Combining GLP-1 Receptor Agonists with Basal Insulin: Realizing the Potential in Type 2 Diabetes

PROGRAM FACULTY

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Director, Endocrine Fellowship Program
Director, Diabetes Care Center
University of Washington Medical Center
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Endocrinologist, Hunterdon Medical Center
Diabetes and Endocrine Associates of Hunterdon
Flemington, New Jersey
Session 5: Combining GLP-1 Receptor Agonists with Basal Insulin: Realizing the Potential in Type 2 Diabetes

Learning Objectives
1. Implement ADA recommendations for A1C, fasting plasma glucose, and post-prandial glucose targets in the management of patients with type 2 diabetes
2. Assess the clinical profiles of GLP1 receptor agonists and the advantages and disadvantages of prandial insulin
3. Describe the clinical rationale and expected benefits of using antidiabetic therapies with complementary mechanisms of action in the treatment of patients with type 2 diabetes
4. Utilize appropriate strategies to select and intensify antidiabetic therapy to achieve PPG control in patients with type 2 diabetes on basal insulin

Faculty

Dace L. Trence, MD, FACE
Director, Diabetes Care Center
Professor, Division of Metabolism, Endocrinology and Nutrition
University of Washington Medical Center
Seattle, Washington

Dr Dace Trence is currently director of the diabetes care center and professor of medicine at the University of Washington Medical Center, Seattle. She is also the University of Washington endocrine fellowship program director and director of endocrine days; a medical education program for endocrinologists practicing in the Pacific Northwest. She currently serves on the American Association of Clinical Endocrinologists (AACE) board of directors, chairing the AACE publications committee and co-chairing AACE CME committee. She has been on the editorial boards of several journals including Clinical Diabetes. She has had articles published in JCEM, JAMA, Diabetes Care and is a coauthor of “Optimizing Diabetes Care for the Practitioner”. Her current interests include improving educational processes in diabetes self management and clinical training of health care professionals.

Felice Caldarella, MD, FACE, CDE, FACP
Endocrinologist
Hunterdon Medical Center
Diabetes and Endocrine Associates of Hunterdon
Flemington, New Jersey

Dr Felice Caldarella is a graduate of New York University and received his medical degree from SUNY Upstate Medical University. He completed his residency at Brown University, Rhode Island. Dr Caldarella went on to receive subspecialty training in endocrinology, diabetes and metabolism at University of Medicine and Dentistry of New Jersey. He is board certified in endocrinology, diabetes and metabolism. He is a fellow of the American College of Endocrinology and a fellow of the American College of Physicians. He is also a certified diabetes educator. Dr Caldarella was recognized as a New Jersey top doctor in 2011. Dr Caldarella supervises the medically supervised weight loss program at the Center for Advanced Weight Loss.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr Trence has ownership interest as a Stockholder with Sanofi and Medtronic.
Dr Caldarella has served on the speaker’s bureau for NoroNordisk, Salix, and Takeda.

Education Partner Financial Disclosure Statement
The content collaborators at Horizon CME have no relationships to disclose.
### Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>NPH</th>
<th>NSHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASP</td>
<td>insulin aspart</td>
<td>neutral protamine Hagedorn</td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>blood glucose</td>
<td>nonsevere hypoglycemic events</td>
<td></td>
</tr>
<tr>
<td>DET</td>
<td>insulin detemir</td>
<td>oral antidiabetic drugs</td>
<td></td>
</tr>
<tr>
<td>DPP-4I</td>
<td>dipeptidyl peptidase 4 inhibitor</td>
<td>oral hypoglycemic agents</td>
<td>plasma glucose</td>
</tr>
<tr>
<td>FPG</td>
<td>fasting plasma glucose</td>
<td>postprandial glucose</td>
<td></td>
</tr>
<tr>
<td>GIP</td>
<td>glucose dependent</td>
<td>sodium glucose transporter 2</td>
<td></td>
</tr>
<tr>
<td>GLAR</td>
<td>insulin glargine</td>
<td>self monitoring of blood glucose</td>
<td></td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>insulin like peptide 1 receptor agonist</td>
<td>sulfonylurea</td>
<td>type 1 diabetes</td>
</tr>
<tr>
<td>GLU</td>
<td>insulin glulisine</td>
<td>type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>metformin</td>
<td>thiazolidinedione</td>
<td></td>
</tr>
</tbody>
</table>

### Suggested Reading List


SESSION 5
2 – 3:15pm
Combining GLP-1 Receptor Agonists with Basal Insulin: Realizing the Potential in Type 2 Diabetes

SPEAKERS
Dace Trence, MD, FACE
Felice Caldarella, MD, FACE, CDE, FACP

Objectives
• Implement ADA recommendations for A1C, fasting plasma glucose, and post-prandial glucose targets in the management of patients with type 2 diabetes
• Assess the clinical profiles of GLP-1 receptor agonists and the advantages and disadvantages of prandial insulin
• Describe the clinical rationale and expected benefits of using antidiabetic therapies with complementary mechanisms of action in the treatment of patients with type 2 diabetes
• Utilize appropriate strategies to select and intensify antidiabetic therapy to achieve PPG control in patients with type 2 diabetes on basal insulin

Patient Case
• Susan B. is a 46 year old woman diagnosed with type 2 diabetes mellitus 5 yrs ago and has required progression from metformin to added glimepiride. No complications to date of retinopathy, nephropathy, neuropathy. She is trying to diet and exercise, but back pain has become more chronic and is limiting physical exertion.
• Medical history: Hypothyroidism, T2DM, chronic back pain, and hypercholesterolemia
• Meds: Atorvastatin, irbesartan, levothyroxine, metformin 1000 mg BID, glimepiride 4 mg QD, IBU PRN.
• P. Exam: 130/80 mm Hg, Weight 200 lb, BMI 30.9
• Lab: A1c 8.6%, Cr 0.9 mg/dl, LDL-chol 98

Normoglycemia and Recommended Glycemic Targets in T2DM

<table>
<thead>
<tr>
<th>Glucose Control</th>
<th>Healthy Individuals&lt;sup&gt;1,5&lt;/sup&gt;</th>
<th>ADA 2015&lt;sup&gt;1&lt;/sup&gt;</th>
<th>AACE 2013&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C, %&lt;sup&gt;*&lt;/sup&gt;</td>
<td>&lt;6.0 Individualized Target &lt;6.0&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;7.0 most pts &lt;6.0 healthy pts Individualized Target 7.0-8.0&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;6.5 most pts</td>
</tr>
<tr>
<td>Preprandial PG, mg/dL</td>
<td>&lt;100 80-130</td>
<td>&lt;110</td>
<td></td>
</tr>
<tr>
<td>Peak postprandial PG, mg/dL</td>
<td>&lt;140 &lt;180&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;140&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup>Peak postprandial capillary plasma glucose; <sup>+</sup>4-hour postprandial glucose concentration; <sup>+</sup>Patients with known CVD or multiple co-morbidities.

References:
When to Consider Insulin in Type 2 Diabetes

- Patients with symptomatic hyperglycemia
- When combination oral/injectable agents become inadequate (A1C >7.0-7.5%)
- High FPG or high PPG
- Unacceptable side effects of other agents
- Special circumstances (e.g., steroids, infection, pregnancy), hepatic and renal disease
- Patient with hyperglycemia in the hospital
- "Severely" uncontrolled diabetes*

FPG = fasting plasma glucose; PPG = postprandial glucose.


Glycemic Control Declines over Time with Traditional Monotherapy

Most patients on traditional therapies will require another agent to maintain long-term glycemic control

UKPDS: Progressive Deterioration in Glycemic Control over Time

- HbA1C Level
- beta-cell Function


Basal Insulin Therapy – Concept and Physiology

- UKPDS: Progressive Deterioration in Glycemic Control over Time

Postprandial Hyperglycemia Persists after Basal Insulin Therapy

164 patients with baseline A1c ≥7.5% on diet, oral agents, or insulin. Mealtime hyperglycemia persisted after 3 months of intensive treatment.

Pharmacokinetic Profile of Current Basal Insulins

- NPH = neutral protamine Hagedorn

**A Simple Approach to Starting Basal Insulin**

- **Bedtime or morning long-acting insulin OR**
- **Bedtime intermediate-acting insulin**

**Daily dose:** 10 units or 0.1-0.2 units/kg/day

- **Increase dose by 2-4 units every 3 days**
- **In the event of hypoglycemia or FPG level <70 mg/dL:**
  - Reduce bedtime insulin dose by 4 units, or by 10-20%

**Check FBG daily**

- **Continue regimen and check A1C every 3 months**

*FPG = fasting plasma glucose*


**Comparison of Analogue Basal Insulin and NPH Added to Oral Therapy: FPG and A1C**

- **756 patients previously treated with 1-2 OHAs and HbA1c >7.5%**

**Mean Daily Insulin Dose**

- **Insulin Glargine:** 47 Units
- **NPH:** 42 Units

**Mean Daily Insulin Dose**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Daily Insulin Dose (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Glargine</td>
<td>47</td>
</tr>
<tr>
<td>NPH</td>
<td>42</td>
</tr>
</tbody>
</table>

**FPG (mmol/L)**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>FPG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.5</td>
</tr>
<tr>
<td>4</td>
<td>5.2</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
</tr>
<tr>
<td>12</td>
<td>4.9</td>
</tr>
<tr>
<td>16</td>
<td>4.8</td>
</tr>
<tr>
<td>20</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**HbA1c (%)**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>5.8</td>
</tr>
<tr>
<td>8</td>
<td>5.6</td>
</tr>
<tr>
<td>12</td>
<td>5.4</td>
</tr>
<tr>
<td>16</td>
<td>5.2</td>
</tr>
<tr>
<td>20</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*All of the studies compared subjects on insulin versus metformin and insulin. All found less weight gain, a lower insulin dosage, and mostly HbA1c, HbA1c-hemoglobin A1c.

What if Basal Insulin Is Not Enough?

Patient Case Cont’d

• Susan B. was started on basal insulin at 10 units hs.
• Two weeks later she calls to report that her fasting glucoses are now in the 140-150 mg/dl range. You advise a 3 unit increase in the insulin dose, fasting glucose one month later is at 120-130 mg/dl
• 6 months later, she notes that blood sugars have been “up and down”. She has had several “lows” that have been embarrassing, as they have occurred at physical therapy sessions started for back pain. And she is concerned that she has gained 5 lbs
• You order a blinded 3-day continuous glucose monitor

Patient Case: Glucose Readings Continued

Stepwise Glycemic Deterioration in T2DM

Basal and Postprandial Contributions to Hyperglycemia by A1C Range

Matching Treatment to Disease Progression Using a Stepwise Approach
Steps in Transition from Basal to Basal-Bolus Insulin Therapy in T2DM


Above target:
- A1c >7.0%
- FPG >110 mg/dL

STEP 1
- Basal Insulin
  - Weekly titration based on FPG
  - All oral agents continued
  - A1c <7.0%, FPG <110 mg/dL

Maintain treatment regimen with monitoring of FPG and A1c

STEP 2
- Add insulin
  - Main Meal

STEP 3
- Add insulin
  - Next Largest Meal

STEP 4
- Add insulin
  - Last Meal

Regimens with Insulin Analogaues and A1C <7% in Type 2 Diabetes Patients

- Systematic review of RCT – 48 trials, 85 arms, 30,588 patients with a primary outcome of A1C <7% in patients with T2DM
  - Basal insulin (n=17,588): 41.4%
  - Biphasic insulin (n=9,237): 46.5%
  - Prandial insulin (n=1,059): 39.6%
  - Basal-bolus insulin (n=2,114): 53.9%

- Incidence of hypoglycemia ranged from 0 to 4.71 events/patient/30 days
- Weight gain ranged from 1.75 kg for basal to 3 kg for biphasic insulin.


OSIRIS Study: Change in A1C and Weight

HbA1c (%)
- 9.0
- 8.0
- 7.0
- 6.5
- 5.0

Weeks
- Period 1
- Period 2
- Period 3

SimpleSTEP
- ExtraSTEP


Insulin Intensification: OSIRIS Study Design

Group 1: GLAR + MET + 3xGLU
Group 2: GLAR + MET + 1, 2, or 3xGLU
Group 3: GLAR + MET + SU + 1, 2, or 3xGLU


Insulin Intensification: STEP-WISE Study Design

Group 1: GLAR + MET + 3xGLU
Group 2: GLAR + MET + 1, 2, or 3xGLU
Group 3: GLAR + MET + SU + 1, 2, or 3xGLU


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Basal Bolus Insulin Regimen: Percent of Patients with A1C <7%

- 12 trials, with 2114 patients
- A1c <7% was achieved in 53.9%
- Hypoglycemic events (mean/patient/30 days): 0.88 (0.35-1.3)
- Mean weight gain ~2.75 kg
- Mean final insulin dose: 0.89 U/kg
- Escalation from basal to basal-bolus increases success rate in an additional ~12% to 14% of patients
- HbA1c <7% is achieve in ~54% of patients

Study (first author, year, reference)

- Hollander, 2008 (44)
- Rosenstock, 2008 (46)
- Bergenstal, 2008 (47)
- Lankisch, 2008 (49)
- Liebl, 2009 (50)
- Riddle, 2009 (53)
- Raskin, 2009 (59)
- Fritsche, 2009 (65)

Pooled Estimate (95% CI) 53.9% (43.5%-64.0%)

Adding Prandial Insulin to Basal

Advantages

- Treats postprandial hyperglycemia
- Increases success rate in achieving A1c <7%

Disadvantages

- Increases weight gain
- Increases hypoglycemia risk
- Less convenient with multiple injections
- Increases success rate only by an additional 12% to 14%

How Often Does Hypoglycemia Occur in Diabetes?

Risk of Hypoglycemia Increases as Therapy Intensifies

For all therapies, the significance of differences between levels is p<0.0001

All Hypoglycemia Negatively Affects Quality of Life in Patients with T2DM

Hypoglycemia is also associated with lower treatment satisfaction, poorer adherence, and greater resource utilization*
Severe Hypoglycemia Is Associated with Increased Risk of Mortality and CV Events


Advance Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death – any cause</td>
<td>3.45 (2.34-5.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death – CV cause</td>
<td>3.78 (2.34-6.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death – non-CV cause</td>
<td>2.38 (1.67-4.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

VADT Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular events</td>
<td>1.88 (1.03-3.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death – any cause</td>
<td>6.37 (2.57-15.79)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Death – CV cause</td>
<td>3.73 (1.34-10.36)</td>
<td>0.0117</td>
</tr>
</tbody>
</table>

Insulin in Combination with GLP-1 Receptor Agonists

Dace Trence, MD, FACE
Director, Diabetes Care Center
Professor, Division of Metabolism, Endocrinology and Nutrition
University of Washington Medical Center
Seattle, WA

Incretin Physiology

- Secretion of GLP-1
  - Stimulates glucose-dependent insulin secretion from β-cells
  - Suppresses glucagon secretion from α-cells
  - Slows gastric emptying
  - Reduces food intake
- Secretion of GIP
  - Increases glucose-dependent insulin release
  - Degraded by DPP-4 enzyme

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide.


GLP-1 and GIP is secreted from L-cells of the jejunum and ileum. That in turn...

Insulin Glargine

Exenatide

<table>
<thead>
<tr>
<th>Week</th>
<th>0 2 4 8 12 18 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>8.5 8.0 7.5 7.0 6.5 6.0 5.5</td>
</tr>
</tbody>
</table>

Exenatide 10 mcg BID

Insulin Glargine (dose 25 U/day)

Mean ± SE shown


Pharmacokinetic Profile of GLP-1 RAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Half-life</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>5-10 mcg SC twice daily</td>
<td>2.4 hours</td>
<td>Short</td>
</tr>
<tr>
<td>Lixisenatide*</td>
<td>10-20 mcg SC daily</td>
<td>2-4 hours</td>
<td>Short</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>30-50 mg SC once weekly</td>
<td>6-7 days</td>
<td>Long</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75-1.5 mg SC once weekly</td>
<td>5 days</td>
<td>Long</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>2 mg SC once weekly</td>
<td>2.4 hours</td>
<td>Long</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6-1.8 mg SC once daily</td>
<td>13 hours</td>
<td>Long</td>
</tr>
</tbody>
</table>

*Available in Europe. Not FDA approved.

**Postprandial Glucose Effect of Short- and Long-acting GLP-1 RAs: EXN vs. LIRA**

EXN preferentially affects PPG compared to Liraglutide. EXN reduced PPG significantly more after breakfast and dinner than LIRA, *p*<0.001.

Self-Measured Plasma Glucose (mmol/L)

<table>
<thead>
<tr>
<th>Time</th>
<th>EXN Baseline</th>
<th>EXN Week 26</th>
<th>LIRA Baseline</th>
<th>LIRA Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 AM</td>
<td>7</td>
<td>7</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

PPG = postprandial glucose; BF = breakfast; EXN = exenatide; LIRA = liraglutide.


**PPG Effect of Short- and Long-acting GLP-1 RAs: LIXI* vs. LIRA**

LIXI = lixisenatide; PPG = postprandial glucose. *Not FDA approved.


**Potential Benefits of Combining GLP-1 RAs with Basal Insulin**

- Minimize weight gain
- Minimize hypoglycemia risk
- Treat postprandial glucose excursions
- Reduce or eliminate the need for prandial insulin
- Reduce insulin requirements


**Adding Prandial Insulin vs. GLP-1 RAs When Basal Is Not Enough**

Basal Bolus  
Add Prandial Insulin before Each Meal

Basal Plus  
Add Prandial Insulin at Main Meal

Basal  
Add Basal Insulin and Titrate

Lifestyle Changes plus Metformin  
(± other agents)

**Exenatide BID Added to Basal Insulin: Efficacy and Safety**

Adults with T2DM and HbA1c = 7.1% to 10.5% receiving glargine ± metformin ± pioglitazone were randomized to exenatide (10 mcg twice a day) or placebo for 30 weeks.

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk of hypoglycemia</td>
<td>Increased risk of hypoglycemia</td>
</tr>
<tr>
<td>Associated with weight loss</td>
<td>Associated with weight gain</td>
</tr>
<tr>
<td>Mainly controls PPG especially with short-acting agents</td>
<td>Controls fasting glucose</td>
</tr>
<tr>
<td>Glucose depend mechanism of action</td>
<td>Insulin supplementation and individualized dosing</td>
</tr>
</tbody>
</table>

PPG = postprandial glucose.


Exenatide BID Added to Basal Insulin: Efficacy and Safety

Outcomes

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Basal insulin</th>
</tr>
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<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Basal insulin</td>
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**Efficacy**

<table>
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<th>GLP-1 RA</th>
<th>Basal insulin</th>
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<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Basal insulin</td>
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</table>

**Hypoglycemia**

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Basal insulin</td>
</tr>
</tbody>
</table>

Only 1 reported event of major hypoglycemia (PBO group)

*| p<0.001; BID = twice daily; PBO = placebo; EXN = exenatide.

Liraglutide Added to Basal Insulin in T2DM over 38 Weeks: Effects on A1c and Weight


<table>
<thead>
<tr>
<th>∆A1C (%)</th>
<th>MET + LIRA (n=161)</th>
<th>MET + LIRA + DET (n=162)</th>
<th>MET + LIRA (OBS) (n=498)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.75</td>
<td>4.05</td>
<td>4.50</td>
</tr>
<tr>
<td>-2.0</td>
<td>4.50</td>
<td>2.75</td>
<td>3.25</td>
</tr>
<tr>
<td>-2.5</td>
<td>3.25</td>
<td>1.50</td>
<td>2.00</td>
</tr>
<tr>
<td>-0.5</td>
<td>2.00</td>
<td>0.25</td>
<td>0.75</td>
</tr>
</tbody>
</table>

No major hypoglycemia in any group during weeks 12-38. Transient nausea in 21% during weeks 0-12, 4% during weeks 12-38.

GLP-1 RAs in Combination with Insulin in T2DM – Systematic Review

Results reported as available from 7 RCTs and 15 clinical practice or observational studies including at least 30 patients with T2DM*

HbA1C

GLP-1 RA Added to Insulin

GLP-1 RA + Insulin (sequence not specified)

Adding Rapid-Acting Insulin or GLP-1 RA to Basal Insulin: Outcomes in a Community Setting

Percentage of Patients with >1 Healthcare Visit


Mean Healthcare Costs at 1-year Follow-up (matched analysis):

All-cause and Diabetes-related

ED = emergency department.


Basal Insulin and GLP-1 RA Combination

Fixed-Ratio Formulation of Insulin Glargine/Lixisenatide*

Primary outcome: A1C reduction

*Not FDA approved. GLARG = insulin glargine; LIXI = lixisenatide.

**Fixed-Ratio Formulation of Insulin Glargine/Lixisenatide* in T2DM over 24 Wks**

- **A1C**
  - LS mean difference: -0.17, \( P = 0.013 \)
  - GLARG (n = 146)
- **2-hour PPG**
  - LS mean difference: -57, \( P < 0.0001 \)
  - GLARG (n = 146)
  - LIXI (n = 161)

*Not FDA approved; †Superiority. PPG = postprandial plasma glucose; GLARG = insulin glargine; LIXI = lixisenatide.


**Fixed-Ratio Combination of Insulin Degludec* and Liraglutide**

- 1663 T2DM patients on MET + PIO; 26 week open-label trial
- Patients achieving A1C <7%
  - DEG 1 U/LIRA 0.036 mg: 81%
  - DEG: 65%
  - LIRA: 60%
- DEG 1 U/LIRA 0.036 mg vs. DEG
  - Weight change: -2.22 kg, \( P < 0.001 \)
  - Hypoglycemia: RR 0.68, \( P < 0.002 \)
- DEG 1 U/LIRA 0.036 mg vs. LIRA
  - Weight change: 2.44 kg, \( P < 0.001 \)
  - Hypoglycemia: RR 7.6, \( P < 0.001 \)

*Not FDA approved. DEG = insulin degludec; LIRA = liraglutide; MET = metformin; PIO = pioglitazone; RR = risk ratio.


**Patient Case Cont’d**

- Susan B. was started on exenatide BID. Over the next 6 months her A1c improved to 7.2%.
- She has not experienced any episodes of hypoglycemia and has lost 4 lbs of weight.
- She is extremely happy and thanks you for helping her get control of her diabetes.

**Summary**

- Insulin + DPP-4 inhibitor combination therapy in T2DM improves glycemic control, reduces hypoglycemia, and is typically considered weight-neutral
- Insulin + GLP-1 RA combination therapy in T2DM improves glycemic control, reduces hypoglycemia, and can induce weight loss
- Insulin + GLP-1 RA combination therapy is being very actively investigated in T1DM and T2DM