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

Robert J. Tanenberg, MD, FACP
Professor of Medicine
Division of Endocrinology
Medical Director, Diabetes and Obesity Institute, East Carolina University
Medical Director, Inpatient Diabetes Program, Vidant Medical Center
Greenville, North Carolina

Christopher Newton, MD
Endocrinologist
Atlanta Diabetes Associates
Atlanta, Georgia

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>ADA 2015</th>
<th>AACE 2013*+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Individuals</td>
<td>&lt;6.0</td>
<td>&lt;7.0 most pts</td>
</tr>
<tr>
<td>Individualized Target</td>
<td>&gt;6.0*</td>
<td>&lt;7.0 most pts</td>
</tr>
<tr>
<td>Individualized Target</td>
<td>&gt;7.0</td>
<td>&gt;6.5 most pts</td>
</tr>
</tbody>
</table>

#### Preprandial PG,
- Normal plasma glucose: <100 mg/dL
- Preprandial glucose concentration: <110 mg/dL

**APA** American Association of Clinical Chemistry

### 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

*Defined as fasting glucose >250 mg/dL, random glucose > 300 mg/dL, A1C >10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) by ADA 2009 Consensus Statement. Other oral glucose controlled, oral agents can be added and insulin withdrawn if glucose is >140 mg/dL. A1C >7.5% at least 3 months prior to treatment. Inzucchi SE, et al. Diabet Care. 2012;35(6):1364-1379.

### Glycemic Control Declines over Time with Traditional Monotherapy

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

#### Adequately Controlled and Treated with Metformin*

- 3 yr
  - 44%
  - 38%
  - 13%
- 6 yr
  - 36%
- 9 yr
  - 28%

#### Adequately Controlled and Treated with Sulfonylureas†

- 3 yr
  - 40%
- 6 yr
  - 34%
- 9 yr
  - 24%

*Overweight drug-naïve patients. Normal weight and overweight drug-naïve patients.


### Basal Insulin Therapy – Concept and Physiology

### UKPDS: Progressive Deterioration in Glycemic Control over Time

#### HbA1C Level

- Median A1c (%)
  - Conventional
  - Intensive

#### beta-cell Function

- B-cell Function (%)
  - 100
  - 80
  - 60
  - 40

#### Time from Randomization (y)

- 0
- 3
- 6
- 9
- 12
- 15

#### Years from Diagnosis (y)

- -12
- -10
- -8
- -6
- -4
- -2
- 2
- 4
- 6

### 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.

#### Glucose (mg/dL)

- A1c >7% (n=44)
- A1c >7% (n=120)

#### Hours

- 0
- 6
- 12
- 18
- 24

#### Postprandial Hyperglycemia Persisted after Basal Insulin Therapy

Pharmacokinetic Profile of Basal Insulins

NPH = neutral protamine Hagedorn


0:00 12:00 16:00 20:00 24:00

Plasma Insulin Levels

Intermediate (NPH insulin)

Long (Insulin detemir)

Long (Insulin glargine)

Ultra long (U300 glargine)

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

until FPG is 70-130 mg/dL

Check FBG daily

Continue regimen and check A1C every 3 months

In the event of hypoglycemia or FPG level <70 mg/dL:

Reduce bedtime insulin dose by 4 units, or by 10-20%

A Simple Approach to Starting Basal Insulin

0:00 12:00 16:00 20:00 24:00

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

* p<0.05 vs. insulin glargine; hypoglycemia is defined as PG ≤ 72 mg/dL.

B = Breakfast; L = Lunch; D = Dinner.


Comparison of Analogue Basal Insulin and NPH Added to Oral Therapy: Hypoglycemia

Patients (%) with ≥ 1 Hypoglycemia Episode

* * * * *

Effect of OHA treatment on A1C in Type 2 Diabetes


OHAs = oral hypoglycemic agents


Combined Effects of Metformin with Insulin Therapy in Type 2 Diabetes


Strowig et al [30]

Wulfels et al [31]

Insulin Insulin + Metformin Insulin Insulin + Metformin Insulin Insulin + Metformin

Subject (n) 24 19 22 21 31 27 182 171

Duration (mo) 12 12 6 6 4 4 12 6

Insulin dose at end (U) 53 36 120 92 135 82 71 64

NPH = neutral protamine Hagedorn; OHAs = oral hypoglycemic agents; HbA1c = hemoglobin A1c.
Insulin Regimens with Analogues and A1C <7% in T2DM Patients

• 29 trials, with 17,588 patients
• HbA1c <7% was achieved in 41.4% (95% CI, 35.6-47.4%)
• Predictors of response were: first time insulin users, final lower insulin dose and use of 2 oral drugs
• Hypoglycemia ranged from 0 to 4.71 events/patient/30 days
• Weight gain ~1.75 kg

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

Stepwise Glycemic Deterioration in T2DM

Relative Contribution of FPG and PPG to A1C
Matching Treatment to Disease Progression Using a Stepwise Approach

Lifestyle Changes plus Metformin (g other agents)

Progressive Deterioration of β-cell Function


Insulin Intensification: OSIRIS Study Design


**OSIRIS Study:** Change in A1C and Weight


**STEP-WISE Study: Change in A1C**


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


GLAR = insulin glargine; GLU = insulin glulisine; MET = metformin; SU = sulfonylurea.
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

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 Type 2 Diabetes?

Hypoglycemia

Risk of Hypoglycemia Increases as Therapy Intensifies

All Hypoglycemia Negatively Affects Quality of Life in Patients with T2DM

SU = sulfonylurea.

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>3.45 (2.34-5.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death – any cause</td>
<td>3.38 (2.31-4.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death – CV cause</td>
<td>3.7 (2.67-5.79)</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>&lt;0.001</td>
</tr>
</tbody>
</table>

Insulin in Combination with GLP-1 Receptor Agonists

Christopher Newton, MD
Endocrinologist
Atlanta Diabetes Associates
Atlanta, Georgia

Incretin Physiology

After food ingestion...

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

- Secretion of GIP
  - Increases glucose-dependent insulin release
  - Degraded by DPP-4 enzyme

Advantages

- No hypoglycemia
- Weight loss
- ↓ some CV risk factors (i.e., lipids, BP, hs-CRP)
- ↓ PPG (more with short-acting agents)

Disadvantages

- GI side effects (nausea, vomiting, diarrhea)
- Injection
- ↑ heart rate

hs-CRP = high sensitivity C-reactive protein; BP = blood pressure; PPG = postprandial glucose.

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

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-acting</td>
</tr>
<tr>
<td>Liraglutide*</td>
<td>10-20 mcg SC daily</td>
<td>2-4 hours</td>
<td>Short-acting</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>30-50 mcg SC once weekly</td>
<td>6-7 days</td>
<td>Long-acting</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75-1.5 mcg SC once weekly</td>
<td>5 days</td>
<td>Long-acting</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>2 mg SC once weekly</td>
<td>2.4 hours</td>
<td>Long-acting</td>
</tr>
</tbody>
</table>

*Available in Europe. Not FDA approved.

Short-acting GLP-1 RA vs. Basal Insulin: Changes in A1C and Weight Over Time
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>LIRA Baseline</th>
<th>EXN Week 26</th>
<th>LIRA Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF + 90 min</td>
<td>8</td>
<td>10</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Lunch + 90 min</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Dinner + 90 min</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

\( \ast p<0.001 \).

PPG effect of short- and long-acting GLP-1 RAs: LIXI* vs. LIRA

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


Why Combine GLP-1 RAs with Basal Insulin

<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>Maintly controls PPG more with short-acting agents</td>
<td>Controls fasting glucose</td>
</tr>
</tbody>
</table>

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

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.

**Efficacy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PBPO</th>
<th>EXN BID</th>
<th>( p )- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>0.7</td>
<td>1.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Discontinuation due to adverse events (% of pts)</td>
<td>10</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\( \ast p<0.001 \); BID = twice daily; PBPO = placebo; EXN = exenatide.
**Exenatide BID Added to Basal Insulin: Effect on PPG**

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.

**SMBG Changes**
- Glargine + EXN (Baseline)
- Glargine + EXN (30 wk)
- Glargine + PBO (Baseline)
- Glargine + PBO (30 wk)

**Change in HbA1c (%)**
- 1.5
- 1.8

**Hypoglycemia (%)**
- Nocturnal hypo: 5.0
- Minor hypo (E/Y): 1.0

*Not FDA approved.*

**Exenatide BID Added to Basal Insulin Effect on Insulin Dose and Weight**

Baseline insulin doses = 49.5 and 47 U/day in EXN BID and PBO groups, respectively. Respective increases = 13 and 20 U/day; EXN = exenatide; PBO = placebo.

**Exenatide BID Added to Basal Insulin**

**Glucose Level (mmol/L)**
- Fasting
- 2-hr PP
- Premeal
- Midday
- Evening
- 2-hr PP
- 0300 Hours

**Lixisenatide* Added to Basal Insulin in T2DM over 24 Weeks: Efficacy**

**Change in A1C (%)**
- 0.11
- 0.0

**Weight (%)**
- 2.1
- 0.4

*Not FDA approved.*

**Lixisenatide* Added to Basal Insulin over 24 Weeks: Weight & Hypoglycemia**

**Weight Change**
- With SU
- Without SU

**Weight Change**
- 0.0
- 0.5

*Not FDA approved.*

**GLP-1 RAs Added to Basal Insulin: Comparison with Prandial Insulin**

**Delta A1C (%)**
- 0.9
- 0.5

**Delta Weight (kg)**
- 2.5
- 0.9

**Minor hypoglycemia (%)**
- 1.0
- 0.0

**Combining GLP-1 RAs and Basal Insulin**

**Outcome**

**GLP-1 RA Added to Basal Insulin**
- EXN BID
- PBO
- DET + LIRA
- LIRA

**Basal Insulin Added to GLP-1 RA**
- EXN BID
- PBO
- DET + LIRA
- LIRA

**A1C (%)**
- 1.7
- 1.0
- 0.5
- 0.0

**Weight (%)**
- 1.87
- 0.96
- 0.16
- 0.95

GLP-1 RAs and basal insulin combined improve glycemic control relative to either class alone, regardless of order of addition. 1-4

Combining GLP-1 RAs and basal insulin dose to decrease hypoglycemia risk with GLP-1 RAs.

**Baseline insulin dose = 49.5 and 47 U/day in EXN BID and PBO groups, respectively.**

*Not FDA approved.*
Liraglutide Added to Basal Insulin in T2DM over 38 Weeks: Effects on A1c and Weight

Efficacy

After MET + LIRA Run-in At 38 Weeks

∆A1C (%)

0
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
-7.5
-8.0
-8.5
-9.0
-9.5
-10.0

MET + LIRA (n=162)
MET + LIRA + DET (n=162)
MET + LIRA (OBS) (n=468)

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

Baseline Endpoint

9
8
7
6
5
4
3
2
1
0

Body Weight (kg)

Baseline Endpoint

90
80
70
60
50
40
30
20
10
0

Insulin Dose (Units)

Baseline Endpoint

150
120
90
60
30
30
60
90
120
150

Insulin Added to GLP-1 RA
GLP-1 RA Added to Insulin
GLP-1 RA + Insulin (sequence not specified)


Percentage of Patients with ≥1 Healthcare Visit

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

Mean All Healthcare Costs (USD)

Health Care 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**
  - Change in A1C (%)
  - LS mean difference: -0.17, \( P<0.001 \)
  - GLARG 2 U/LIXI 1 µg (n = 161)
  - GLARG = insulin glargine; LIXI = lixisenatide.

- **2-hour PPG**
  - LS mean difference: -57, \( P<0.001 \)


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

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.