New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

Learning Objectives

- Differentiate the clinical characteristics and benefits of current and emerging basal insulins
- Identify strategies to manage hypoglycemia in patients with T2DM, taking into account how treatment choice affects hypoglycemia risk
- Implement strategies to intensify treatment in patients inadequately controlled on basal insulin

T2DM Is a Progressive Disease

PD = impaired fasting glucose; IGT = impaired glucose tolerance.
New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

Clinical Inertia Leaves Patients Unnecessarily Exposed to Hyperglycemia

Median Time to Addition of Another OAD or Insulin

<table>
<thead>
<tr>
<th>Patients taking 1 OAD</th>
<th>Patients taking 2 OADs</th>
<th>Patients taking 3 OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 years, mean A1C: 8.7%</td>
<td>&gt;7.2 years, mean A1C: 9.1%</td>
<td>&gt;7.1 years, mean A1C: 9.7%</td>
</tr>
</tbody>
</table>

Years

Indicates that <50% of subjects have intensified treatment.
Mean time between A1C measurements was 6.2 to 7 months.
OAD = oral antidiabetes drug.

Barriers to Taking Insulin

<table>
<thead>
<tr>
<th>Patient Barrier</th>
<th>Clinician Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of hypoglycemia</td>
<td>Clinical inertia</td>
</tr>
<tr>
<td>Lifestyle interference</td>
<td>Concern that patients will resist insulin therapy</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Lack of time:</td>
</tr>
<tr>
<td>Pain associated with blood testing and injections</td>
<td>- To educate patients and their families on the role of insulin replacement therapy</td>
</tr>
<tr>
<td>Patient perception that insulin therapy is complicated and time consuming</td>
<td>- For intensive monitoring needed during the initial phase of insulin initiation and titration</td>
</tr>
<tr>
<td>Social concerns</td>
<td>- For education required for the management of any increase of hypoglycemia from insulin therapy</td>
</tr>
</tbody>
</table>

Insulin Therapy: Mechanism of Action, Physiologic Action, Pros and Cons

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Mechanism of Action</th>
<th>Physiologic Action</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin analogs</td>
<td>- Degludec</td>
<td>- Activates insulin receptors</td>
<td>- Nearly universal response</td>
<td>- Hypoglycemia risk</td>
</tr>
<tr>
<td></td>
<td>- Detemir</td>
<td>- Increases glucose disposal</td>
<td>- Unlimited efficacy (in theory)</td>
<td>- Weight gain</td>
</tr>
<tr>
<td></td>
<td>- Glargine U-100</td>
<td>- Decreases hepatic glucose production</td>
<td>- Decreases microvascular risk</td>
<td>- Training requirements</td>
</tr>
<tr>
<td></td>
<td>- Glargine U-300</td>
<td></td>
<td></td>
<td>- Patient reluctance</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>Human NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human regular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting analogs</td>
<td>Aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lispro</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Degludec is considered an ultra–long-acting basal insulin.
NPH = neutral protamine Hagedorn.
What to Keep in Mind About Insulin Therapy

- Discuss insulin physiology to increase patients’ awareness of the role insulin plays in T2DM
- Consider basal insulin for patients presenting with markedly elevated A1C or those inadequately controlled on existing treatment
- Avoid using insulin as a “threat” or “last resort”
- Prevent clinical inertia through timely intensification of therapy

Educating Patients About Their Medications May Improve Adherence and Reduce Patient Concerns That May Interfere With Adherence

<table>
<thead>
<tr>
<th>Adherence Category</th>
<th>Received Information From Primary Care Doctor</th>
<th>Received Information From Other Sources</th>
<th>Complained About Medication Interfering With Lifestyle</th>
<th>Worried About Side Effects of Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly adherent (0%-10% doses missed)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mostly adherent (11%-26% doses missed)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somewhat nonadherent (27%-47% doses missed)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Nonadherent (47%-100% doses missed)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

- Patients who were referred to certified diabetes educators and community programs had the highest adherence

(Online survey of self-reported number of missed medication doses among 867 patients with diabetes, 86% with T2DM).


Shared Treatment Decision-Making: Mayo Clinic Online Decision Aid and Brochure

[Online link to Mayo Clinic Online Decision Aid and Brochure]

New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

Case Study: Juan, a 44-Year-Old Sales Manager With a 2-Year History of T2DM

- Obese (5 ft 9 in, 205 lb, BMI: 30.0 kg/m²)
  - BP: 130/85 mm Hg on ACE inhibitor
  - LDL-C: 98 mg/dL
- Current medications: MET 2000 mg/day and SGLT2 inhibitor
- A1C: 9.1%
- Symptoms of polyuria and polydipsia
- You discuss additional treatment options with Juan, including the possibility of adding basal insulin, but he is reluctant to initiate an injectable agent
- He promises to focus on lifestyle recommendations and lose weight

Patient Characteristics to Consider When Individualizing Glycemic Targets

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>More stringent</th>
<th>A1C: 8.5%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks associated with hypoglycemia or other drug adverse effects</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
<td>Short</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Short</td>
<td>Medium</td>
<td>Long</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Patient-related and expected treatment effects</td>
<td>Absent</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>Limited</td>
<td>Limited</td>
<td>Unlimited</td>
</tr>
</tbody>
</table>
Case Study: 3-Month Follow-up

- A1C: 9.0%
- Despite his efforts to lose weight, Juan has only lost 3 lb and says he struggles to find the time to exercise
- You discuss insulin initiation again, and Juan agrees to begin treatment with insulin detemir

Case Study: Next 3-Month Follow-up

- A1C: 7.5%
- Reports no issues with injecting his insulin, which he does before bedtime
- Has experienced episodes of nocturnal hypoglycemia, which alarmed him and caused him to stop titrating his insulin at 32 units
- SMBG on several occasions showed hyperglycemia in the late afternoon
- Has gained 10 lb

Hypoglycemia: Definitions and Symptoms

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Counter-regulatory Symptoms</th>
<th>Neuroglycopenic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose &lt;70 mg/dL is considered &quot;alert&quot; level for action to prevent further complications</td>
<td>Tachycardia</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Severe: patient requires assistance from another person to take corrective action (eg, carbohydrates or glucagon)</td>
<td>Shakiness</td>
<td>Weakness</td>
</tr>
<tr>
<td>Tiredness</td>
<td>Anxiet</td>
<td>Irritability</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Pupil dilation</td>
<td>Headache</td>
</tr>
<tr>
<td>Hunger</td>
<td>Difficulty concentrating</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Pupil dilation</td>
<td>Confusion</td>
<td>Altered vision</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>Severe loss of consciousness, seizure, coma, death</td>
<td></td>
</tr>
</tbody>
</table>
Importance of Minimizing Hypoglycemia

- Undermines adherence and achievement of glycemic goals
- Contributes to clinical inertia
- Incidence: 25% of insulin-treated patients have ≥1 episode/year
- Consequence: 18.5% of patients report reducing insulin dose after a single episode of nocturnal hypoglycemia

Risk Factors for Hypoglycemia
- Older age
- Longer disease duration
- Concomitant medications
- Renal dysfunction
- Hypoglycemia unawareness
- Cognitive dysfunction
- Peripheral neuropathy
- Intense glucose-lowering strategy

Basal Insulin Analogs Versus NPH

- Basal insulin analogs are recombinant insulins designed to slow insulin absorption and produce a minimally peaking ~24-hour profile
- Compared with NPH, insulin glargine and detemir lower A1C to a similar extent, but:
  - Glargine is associated with less hypoglycemia, especially nocturnal episodes
  - Detemir is associated with less within-patient glycemic variability and less weight gain

<table>
<thead>
<tr>
<th>Onset of Action</th>
<th>Peak Action</th>
<th>Effective Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>2-4 hours</td>
<td>4-10 hours</td>
</tr>
<tr>
<td>Glargine</td>
<td>2-4 hours</td>
<td>None</td>
</tr>
<tr>
<td>Detemir</td>
<td>2-4 hours</td>
<td>12-14 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean of Self-Monitored FPG Values from Preceding 2 Days</th>
<th>Increase in Insulin Dose, IU/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-120 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td>120-140 mg/dL</td>
<td>4</td>
</tr>
<tr>
<td>140-180 mg/dL</td>
<td>6</td>
</tr>
<tr>
<td>≥180 mg/dL</td>
<td>8</td>
</tr>
</tbody>
</table>

Treat-to-Target Forced Titration Schedule

- Start with 10 IU/day bedtime basal insulin dose and adjust weekly
- Small decreases (2-4 IU/day per adjustment) in dose are allowed in instances of SMPG ≥56 mg/dL or the occurrence of a severe hypoglycemic episode
Why Do We Need Improved Basal Insulins?

- Despite improvements over NPH, many patients on insulin detemir and insulin glargine U-100 have suboptimal glycemic control in clinical settings
  - Duration of action may be <24 hours
  - Some patients require twice-daily dosing
  - Associated with a degree of glycemic variability
  - Nocturnal hypoglycemia still occurs

Why Does Volume of Distribution Matter?

- When daily insulin requirements are >200 units/day, the volume of U-100 injected insulin is a challenge
  - Physically too large for a single subcutaneous administration
  - Multiple injections required to deliver single dose
  - Increased injections = adherence issues, poor glycemic control
  - Discomfort and unpredictable absorption

Concentrated insulins help address this problem

Example

- Gla-300 has the same number of units of insulin as Gla-100 in two-thirds less volume
- Depot surface area reduced by one-half, leading to slower release and prolonged action profile

Pharmacokinetic Profile of Insulins

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration</th>
</tr>
</thead>
</table>
| Rapid-acting
  - Lispro (U-100, U-200)
  - Aspart
  - Glulisine | 15-30 minutes | 30 minutes to 1.5 hours | 3-5 hours |
| Short-acting
  - Regular insulin (U-100, U-500) | 30 minutes to 1 hour | 2-4 hours | 4-8 hours |
| Intermediate-acting
  - NPH insulin | 1-3 hours | 4-10 hours | 10-18 hours |
| Long-acting
  - Glargine (U-100), glargine “follow-on biologic” (U-100), glargine U-300
  - Detemir
  - Degludec (U-100, U-200) | 2-3 hours | None | ≤24 hours |

New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

Insulin Degludec

- Forms long, soluble hexamer chains that slowly break down to release insulin
- “Ultra-long” duration of action (≥42 hours) allows greater flexibility in dosing without compromising safety or glycemic control
- At steady state, exposure is evenly distributed over 24 hours (with glargine, exposure is higher during first 12 hours)
- Appropriate for any patient with T2DM requiring basal insulin
- Available in 2 strengths: 100 U/mL and 200 U/mL
  - 200 U contains same amount of insulin in half the volume without affecting glycemic control or hypoglycemia risk
- 100-U injection pen allows 1-U increments; 200-U injection pen offers only 2-U increments


Once-Daily Insulin Degludec Versus Gla-100: 2-Year Results of BEGIN Once Long

- Similar reductions in A1C, maintained through 2 years

<table>
<thead>
<tr>
<th>Hypoglycemia Rate</th>
<th>Degludec</th>
<th>Gla-100</th>
<th>Side Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, weeks 0-52</td>
<td>1.52</td>
<td>1.05</td>
<td>0.82 (0.64-1.04)</td>
<td>0.106</td>
</tr>
<tr>
<td>Nocturnal, weeks 0-52</td>
<td>.25</td>
<td>.38</td>
<td>0.64 (0.42-0.98)</td>
<td>0.038</td>
</tr>
<tr>
<td>Overall, weeks 0-104</td>
<td>1.72</td>
<td>2.05</td>
<td>0.84 (0.68-1.04)</td>
<td>0.115</td>
</tr>
<tr>
<td>Nocturnal, weeks 0-104</td>
<td>.27</td>
<td>.46</td>
<td>0.57 (0.40-0.81)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

*Episodes per patient-year of exposure.
1-year, parallel-group, randomized noninferiority trial and 1-year extension; all patients also took MET ± DPP-4 inhibitor.
DPP-4 = dipeptidyl peptidase-4.

BEGIN-FLEX: Flexible Insulin Degludec Dosing Compared With Fixed-Dose Glargine

- Primary outcome: noninferiority of flexible insulin degludec dosing (9- to 40-hour intervals between doses) compared with glargine

Day of the week | Mon | Tue | Wed | Thu | Fri | Sat | Sun | Mon |
--- | --- | --- | --- | --- | --- | --- | --- | --- |
Dosing time | AM | PM | AM | PM | AM | PM | AM | AM |
Interval between doses (hours) | 36-40 | 8-12 | 36-40 | 8-12 | 36-40 | 24 | 8-12 |

- Flexible insulin degludec dosing was noninferior to fixed-dose glargine after 26 weeks
- No statistically significant differences in rates of hypoglycemia
- Dosing intervals of 8-40 hours did not compromise glycemic control or safety

New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

Insulin Glargine 300 U/mL (Gla-300)

- Ultra-long-acting basal insulin analog delivers 300 U/mL glargine, with more constant and prolonged pharmacodynamic and pharmacokinetic profile than Gla-100
- Appropriate for any patient with T2DM using basal insulin
- Compared with Gla-100 in the EDITION trials (randomized, controlled, multicenter, 6-month studies)
  - EDITION 1: existing basal-bolus insulin therapy
  - EDITION 2: existing OADs + basal insulin
  - EDITION 3: insulin-naïve patients inadequately controlled on OADs

Gla-300 Versus Gla-100: Similar Glycemic Control With Less Nocturnal Hypoglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Baseline A1C, %</th>
<th>Change in A1C at 6 Months, %</th>
<th>Nocturnal Hypoglycemia, a RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDITION 1</td>
<td>Gla-100 403</td>
<td>8.16</td>
<td>-0.83</td>
<td>0.79 (0.67-0.93)</td>
</tr>
<tr>
<td></td>
<td>Gla-300 404</td>
<td>8.15</td>
<td>-0.83</td>
<td></td>
</tr>
<tr>
<td>EDITION 2</td>
<td>Gla-100 406</td>
<td>8.24</td>
<td>-0.56</td>
<td>0.77 (0.61-0.99)</td>
</tr>
<tr>
<td></td>
<td>Gla-300 405</td>
<td>8.24</td>
<td>-0.57</td>
<td></td>
</tr>
<tr>
<td>EDITION 3</td>
<td>Gla-100 439</td>
<td>8.57</td>
<td>-1.46</td>
<td>0.76 (0.59-0.99)</td>
</tr>
<tr>
<td></td>
<td>Gla-300 439</td>
<td>8.51</td>
<td>-1.42</td>
<td></td>
</tr>
</tbody>
</table>

a ≥1 confirmed or severe event.

RR = relative risk.

Reduced Hypoglycemia With Glargine U-300 Versus Glargine U-100

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Mean Age, Years</th>
<th>Male, %</th>
<th>A1C, %</th>
<th>FPG, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U-300 (n = 460)</td>
<td>57</td>
<td>46</td>
<td>8.3</td>
<td>147</td>
</tr>
<tr>
<td>Glargine U-100 (n = 460)</td>
<td>58</td>
<td>45</td>
<td>8.3</td>
<td>147</td>
</tr>
</tbody>
</table>

Results

- Rates of hypoglycemia (overall, nocturnal, and symptomatic nocturnal) were statistically lower in patients treated with glargine U-300 reaching SMPG <130 mg/dL, and in patients not reaching SMPG <100 or <130 mg/dL.
- Rates for nocturnal hypoglycemia were significantly lower in patients treated with glargine U-300 regardless of level of SMPG achievement
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Basal Insulins: Dosing and Risk of Hypoglycemia

- Detemir and Gla-100 require standard dosing times to avoid hyperglycemia; bedtime dosing may lead to nocturnal hypoglycemia
- Insulin degludec and Gla-300 have duration of action >24 hours, allowing flexibility in degludec dosing
- Insulin degludec and Gla-300 are associated with lower rates of hypoglycemia

Case Study (cont’d)

- You switch Juan from insulin detemir to insulin glargine 300 U
- 3-month follow-up:
  - Juan returns and reports no issues with his new basal insulin and no hypoglycemia
  - He is still taking MET and an SGLT2 inhibitor
  - At this visit:
    - A1C: 7.2%
    - PPG: 180 mg/dL

PPG Undermines Glycemic Control When FPG is Controlled but A1C Remains >7.0%

- PPG is increasingly important as A1C nears 7.0%; at A1C <7.3%, ~70% of hyperglycemia is PPG
- Elevated PPG reflects loss of insulin response and often is present years prior to elevated FPG
- Elevated PPG is present in most patients with T2DM and has been associated with increased CV risk independent of FPG levels
- Basal insulin and most oral agents have minimal effects on PPG; intensifying doses may lead to hypoglycemia

CV = cardiovascular

PPG = postprandial glucose.
Elevated PPG is highly prevalent among patients with T2DM and has been associated with adverse CV outcomes.

Elevated PPG is the predominant factor in residual hyperglycemia when FPG levels are controlled, especially as A1C drops below 8.0%.

Diabetes medications have differential effects on PPG that should be considered when combining therapies to achieve glycemic goals.

Rapid-acting insulin analogs (insulin aspart, glulisine, lispro):
- Mimic normal human postprandial insulin response
- Minimize risk of hypoglycemia or weight gain
- Have beneficial effects on PPG
- Are as effective as regular human insulin, with less hypoglycemia
- Onset of action: ≤15 minutes

GLP-1 RAs with postprandial effects:
- Short acting by delaying gastric emptying
  - Long-term or continuous stimulation reduces effect
- GLP-1 RAs with postprandial effects therefore have greater control of PPG
- Associated with substantial weight loss and A1C reductions similar to basal insulin analogs
  - Effectively reduce A1C in patients inadequately controlled on basal insulin
    - Can be added to existing basal insulin + OAD
    - Basal insulin can be added to existing OAD + GLP-1 RA

GLP-1 RA = glucagon-like peptide-1 receptor agonist.

GLP-1 RAs are effective in reducing postprandial glucose levels.
New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

GLP-1 RAs Versus Prandial Insulin Analogs Added to Basal Insulin

- Exenatide twice daily versus insulin lispro 3 times daily
  - Similar A1C reductions (−1.13% vs −1.10%)
  - Less nocturnal hypoglycemia with exenatide
  - More nausea with exenatide
- Liraglutide once daily versus insulin aspart once daily
  - Greater A1C reduction (−0.74% vs −0.39%; *P* = .0024)
  - Less confirmed nocturnal hypoglycemia
  - More gastrointestinal side effects with liraglutide

Recently Approved Combinations of Basal Insulin and GLP-1 RAs With Postprandial Effects

- Insulin degludec + liraglutide
- Insulin glargine + lixisenatide

Fixed Combination of Insulin Glargine + Lixisenatide in T2DM Inadequately Controlled With Oral Agents

- 4-week run-in to optimize MET and stop other OADs
- N = 1170
- Mean diabetes duration: 8.9 years
- BMI: ~31.7 kg/m²
- **Primary outcome**: A1C change at 30 weeks
- **Results**: Greater reductions in A1C from baseline were achieved with a fixed combination of insulin glargine + lixisenatide compared with either component alone

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Mean ± SE A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>BL = baseline</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
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<tr>
<td>12</td>
<td></td>
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<tr>
<td>18</td>
<td></td>
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<td>24</td>
<td></td>
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<tr>
<td>30</td>
<td></td>
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<tr>
<td>32</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
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<tr>
<td>40</td>
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</table>

<table>
<thead>
<tr>
<th>LOCF</th>
<th>Mean ± SE A1C (mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB</td>
<td>6.5%</td>
</tr>
<tr>
<td>6</td>
<td>6.5%</td>
</tr>
<tr>
<td>8</td>
<td>6.5%</td>
</tr>
<tr>
<td>12</td>
<td>6.5%</td>
</tr>
<tr>
<td>24</td>
<td>6.5%</td>
</tr>
<tr>
<td>30</td>
<td>6.5%</td>
</tr>
<tr>
<td>32</td>
<td>6.5%</td>
</tr>
<tr>
<td>36</td>
<td>6.5%</td>
</tr>
<tr>
<td>40</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

R0 = screening; LOCF = last observation carried forward; SB = screening value; SE = standard error.

New and Emerging Strategies in Type 2 Diabetes Mellitus Using Basal Insulin

**Fixed Combination of Insulin Glargine + Lixisenatide in T2DM Inadequately Controlled on Basal Insulin and Metformin**
- 4-week run-in: insulin glargine introduced and/or further titrated; OADs other than MET stopped
- Basal insulin-treated patients (N = 736)
- Mean diabetes duration: 12 years
- BMI: 31 kg/m²
- **Primary Outcome:** Change in A1C levels at 30 weeks
- **Results:** Greater reductions in A1C from baseline with fixed combination of insulin glargine + lixisenatide compared with insulin glargine alone; A1C goals reached by more patients with combination therapy

**Results:**
- **A1C <7% (<53 mmol/mol):**
  - 25.5%
  - 95% Cl: 18.9-32.1
  - P <.0001
- **A1C ≤ 6.5% (<48 mmol/mol):**
  - 19.8%
  - 95% Cl: 13.9-25.6
  - P <.0001

**Improvement in A1C was accompanied by a mean body weight reduction of -0.5 kg with combination insulin degludec + liraglutide, compared with a weight increase of 1.0 kg with degludec and a weight loss of 3.0 kg with liraglutide**

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**Fixed Combination of Insulin Degludec + Liraglutide Compared With Individual Components**
- In the DUAL I trial (insulin-naïve patients) and DUAL II trial (patients previously treated with basal insulin), A1C was significantly lowered with the combination of insulin degludec + liraglutide

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**Fixed Combination of Insulin Degludec + Liraglutide Compared With Individual Components (cont'd)**

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**References:**
Combinations of Basal Insulin and GLP-1 RAs With Postprandial Effects: Safety

- Insulin degludec + liraglutide
  - Well tolerated
  - Mild to moderate gastrointestinal symptoms: nausea, diarrhea, constipation, cramping
  - Hypoglycemia (1.8 events/patient-year in DUAL I trial; 1.5 in DUAL II trial)
  - Skin reactions at the injection site
  - Rate of first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke among patients with T2DM was lower with liraglutide vs placebo (LEADER trial)
- Insulin glargine + lixisenatide
  - Well tolerated
  - Mild to moderate nausea
  - Hypoglycemia (1.4 events/patient-year in LixiLan-0 trial; 3.03 in LixiLan-L trial)
  - Rare instances of severe allergic reactions
  - No increased CV risk in high-risk post-acute coronary syndrome population

GLP-1 RAs With Postprandial Effects and Prandial Insulin to Control PPG

- Both prandial insulin and GLP-1 RAs with postprandial effects reduce A1C and strongly decrease PPG
- Compared with rapid-acting insulin analogs, addition of GLP-1 RAs leads to significant body weight reduction
- Fixed-dose combinations of basal insulin analogs and GLP-1 RAs are available

Case Study (cont’d)

- After adding a GLP-1 RA with postprandial effects to his existing insulin and oral therapies, Juan successfully avoids weight gain and does not have any issues with hypoglycemia
  - At 3-month follow-up:
    - He has lost 4 lb
    - He has not had any nocturnal or other hypoglycemia
    - A1C: 6.6%
### Intensifying Basal Insulin Therapy

- Start basal and titrate up 2-4 U once to twice weekly to reach FPG goal
- If FPG goal reached but A1C goal not reached:
  - Add GLP-1 RA
    - Once- or twice-daily GLP-1 RA with postprandial effects
    - Can consider SGLT2 inhibitor or DPP-4 inhibitor
      - GLP-1 RA is more effective at reducing PPG than SGLT2
    
  - Add prandial insulin
    - 1 rapid insulin injection before largest meal (4 U or 10% basal dose)
    - For A1C >8.0%, consider reducing basal dose
    - Titrate 1-2 U once to twice weekly until SMBG target reached

### PCE Action Plan

- Recommend insulin therapy at any stage of T2DM for patients requiring substantial A1C reductions
- Consider ultra–long-acting basal insulin for patients who require flexible dosing times, units of insulin >0.5 U/kg, and need to avoid hypoglycemia
- Assess PPG and address if elevated in patients whose A1C remains high despite adequate FPG control
- Consider a GLP-1 RA with postprandial effects or prandial insulin for patients who require additional A1C and PPG control on basal insulin