¹,²

DPP4i, dipetidyldipeptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Prandial Insulin Intensification

- Consider prandial insulin when basal insulin TDD is >0.5 U/kg\(^1\)
  - Beyond this dose, hypoglycemia risk increases without A1C benefit\(^1\)
- **Basal plus**: Cover largest meal with prandial insulin; add additional meal coverage in stepwise fashion, as needed\(^1,2\)
  - Rapid-acting injectable insulin analogs and inhaled insulin associated with less hypoglycemia than regular human insulin\(^1\)
- **Basal-bolus**: Most effective insulin regimen\(^1\)
  - Greater flexibility for patients who have variable mealtimes and/or meal carbohydrate content\(^1\)
  - Associated with weight gain; MDI and cost may impede adherence\(^1,3\)
- Titrate dose based on blood glucose and formulation PD profile\(^2\)
  - Some oral agents may need to be discontinued\(^2\)

---

## Available Prandial Insulins

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Insulin Lispro&lt;sup&gt;1,2,3&lt;/sup&gt;</th>
<th>Insulin Aspart&lt;sup&gt;1,4,5&lt;/sup&gt;</th>
<th>Insulin Glulisine&lt;sup&gt;1,6&lt;/sup&gt;</th>
<th>Regular Human Insulin&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Inhaled Insulin&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Analog; rapid-acting ≤15 minutes</td>
<td>Analog; faster-acting ≤15 minutes</td>
<td>Analog; rapid-acting ≤5 minutes</td>
<td>0.25-0.5 hours 1 hour ~5 minutes</td>
<td>1 hour ~12 minutes</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td>1 hour~2 hours</td>
<td>1-3 hours</td>
<td>1 hour</td>
<td>0.5-1 hour 2-4 hours</td>
<td>2-4 hours 35-55 minutes</td>
</tr>
<tr>
<td><strong>Effective duration</strong></td>
<td>3-5 hours</td>
<td>5-6 hours</td>
<td>3-5 hours</td>
<td>4 hours 5-8 hours</td>
<td>5-8 hours 1.5-3.0 hours</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>1 hour 44 minutes</td>
<td>1.4 hours</td>
<td>1.1 hours</td>
<td>42 minutes 1.5 hours</td>
<td>2.0-3.5 hours</td>
</tr>
</tbody>
</table>

Responses to inhaled insulin are dose-dependent. Only consider inhaled insulin on an individual basis. Dose conversion is required, as is initial and ongoing evaluation of lung function. Contraindicated in patients with chronic lung disease<sup>7</sup>

**Prandial Insulin Action Profiles**


- **Relative Insulin Effects**
  - **Endogenous (ie, normal insulin function)**
  - **Rapid-acting (ie, aspart, lispro)**
  - **Short-acting (ie, regular)**
  - **Ultra-rapid-acting (ie, regular)**
  - **Inhaled Insulin**

* ~12 units; patients with type 1 diabetes
A1C Reductions and Hypoglycemia With Inhaled Insulin (Afrezza®)

- A1C reductions with inhaled insulin were significantly greater than placebo.¹
- Patients taking inhaled insulin had a higher incidence of hypoglycemia vs placebo.¹
  - All events, 67.8% vs 30.7%; \( P<0.0001 \)
  - Severe events, 5.7% vs 1.7%; \( P=0.09 \).
- Patients receiving inhaled insulin weight gain (~1 lb) vs weight loss (~2.4 lb) with placebo (\( P<0.0001 \)).¹
- Coughing was most common adverse event with inhaled insulin.¹,²

Double-blind, 24-week RCT (N=176) comparing prandial inhaled insulin vs prandial inhaled placebo (patients with T2D)¹

---

### Inhaled Insulin, Dose Conversion Table

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>Inhaled Insulin Dose</th>
<th># of Cartridges Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td>4 unit (blue)</td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td>8 unit (green)</td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>12 unit (yellow)</td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td>12 unit (yellow)</td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td>12 unit (yellow)</td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td>12 unit (yellow)</td>
</tr>
</tbody>
</table>

Basal-Bolus Insulin Regimens in T2D

• **Advantages**\(^1\)
  - Effective in approximately two-thirds of patients in achieving A1C goals

• **Disadvantages**\(^2,3\)
  - Multiple injections
  - Low adherence
  - Potential for weight gain
  - Hypoglycemia risk

---

The Basal-Bolus Approach to Insulin Delivery

Basal Insulin

Prandial Insulin

Basal + Prandial (Bolus) Insulin

Plasma Insulin

Breakfast  Lunch  Dinner
Achievement of A1C <7% with Basal-Bolus Insulin Regimens in T2D

- Systematic review of 8 RCTs (N=2114) evaluated effectiveness of basal-bolus insulin regimens
- A1C <7% achieved in 53.9% (95% CI: 43.5%, 64.0%)
- Hypoglycemic events (mean/patient/30 days): 0.88 (95% CI: 0.35, 1.3)
- Weight gain: 2.8 kg (95% CI: 1.8, 3.7)
- Escalation from basal to basal-bolus increases success rate in an additional ~12%-14% of patients

<table>
<thead>
<tr>
<th>Study (First author, year)</th>
<th>Proportion of patients with A1C &lt;7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoolander, 2008</td>
<td></td>
</tr>
<tr>
<td>Hoolander, 2008</td>
<td></td>
</tr>
<tr>
<td>Rosenstock, 2008</td>
<td></td>
</tr>
<tr>
<td>Bergenstal, 2008</td>
<td></td>
</tr>
<tr>
<td>Bergenstal, 2008</td>
<td></td>
</tr>
<tr>
<td>Lankisch, 2008</td>
<td></td>
</tr>
<tr>
<td>Lankisch, 2008</td>
<td></td>
</tr>
<tr>
<td>Liebl, 2009</td>
<td></td>
</tr>
<tr>
<td>Riddle, 2009</td>
<td></td>
</tr>
<tr>
<td>Raskin, 2009</td>
<td></td>
</tr>
<tr>
<td>Fritsche, 2009</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; RCT, randomized controlled trial.
Premixed Insulin Analogues in Patients With T2D

Initiation and Titration

- Insulin naïve patients → 10-12 units or 0.3 u/kg
- Split dose (50/50 morning and evening)
- Existing basal → unit-to-unit conversion
- Existing basal-bolus → reduce TDD by 20%-30%
- Titrate 1-2 units, or 10%-15%, 1-2x weekly, until goal
- Increase TDD by 10% if FPG or premeal blood glucose >180 mg/dL

Dose Adjustment

<table>
<thead>
<tr>
<th>Lowest pre-meal blood glucose level</th>
<th>Adjustment for next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥126 mg/dL</td>
<td>+2 units</td>
</tr>
<tr>
<td>73-124 mg/dL</td>
<td>0</td>
</tr>
<tr>
<td>≤72 mg/dL</td>
<td>-2 units</td>
</tr>
</tbody>
</table>

Benefits

- Simple and convenient (twice-daily administration)
- Basal-bolus in 1 medication

Disadvantages

- Higher risk of hypoglycemia
- Less flexibility

Premixed insulin combines long- and short-acting insulin in a single formulation

FPG, fasting plasma glucose; T2D, type 2 diabetes; TDD, total daily dose.

INITIATE Study: More Patients With T2D Reached A1C Target With BIAsp 70/30 Than Glargine

- 28-week randomized, open-label, treat-to-target study
- The efficacy and safety of BIAsp 70/30 were compared with once-daily insulin glargine in patients with T2D (N=209) inadequately controlled on OADs
- Significantly more BIAsp 70/30 patients reached target A1C vs glargine patients
  - A1C <7.0%: 66% vs 40%
  - A1C ≤6.5%: 42% vs. 28%
Insulin Pump Therapy in Patients With T2D

According to AACE Guidelines, insulin pump therapy may improve QoL and can be considered in patients with T2D who are insulin-dependent and not meeting glycemic goals with MDIs

<table>
<thead>
<tr>
<th>Ideal Candidates</th>
<th>Poor Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Motivated to achieve optimal glycemic control</td>
<td>• Not motivated to achieve glucose control</td>
</tr>
<tr>
<td>• Currently performing ≥4 daily insulin injections and ≥4 SMBG measurements</td>
<td>• Unwilling to perform frequent MDI or SMBG</td>
</tr>
<tr>
<td>• Able and willing to safely and effectively use this complex and time-consuming therapy</td>
<td>• Previous nonadherence to insulin injections</td>
</tr>
<tr>
<td>• C-peptide positive, but with suboptimal control using maximized basal-bolus injections</td>
<td>• Unrealistic expectations of pump injections</td>
</tr>
<tr>
<td>• Trained in carbohydrate counting and to calculate insulin correction doses</td>
<td>• Belief that pump use will remove patient responsibility for diabetes management</td>
</tr>
<tr>
<td>• Willing to maintain frequent contact with health care team</td>
<td>• Concerned that pump will interfere with lifestyle (eg, sports or sexual activity)</td>
</tr>
<tr>
<td></td>
<td>• History of serious psychiatric conditions (eg, psychosis, severe depression)</td>
</tr>
</tbody>
</table>

U-500R Insulin Therapy

- U-500 is a highly concentrated human insulin, introduced in 2016; it is potentially appropriate for the following patients:
  - Require >200 units of insulin per day
  - With T2D and obesity and/or severe insulin resistance
  - With gestational diabetes and severe insulin resistance
  - Postoperative or post-transplant or on high-dose glucocorticoid therapy
  - With severe systemic infection
  - With genetic defects of insulin action and rare forms of immune-mediated diabetes, such as anti-insulin receptor antibodies (type B insulin resistance syndrome)

T2D, type 2 diabetes; U-500R, human regular U-500 insulin.

Cardiovascular Safety of Insulin ORIGIN Trial: Early Use of Insulin Glargine in Patients With T2D or Pre-diabetes

- RCT of patients (N=12,537) with T2D, IGT, or IFG, at high CV risk, and treated with insulin glargine vs SOC.
- CV outcomes were similar for both groups over a median 6.2 years of follow-up.
- SH rates were higher with insulin glargine vs SOC (1.0 vs 0.3 per 100 PY).

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First coprimary outcome</td>
<td>1.02 (0.94–1.11)</td>
<td>0.63</td>
</tr>
<tr>
<td>Second coprimary outcome</td>
<td>1.04 (0.97–1.11)</td>
<td>0.27</td>
</tr>
<tr>
<td>Microvascular outcomes</td>
<td>0.97 (0.90–1.05)</td>
<td>0.43</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.98 (0.90–1.08)</td>
<td>0.70</td>
</tr>
<tr>
<td>Total myocardial infarctions</td>
<td>1.02 (0.88–1.19)</td>
<td>0.75</td>
</tr>
<tr>
<td>Total strokes</td>
<td>1.03 (0.89–1.21)</td>
<td>0.69</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>1.00 (0.89–1.13)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>0.90 (0.77–1.05)</td>
<td>0.16</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1.06 (0.91–1.25)</td>
<td>0.24</td>
</tr>
<tr>
<td>Angina</td>
<td>0.95 (0.85–1.09)</td>
<td>0.29</td>
</tr>
<tr>
<td>unstable</td>
<td>0.91 (0.76–1.08)</td>
<td>0.28</td>
</tr>
<tr>
<td>new</td>
<td>0.72 (0.56–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>worsening</td>
<td>1.02 (0.89–1.16)</td>
<td>0.80</td>
</tr>
<tr>
<td>Limb or digit amputation</td>
<td>0.89 (0.60–1.31)</td>
<td>0.55</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>1.00 (0.94–1.07)</td>
<td>0.90</td>
</tr>
<tr>
<td>Non-CV hospitalization</td>
<td>0.99 (0.94–1.05)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; CV, cardiovascular; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ORIGIN, Outcome Reduction with Initial Glargine Intervention; PY, person-years; RCT, randomized controlled trial; SH, severe hypoglycemia; SOC, standard of care; T2D, type 2 diabetes.

Cardiovascular Safety of Insulin DEVOTE Trial: Efficacy and Safety of Insulins Degludec vs Glargine in Patients With T2D

RCT of patients (N=7367) with T2D; 85% with established CVD or CKD
- Degludec was noninferior vs glargine for major CV outcomes
- Degludec significantly reduced hypoglycemia rates vs glargine

Primary Composite Outcome (MACE)

Severe Hypoglycemia

Hypoglycemia With Insulin Therapy: Risks Associated With Hypoglycemia

- Hypoglycemia is a common side-effect of insulin therapy.
- Hypoglycemia and the fear of hypoglycemia limit patients’ ability to achieve and maintain optimal glycemic control.
- Severe and prolonged hypoglycemia increases morbidity and mortality.

<table>
<thead>
<tr>
<th>Organ/System</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Abnormal prolonged cardiac repolarization</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrythmia</td>
</tr>
<tr>
<td></td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td></td>
<td>Sudden death</td>
</tr>
<tr>
<td>Eyes</td>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Worsening of retinopathy</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Brain damage, intellectual decline</td>
</tr>
<tr>
<td></td>
<td>Unusual behavior</td>
</tr>
<tr>
<td></td>
<td>Seizure, coma</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack, stroke</td>
</tr>
<tr>
<td></td>
<td>Focal neurological lesions (rare)</td>
</tr>
<tr>
<td>Other</td>
<td>Falls</td>
</tr>
<tr>
<td></td>
<td>Accidents with injury</td>
</tr>
</tbody>
</table>

Hypoglycemia Risk Factors in Patients With T2D

Impaired hypoglycemia awareness increases subsequent hypoglycemia risk by ~5-fold

1. Diabetes complexity
   - Diabetes duration
   - Impaired hypoglycemia awareness
   - High glycemic variability
   - Prior hypoglycemic events
   - Glycemic control
     - U-shaped relationship with HbA1c
   - Fear of hypoglycemia
   - Fear of hyperglycemia

2. Multi-morbidity
   - Functional impairment, frailty
   - Comorbid health conditions:
     - Microvascular complications
     - Cardiovascular complications
   - Kidney disease, cardiovascular disease, heart failure, cerebrovascular disease, liver disease, lung disease, depression
   - Cognitive impairment, dementia

3. Pharmacotherapy
   - High risk medications:
     - Insulin, sulfonylurea
   - Glucose-lowering polypharmacy
   - Non-diabetes medications
     - Example: beta blockers
   - Complex treatment regimens
   - Medication misadventures
     - Dosing errors, discordance with meals, etc.

4. Patient context and environment
   - Inadequate caregiver support or supervision
   - Food insecurity
   - Poor health literacy
   - Financial burden
   - Non-clinical or competing clinical demands
   - Fasting, either for medical tests/procedures or personal/religious reasons
     - Example: Ramadan

5. Healthcare system
   - Performance measurement, reporting, and benchmarking that focus on lowering HbA1c
   - Inadequate diabetes support/resources, including DSME and clinical monitoring
   - Payer decisions regarding DSME, glucose monitoring, drug formulary, and diabetes technologies
   - Lack of integration of patient health information, including glucose monitoring data and self-reported hypoglycemia, into clinical EHR

DSME, diabetes self-management education; EHR, electronic health records; T2D, type 2 diabetes.

Less Hypoglycemia With Insulin Glargine and Detemir vs NPH Insulin

Data from 6 RCTs used to model hypoglycemia rates with insulin glargine vs NPH in 3656 patients with T2D

Association between confirmed hypoglycemia (<65 mg/dL)* and end-of-study A1C (P=0.021)

*Per 100 person-years

26-week RCT comparing insulin detemir vs NPH as add-on to OADs in 475 insulin-naïve patients with T2D

Relationship between confirmed hypoglycemia incidence and A1C (previous 12 weeks and at study end) (P<0.001)

NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; RCT, randomized controlled trial; T2D, type 2 diabetes.

Rates of Hypoglycemia Lower With Insulin Degludec vs Insulin Glargine

Meta-analysis of 5 trials in patients with T2D (N=3372) in the iDeg development program, comparing iDeg once daily to iGlar once daily$^{1,2}$

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iDeg, insulin degludec; iGlar, insulin glargine; T2D, type 2 diabetes.

Nocturnal Hypoglycemia Lower With Insulin Glargine U300 vs Glargine U100 in Patients With T2D

Multicenter, randomized, open-label, 2-arm, parallel-group, TTT trials

Meta-analysis (12 months) of adults with T2D randomized to Gla-300 or Gla-100

- **EDITION 1**: Insulin with or without metformin
- **EDITION 2**: Insulin in combination with other antihyperglycemic drugs
- **EDITION 3**: Insulin-naive

<table>
<thead>
<tr>
<th>Nocturnal (12 AM to 5:59 AM) confirmed (≤70 mg/dL), or SH</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C ≤7.0%</td>
<td>1.24</td>
<td>1.03–1.50</td>
</tr>
<tr>
<td>A1C &lt;7.5%</td>
<td>1.17</td>
<td>1.02–1.35</td>
</tr>
<tr>
<td>A1C reduction ≥0.5%</td>
<td>1.18</td>
<td>1.04–1.33</td>
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<th>Anytime (24 hours) confirmed (≤70 mg/dL), or SH</th>
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<tr>
<td>A1C ≤7.0%</td>
<td>1.18</td>
<td>0.84–1.67</td>
</tr>
<tr>
<td>A1C &lt;7.5%</td>
<td>1.26</td>
<td>0.97–1.67</td>
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<tr>
<td>A1C reduction ≥0.5%</td>
<td>1.32</td>
<td>1.04–1.68</td>
</tr>
</tbody>
</table>

CI, confidence interval; Gla-100; insulin glargine 100 units; Gla-300, insulin glargine 300 units; RR, relative risk; SH, severe hypoglycemia; T2D, type 2 diabetes; TTT, treat-to-target.

Hypoglycemia Lower With Insulin Glargine U300 vs Glargine U100 in Patients With T2D

- EDITION 1, 2, and 3 meta-analysis compared the efficacy and safety of insulin Gla-300 (n=1247) vs Gla-100 (n=1249) over 6 months in patients with T2D.
- They found comparable mean A1C reductions, tolerability, and safety between treatment groups.
- There was less hypoglycemia with Gla-300:
  - Hypoglycemia at any time: Rate ratio (95% CI), 0.86 (0.77, 0.97); P=0.0116
  - Nocturnal hypoglycemia: Rate ratio (95% CI), 0.69 (0.57, 0.84); P=0.0002

CI, confidence interval; Gla-100; insulin glargine 100 units; Gla-300, insulin glargine 300 units; T2D, type 2 diabetes.
Open-Label, Randomized Trials Evaluating Hypoglycemia in Patients With T2D Using LixiLan (FRC of iGlar + Lixisenatide)


FRC, fixed-ratio combination; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; PG, plasma glucose; T2D, type 2 diabetes.

**LixiLan-O Trial:** Patients with T2D inadequately controlled on oral agents (insulin-naïve) randomized to iGlarLixi, iGlar, or Lixi

**LixiLan-L Trial:** Patients with T2D inadequately controlled on basal insulin and metformin randomized to iGlarLixi or iGlar

Symptomatic hypoglycemia (PG ≤70 mg/dL)

- iGlarLixi (n=469): 25.6%
- iGlar (n=467): 14.1%
- Lixi (n=233): 6.4%

Symptomatic hypoglycemia (PG<60 mg/dL)

- iGlarLixi (n=366): 40%
- iGlar (n=365): 42.5%
- LixiLan-L Trial: Patients with T2D inadequately controlled on oral agents (insulin-naïve) randomized to iGlarLixi, iGlar, or Lixi

**P<0.01 for incidence of severe symptomatic hypoglycemia, iGlar vs iGlarLixi**

Severe hypoglycemia

- Symptomatic hypoglycemia (PG≤70 mg/dL)
  - iGlar (n=365): 1.1%
  - iGlarLixi (n=366): 0.3%

**P<0.01 for incidence of severe hypoglycemia, iGlar vs iGlarLixi**

LixiLan-O Trial: Patients with T2D inadequately controlled on oral agents (insulin-naïve) randomized to iGlarLixi, iGlar, or Lixi

LixiLan-L Trial: Patients with T2D inadequately controlled on basal insulin and metformin randomized to iGlarLixi or iGlar
Novel and in Development: Hepatic-Directed Vesicle Insulin for Prandial Use

- HDVI uses a hepatocyte-targeting moiety to improve the hepatic distribution of subcutaneous insulin.
- This multicenter, randomized, 6-month study compared HDVI vs insulin lispro (N=176 patients with T1D).
- Overall, A1C reductions met a preset noninferiority margin—no significant differences between treatments for insulin dosage or hypoglycemia.
- Specific to patients with baseline A1C ≥8.5%:
  - Severe hypoglycemia incidence in the HDVI and lispro arms were 69 and 97 events per 100 person-years (P=0.03).
  - Insulin dosages were reduced by 25% in patients who received HDVI vs lispro (P=0.02), despite similar A1C outcomes.

Novel and In Development:
A Jet Injector, Needle-Free Delivery System

Postprandial glucose and insulin concentrations following insulin aspart administration via jet injector or pen; Chinese patients with T2D (N=60)

**Postprandial glucose and insulin concentrations**

- **Postprandial glucose concentration (mmol/L)**
  - Pen ■
  - Jet Injector △
  - *P<0.05 vs insulin pen

- **Postprandial insulin concentration (μIU/mL)**
  - Pen ■
  - Jet Injector △
  - *P<0.05 vs insulin pen

InsuJet™ uses a high-pressure narrow jet to penetrate the skin. Insulin disperses into subcutaneous adipose tissue with ≥90% efficiency and minimal skin injury and pain.

T2D, type 2 diabetes.
# Novel and In Development: Long-Lasting, Glucose-Responsive (“Smart”) Insulin

**Smart Insulin** is longer-acting than injected insulin. It remains inactive until low blood glucose is detected; insulin action ceases once blood glucose normalizes.

Multiple products are under investigation. Barriers to successful development have included device materials, immune response, and other efficacy and safety concerns.1

### Patch
- Adhesive patch placed on skin; delivers insulin via glucose-sensitive microneedles1
- Potential duration of action: ~1 day2
- Development status: Animal testing2

### Nano-implant
- Battery-operated device, inserted under skin; contains insulin-loaded nanoparticles1,3
- Potential duration of action: Several months3
- Development status: Animal testing3

### Oral
- Prevents gastrointestinal protein-drug breakdown; permits small intestine permeation4
- Duration of action: 1 day5,6
- Development status: Phase 25,6

### Gel
- Closed-loop, insulin/boronate gel-based system7,8
- Gel dehydrates in response to osmotic pressure, signaling low blood glucose and triggering insulin diffusion8
- Potential duration of action: ~1 week
- Development status: Early animal research7,8

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Summary

• As T2D is progressive in nature, many patients eventually require insulin therapy.
• The choice of initial insulin should be individualized and guided by patient characteristics; however, initiating insulin therapy with a single daily dose of basal insulin is the preferred approach.
• Some evidence suggests that short-term, early intensive insulin treatment may improve glycemic control and preserve beta-cell function in newly diagnosed T2D patients with severe and symptomatic hyperglycemia.
• Patients whose glycemia remains uncontrolled with basal insulin and other oral agents may require the progressive addition of mealtime (prandial) insulin or a GLP1-RA.
• Intensification of insulin therapy should not be delayed if the patient is not meeting goals.
• Newer insulin analogs have similar cardiovascular risk profiles and reduced hypoglycemia rates compared to older insulin formulations.
• Future technology advances and routes for insulin delivery are likely to make insulin more user-friendly, patient-specific, and convenient.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.
Contributors

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  - Dr. Amit Gupta, DNB, FACP, FRCP (Glasg), FRCP (Edin)
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