Insulin Therapy in Type 2 Diabetes:

When and How Do We Start?
When Do We Add?
How do The Guidelines Guide Us?

Guillermo Umpierrez, MD, FACP, FACE
Professor of Medicine
Emory University School of Medicine

Dr. Guillermo Umpierrez,
Personal/Professional Financial Relationships with Industry

<table>
<thead>
<tr>
<th>External Industry Relationships *</th>
<th>Company Name(s)</th>
<th>Role</th>
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</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
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<tr>
<td>Board of Directors or officer</td>
<td>None</td>
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<tr>
<td>Royalties from external entity</td>
<td>None</td>
<td></td>
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<tr>
<td>Industry funds to Emory for my research</td>
<td>Sanofi-Aventis Merck</td>
<td>Investigator- Initiated Research Projects</td>
</tr>
</tbody>
</table>

*Consulting, scientific advisory board, industry-sponsored CME, expert witness for company, FDA representative for company, publishing contract, etc.
### What Are the Rationales for Different Glycemic Targets?

<table>
<thead>
<tr>
<th>Target</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C ≤ 6.5%¹</td>
<td>• AACE general glycemic goal</td>
</tr>
<tr>
<td></td>
<td>• “Threshold” for the development of microvascular complications</td>
</tr>
<tr>
<td>A1C &lt; 7%²</td>
<td>• ADA general glycemic goal</td>
</tr>
<tr>
<td></td>
<td>• Epidemiological analysis of DCCT and UKPDS</td>
</tr>
<tr>
<td>A1C &lt; 8%³</td>
<td>• ADA less-stringent glycemic target for selected patients</td>
</tr>
<tr>
<td></td>
<td>• Outcomes from ACCORD, ADVANCE, and VADT studies cited in support of less-stringent goal</td>
</tr>
</tbody>
</table>

Hypoglycemia Frequency, Not Severity, Before Enrollment in ACCORD, Increased Risk of Mortality

| Crude, Annualized Mortality Rates and Hazard Ratios Within Treatment Groups |
|-----------------------------|---------------------|---------------------------------|
| Mortality rate (n = 451 deaths) | Hazard ratio for no previous events vs at least 1 event, stratified by glycemia arma (HR [95% CI]) |
| No previous events | ≥ 1 previous event | |
| Hypoglycemic events requiring any assistance, medical or nonmedical (% per year)b |
| Intensive | 1.2% | 2.8% | Unadj: 1.79 (1.32 to 2.44) |
| Standard | 1.0% | 3.7% | Unadj: 2.93 (1.86 to 4.63) |
| Hypoglycemic events requiring medical assistance (% per year)c |
| Intensive | 1.3% | 2.8% | Unadj: 1.72 (1.19 to 2.47) |
| Standard | 1.0% | 4.9% | Unadj: 3.88 (2.35 to 6.40) |

*Hazard ratios are adjusted for the following: age, gender, smoking status, history of CVD, history of HF, peripheral neuropathy, albumin to creatinine ratio, HR, QT score, visual acuity score, statin use, sulfonylurea use, glycemia intervention, enrolled in lipid vs BP trial, intensive BP control group, and fibrate group.

b $P = .076$ for interaction between history of hyperglycemia requiring any assistance and glycemic intervention.

c $P = .009$ for interaction between history of hyperglycemia requiring medical assistance and glycemic intervention.


What Glycemic Targets Should We Aim For?
Recommendations Based on Landmark Clinical Trials in T2DM

| Considerations based on UKPDS, ACCORD, ADVANCE, and VADT. |
|-----------------------------|---------------------|---------------------------------|
| Most Intensive | Less Intensive | Least Intensive |
| 6.0% | 7.0% | 8.0% |

Psychosocial/economic considerations

- Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems
- Less motivated, nonadherent, limited insight, poor self-care capacities, and weak support systems

Hypoglycemia risk

- Low
- Moderate
- High

Patient age, y

- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

Disease duration, y

- 5
- 10
- 15
- 20

Other comorbid conditions

- None
- Few or mild
- Multiple or severe

Established vascular complications

- Cardiovascular disease
- Early microvascular
- Advanced microvascular

**Evidence-Based Recommendations for Individualization of Glycemic Targets in T2DM**

**Approximate A1C Targets Determined by Clinical Characteristics (in the Absence of Severe Hypoglycemia)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration of Disease</th>
<th>Complications</th>
<th>Treatment Intensity (A1C Target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45 y</td>
<td>Any</td>
<td>None and None or early</td>
<td>Most intensive (≤ 6.5%)</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Established and/or Advanced</td>
<td>Less intensive (≈ 7.0%)</td>
</tr>
<tr>
<td>45-65 y</td>
<td>Short*</td>
<td>None and None or early</td>
<td>Intensive (6.5% - 7.0%)</td>
</tr>
<tr>
<td></td>
<td>Long*</td>
<td>None and None or early</td>
<td>Less intensive (≈ 7.0%)</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Established and/or Advanced</td>
<td>Not intensive (7.0% - 8.0%)</td>
</tr>
<tr>
<td>&gt; 65 y</td>
<td>Short*</td>
<td>None and None or early</td>
<td>Less intensive (≈ 7.0%)</td>
</tr>
<tr>
<td></td>
<td>Long*</td>
<td>None and None or early</td>
<td>Not intensive (7.0% - 8.0%)</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Established and/or Advanced</td>
<td>Moderated (≈ 8.0%)</td>
</tr>
<tr>
<td>&gt; 75 y or infirm at any age</td>
<td>Any</td>
<td>Any and/or None</td>
<td>Moderated (≈ 8.0%)</td>
</tr>
</tbody>
</table>

* Evidence base consists of 4 major RCTs: UKPDS, ACCORD, ADVANCE, and VADT.

**Algorithm for the Metabolic Management of T2DM (ADA/ EASD 2009)**

1. **Tier 1:** Well-validated core therapies—the intervention should be changed if A1C is ≥ 7.0%
   - At diagnosis: Lifestyle + Metformin
   - Lifestyle + Metformin + Basal Insulin
   - Lifestyle + Metformin + Sulfonylurea

2. **Tier 2:** Less well validated therapies—the intervention should be changed if A1C is ≥ 7.0%
   - Reinforce lifestyle interventions at every visit and check A1C every 3 months until <7.0% and then at least every 6 months.
   - *Sulfonylureas other than glyburide or chlorpropamide.
   - *Insufficient clinical use to be confident regarding safety.

3. **Tier 3:** Further intensification with GLP-1 agonist or DPP-4 inhibitor
   - Lifestyle + Metformin + Pioglitazone + Basal Insulin

Type 2 Diabetes Oral Medication Choices
Experience and Potency

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Year</th>
<th>Efficacy as monotherapy: % ↓ in HgbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>1995</td>
<td>1.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.5</td>
</tr>
<tr>
<td>Glinides</td>
<td>Oral</td>
<td>1997</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>TZDs</td>
<td>Oral</td>
<td>1999</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Oral</td>
<td>1995</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Oral</td>
<td>2008</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Oral</td>
<td>2008</td>
<td>0.5</td>
</tr>
<tr>
<td>Bromocriptine mesylate</td>
<td>Oral</td>
<td>2009</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>
Most patients on traditional therapies will require another agent to maintain long-term glycemic control.

- Adequately controlled and treated with metformin*
  - 3 yr: 44%
  - 6 yr: 34%
  - 9 yr: 13%

- Adequately controlled and treated with sulfonylureas†
  - 3 yr: 60%
  - 6 yr: 34%
  - 9 yr: 24%

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

Turner RC et al. JAMA. 1999;281:2005

UKPDS: Progressive Deterioration in Glycemic Control Over Time

- Median A1C (%)
  - Conventional
  - Intensive

- B-cell function

Time from randomization (y)


Effects of Metformin on HbA$_{1c}$ in Glyburide-Treated Patients

-1.5
-1
-0.5
0
0.5

Mean Change from Baseline HbA$_{1c}$ (%)

0 1 2 3 4 5 6 7 Weeks

*P =0.001
N=632


Treatment Paradigm

Diet & exercise → Monotherapy → Combination oral agents → Insulin
Treatment Paradigm

Diet & exercise → Monotherapy → Combination oral agents → Insulin

Secondary Failure of Oral Combination Therapy

Lab: FPG >150 mg/dL, HbA\textsubscript{1c} >7%

Causes:
- Decreasing β-cell function
- Non-adherence to treatment
- Obesity
- Insufficient exercise
- Intercurrent illness
Insulin Therapy in Type 2 Diabetes

- Combination oral agents plus basal insulin
  - Bedtime NPH
  - Glargine
  - Detemir

- Insulin Therapy
  - Conventional approach (split-mixed NPH plus Regular insulin)
  - MDI- multi-dose insulin protocols
  - Basal/bolus insulin therapy

Basal Insulin Therapy – Concept and Physiology
Profiles of Long-Acting Human Insulins

Plasma insulin levels

NPH

Detemir

Glargine

Hours

0 2 4 6 8 10 12 14 16 18 20 22 24

Oral agents plus NPH or Basal Insulin

- Continue oral agent(s) at same dosage
- Add single, evening dose of NPH or basal insulin analog starting at 10 U or 0.2/kg
- Adjust dose by SMBG
  - goal FBS < 130 mg/dl

Insulin Effect

NPH

Glargine/Detemir

B L S HS B

Meals
Starting With Basal Insulin Bedtime NPH + Oral Agents

Reduction in A1C at 12 mo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Change in A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH at HS + Glyburide (n=22)</td>
<td>9.8</td>
<td>1.9</td>
</tr>
<tr>
<td>NPH at HS + Metformin (n=19)</td>
<td>9.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Glyburide + Metformin (n=23)</td>
<td>9.9</td>
<td>2.1</td>
</tr>
<tr>
<td>NPH at AM (n=24)</td>
<td>10.1</td>
<td>2.9</td>
</tr>
</tbody>
</table>


Insulin Glargine Trials: Effective Dose Titration Consistently Reduces HbA1c to Target

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Study endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial To Target</td>
<td>8.61</td>
<td>6.99</td>
</tr>
<tr>
<td>LANNET*</td>
<td>8.5</td>
<td>7.14</td>
</tr>
<tr>
<td>APOLLO*</td>
<td>8.71</td>
<td>7.95</td>
</tr>
<tr>
<td>LAPTOP*</td>
<td>8.85</td>
<td>8.80</td>
</tr>
<tr>
<td>Triple Therapy*</td>
<td>8.80</td>
<td>8.80</td>
</tr>
<tr>
<td>INITIATE*</td>
<td>8.80</td>
<td>8.80</td>
</tr>
</tbody>
</table>

Baseline A1c affects results of basal insulin treatment

Pooled analysis of 2193 patients with 24 weeks titrated glargine added to OAD

A1c change from baseline % of patients attaining <7% A1c

Baseline A1c

Despite greater reduction of A1c when baseline is higher, likelihood of reaching 7% is greater when baseline is lower

Riddle MC et al. Diabetes 2009;58(Suppl.1): A125

Insulin Glargine vs NPH Insulin Added to Oral Therapy: FPG and HbA1c

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

Mean daily insulin dose
Insulin glargine: 47 units
NPH: 42 units

Treat to Target Trial: Frequency of Hypoglycemia

Documented PG<56 mg/dL (<3.1 mmol/L)

Cumulative number of events

NPH

Glargine

41% RRR

P <0.003


Less Hypoglycemia with Insulin Glargine vs NPH

Hypoglycemia events per 100 patient-years

T1DM

p=0.004 between treatments

NPH

Insulin glargine

HbA1c (LOCF)

T2DM

p=0.021 between treatments

Head to Head Comparison of Glargine Versus Detemir in Type 2 Diabetes
52-weeks. Once daily Glargine or Detemir - could be titrated to BID Detemir (55%). Baseline A1c 8.6% n = 582

Basal Insulin Therapy with Glargine versus Degludec In T2DM

Simple Way to Start Basal Insulin

- Bedtime or morning long-acting insulin OR
- Bedtime intermediate-acting insulin
- Daily dose: 10 units or 0.2 units/kg

- Check FBG daily

- Increase dose by 2 units every 3 days until FBG is 70–130 mg/dL
- If FBG is >180 mg/dL, increase dose by 4 units every 3 days

In the event of hypoglycemia or FBG level <70 mg/dL
- Reduce bedtime insulin dose by 4 units, or by 10% if >60 units

- Continue regimen and check HbA1c every 3 months


Keys to Success with Basal Insulin Therapy

- Use patient-driven algorithms
**Treat-to-target simply:**
**LANMET study**

- Insulin-naïve T2DM patients (n=110) failed on oral agents
- HbA$_{1c}$ 9.5 ± 0.1%

| OHAs | Insulin glargine + metformin | NPH insulin + metformin |

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**Treat-to-target simply:**
**LANMET study**

- Insulin-naïve T2DM patients (n=110) failed on oral agents
- HbA$_{1c}$ 9.5 ± 0.1%

| OHAs | Insulin glargine + metformin | NPH insulin + metformin |

- Measure FPG daily for 3 days
- If mean of FPG measurements >100 mg/dl
  - ADD 2 UNITS OF BASAL INSULIN
- No increase in dose if FPG <72 mg/dl

LANMET study: HbA1c reduction between treatment groups

Bedtime NPH vs insulin glargine, plus metformin 2 g

Combined Effects of Metformin with Insulin Therapy in Type 2 Diabetes

Table 1. Studies showing the benefits of using metformin with insulin in type 2 diabetes

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Insulin + metformin</td>
<td>Insulin + metformin</td>
<td>Insulin</td>
<td>Insulin + metformin</td>
</tr>
<tr>
<td>Subject, n</td>
<td>24</td>
<td>22</td>
<td>31</td>
<td>182</td>
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<tr>
<td>Duration, mo</td>
<td>12</td>
<td>6</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Insulin dose at end, U</td>
<td>53</td>
<td>120</td>
<td>135</td>
<td>71</td>
</tr>
<tr>
<td>HbA1c at end, %</td>
<td>7.9</td>
<td>7.2</td>
<td>7.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Weight gain, kg</td>
<td>4.6</td>
<td>3.2</td>
<td>0.5</td>
<td>1.3</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 a lower HbA1c.
What if Basal Insulin is Not Enough?

Insufficiency of oral + basal insulin treatment

- 50% of patients with basal insulin do not reach HbA$_{1c}$ target at initiation, with titration of the dose

Insufficiency of oral + basal insulin treatment

- 50% of patients with basal insulin do not reach HbA$_{1c}$ target at initiation, with titration of the dose

- Natural history of pancreatic disease in type 2 diabetes, with expected further degradation of glycemic control
- Hypoglycemic risk during titration of basal insulin, making difficult to reach FBG target
- Very high dose of basal insulin without significant effect on FBG
- Weight gain

Progressive Loss of β-Cell Function in Type 2 Diabetes

Progressive Loss of β-Cell Function in Type 2 Diabetes


Review article

Treatment regimens with insulin analogues and haemoglobin A1c target of <7% in type 2 diabetes: A systematic review

Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 1–10

29 trials, with 17,588 patients
HbA1c < 7% was achieved in 41.4% (95% CI, 35.6–47.4%).
First insulin treatment, lower insulin and use of 2 oral drugs were predictors of response.
Hypoglycemia ranged from 0 to 4.71 events/patient/30 days
Weight gain ~1.75 kg
Postprandial hyperglycemia persists despite treatment of FBG using basal insulin

- Basal insulin therapy reduces the entire 24-hour blood glucose profile, but postprandial hyperglycemia persists.

![Insulin glargine + metformin](image)

Blood Glucose (mmol/l)

- Before breakfast
- After breakfast
- Before lunch
- After lunch
- Before dinner
- After dinner
- 22:00
- 04:00

Baseline

Weeks 25 - 36

Postprandial hyperglycemia persists after basal therapy

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

![Blood glucose profile](image)

Glucose mg/dL

- Before breakfast
- After breakfast
- Before lunch
- After lunch
- Before dinner
- After dinner
- 22:00
- 04:00

A1C >7% (n=44)

A1C ≤7% (n=120)

When basal insulin is not enough: What strategy?

- In clinical practice:
  - Premix insulins
  - Basal plus (stepwise basal-bolus)
  - Basal-bolus
  - Insulin in combination with other hormones

#### Insulin Glargine vs 70/30 Premixed Insulin in OHA Failures

N=371 insulin-naïve patients
Insulin Glargine + OADs vs twice-daily human NPH insulin (70/30)
Follow-up: 24 weeks

<table>
<thead>
<tr>
<th></th>
<th>Twice-daily premixed insulin</th>
<th>Insulin Glargine + OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%)</td>
<td>7.5%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Hypoglycemia* (events/patient year)</td>
<td>1.3%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

p=0.0003

![Graph showing HbA1c and hypoglycemia](image)


*Confirmed symptomatic hypoglycemia (blood glucose <60 mg/dl [<3.3 mmol/l])
Hypoglycemia
Documented Hypoglycemic Episodes (<56 mg/dL)

\[ P < 0.05 \]

Premix insulins

- Efficient on HbA\textsubscript{1c}, but very few clinical studies available
- Mainly to simplify the protocols ++
- Many disadvantages with:
  - Lack of flexibility
  - Risk of hypos
  - Poor reproducibility

Steps in Transition From Basal to Basal-Bolus Insulin Therapy in T2DM

**STEP 1**
Basal Insulin
- Weekly titration based on FPG
- All oral agents continued

**STEP 2**
Add insulin
Above target
Main Meal

**STEP 3**
Add insulin
Above target
Next Largest Meal

**STEP 4**
Add insulin
Above target
Last Meal

Above target: A1C >7.0%, FPG >110 mg/dL

A1C <7.0%, FPG <110 mg/dL

Maintain treatment regimen with monitoring of FPG and A1C

Studies to Support the Basal Plus Strategy

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Design</th>
<th>Primary endpoint</th>
<th>Lead country</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELEONOR</td>
<td>Evaluation of Basal Plus strategy in T2DM on OADs using Telecare system</td>
<td>Lantus® + Met + 1x Apidra® measured by SMBG vs Lantus® + Met + 1 Apidra® using Telecare assistance</td>
<td>Change in HbA1c</td>
<td>ITA</td>
</tr>
<tr>
<td>1,2,3 (Lantus® + Apidra®)</td>
<td>Efficacy of Basal Plus strategy in persons with T2DM on TZDs</td>
<td>Lantus® + TZD + 1x Apidra® vs Lantus® + TZD + 2x Apidra® vs Lantus® + TZD + 3x Apidra®</td>
<td>Change in HbA1c</td>
<td>USA</td>
</tr>
<tr>
<td>OSIRIS</td>
<td>Non-inferiority of Basal Plus strategy compared with basal—bolus regimen</td>
<td>Lantus® + 1,2,3x Apidra® + Met +/– SU vs Lantus® + 3x Apidra®</td>
<td>Change in HbA1c</td>
<td>17 countries</td>
</tr>
<tr>
<td>All-to-Target</td>
<td>Basal/Basal Plus strategy more effective than premixed insulin</td>
<td>Lantus® + 1,2,3x Apidra® vs 2 premix</td>
<td>% subjects HbA1c &lt;7%</td>
<td>USA</td>
</tr>
</tbody>
</table>

Stepwise Intensification: 1-2-3 Study Design

- Insulin glulisine was administered 0-15 minutes before greatest glycemic index meal.
- Initial glulisine dose was 1/10th of the glargine does at randomization.
- Weekly titration to target PPG 70-109 mg/dL and HS level 70-129 mg/dL.

OADs were continued.
GLAR = insulin glargine; GLU = insulin glulisine; OADs= oral antidiabetic agents.

A1C Change From Baseline to Week 24

Following 14-week run-in with insulin glargine:
Mean A1C decreased from >10.0% to ~8.0%.
288 patients achieved A1C ≤7.0%.
Final dose was 0.55 U/kg regardless of reaching target.

mITT = modified intent to treat.
Stepwise Intensification: Change in A1C and Weight

Change in A1C From Randomization to Endpoint

<table>
<thead>
<tr>
<th>Group 1: GLAR + MET + 3×GLU</th>
<th>Group 2: GLAR + MET + 1, 2, or 3×GLU</th>
<th>Group 3: GLAR + MET + SU + 1, 2, or 3×GLU</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.72</td>
<td>-0.47</td>
<td>-0.4</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>0.75</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>1.25</td>
<td>1.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Change in Body Weight, kg

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.03</td>
<td>1.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

\[P = 0.05\]

Raccah D et al. [ADA abstract 555-P]. Diabetes. 2010;59(suppl 1):A151.

Matching treatment to disease progression using a stepwise approach

- **Basal Bolus**: once-daily basal insulin plus rapid-acting insulin before meals

- **Basal Plus**: Add prandial insulin at main meal

- **Basal**: Add basal insulin and titrate

- **Basal Bolus Add prandial insulin before each meal**

- **Lifestyle changes plus metformin (± other agents)**

*Progressive deterioration of \(\beta\)-cell function*

Basal Bolus Insulin: Percent of patients with HbA1c < 7%

12 trials, with 2114 patients

HbA1c < 7% was achieved in 53.9% (95% CI, 43.5–64)

Hypoglycemic events (mean/patient/30 days): 0.88 (0.35–1.3)

Weight gain ~2.75 kg (1.8-3.7)

Final insulin dose: 0.89 U/kg (0.78-1.3)

Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 1–10

Escalation from basal to basal-bolus increases success rate in an additional ~12% to 14% of patients
- HbA1c < 7% is achieved in ~54% of patients
Insulin in Combination With Other Hormones

- Insulin + DPP-4 inhibitors
- Insulin + GLP-1 receptor agonists

US FDA-Approval Status: Incretin-Based Therapies Combined With Insulin

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents With FDA Approval for Use in Combination With Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors¹</td>
<td>Sitagliptin, Saxagliptin</td>
</tr>
<tr>
<td>GLP-1 RAs¹</td>
<td>Exenatide BID</td>
</tr>
<tr>
<td></td>
<td>• Trial in combination with insulin glargine</td>
</tr>
<tr>
<td></td>
<td>• Not studied in combination with prandial insulin</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
</tr>
<tr>
<td></td>
<td>• Trial in combination with insulin detemir</td>
</tr>
<tr>
<td></td>
<td>• Not studied in combination with prandial insulin</td>
</tr>
</tbody>
</table>

Clinical trials are in progress for the DPP-4 inhibitor, linagliptin, and the GLP-1 RA, exenatide ER.²

Exenatide BID Added to Insulin Glargine

EXN BID or PBO Added to GLAR 30-week trial

- GLAR + EXN BID (n = 137)
- GLAR + PBO (n = 122)

More discontinued due to AEs in EXN BID (9%) vs PBO (1%) group (P < .01).


Similar rates of minor hypoglycemia in EXN BID (25%) and PBO (29%) groups

Saxagliptin Improves Glycemic Control With Low Rates of Hypoglycemia Over 24 Weeks in T2DM

- SAXA + INS (n = 304)
- PBO + INS (n = 151)

Hypoglycemia threshold not defined.

## US FDA-Approval Status for Insulin-GLP-1 RA Combinations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approval Status for Combination with Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Approved in combination with insulin glargine&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>NDA filed in 2011; awaiting response from the US FDA&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lixisenatide*</td>
<td>Not FDA approved; studied in combination with insulin glargine&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Not FDA approved.


## Exenatide BID Added to Insulin Glargine

### EXN BID or PBO Added to GLAR 30-week trial

<table>
<thead>
<tr>
<th>GLAR + EXN BID (n = 137)</th>
<th>GLAR + PBO (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>△A1C (%)</td>
<td>△Weight (kg)</td>
</tr>
<tr>
<td>-0.2</td>
<td>-1.5</td>
</tr>
<tr>
<td>-0.1</td>
<td>-1.0</td>
</tr>
<tr>
<td>-0.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Similar rates of minor hypoglycemia in EXN BID (25%) and PBO (29%) groups

More discontinued due to AEs in EXN BID (9%) vs PBO (1%) group ($P < .01$).

Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With T2DM

Efficacy

Body Weight

Adults with T2DM and A1C = 7.1% to 10.5% receiving GLAR MET PIO were randomized to EXN (10 g BID) or PBO for 30 weeks.

Insulin Detemir Added to Liraglutide

Run-in: Weeks –12 to 0
- 1.8 mg LIRA + MET
- Patients not achieving A1C < 7%
  randomized to study treatments

Study + extension: Weeks 0 to 52
- 26-week study + 26-week extension
- Added insulin detemir or nothing
- Mean starting A1C = 7.6%

Lixisenatide Combined With Basal Insulin Improves Glycemic Control With Less Weight Gain in T2DM Over 24 Weeks

Efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ΔA1C (%)</th>
<th>ΔWeight from baseline (kg)</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIXI + INS ± SU (n = 153)</td>
<td>-0.77</td>
<td>0.38</td>
<td>39.6%</td>
</tr>
<tr>
<td>PBO + INS ± SU (n = 157)</td>
<td>0.11</td>
<td>0.06</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Hypoglycemia


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
Optimizing Insulin Therapy for Maintenance of Glycemic Control When Basal is Not Enough

Lifestyle changes plus metformin (± other agents)

Optimizing Insulin Therapy for Maintenance of Glycemic Control When Basal is Not Enough

Basal
Add basal insulin and titrate

Lifestyle changes plus metformin (± other agents)
Optimizing Insulin Therapy for Maintenance of Glycemic Control When Basal is Not Enough

- **Basal Plus**
  - Add prandial insulin at main meal

- **Basal**
  - Add basal insulin and titrate

- **Lifestyle changes plus metformin (± other agents)**

---

Optimizing Insulin Therapy for Maintenance of Glycemic Control When Basal is Not Enough

- **Basal Bolus**
  - Add prandial insulin before meals

- **Basal Plus**
  - Add prandial insulin at main meal

- **Basal**
  - Add basal insulin and titrate

- **Lifestyle changes plus metformin (± other agents)**
Basal Bolus
Add prandial insulin before meals

Basal Plus
Add prandial insulin at main meal

Basal
Add basal insulin and titrate

Basal plus DPP4-inhibitors
or
GLP1 Analogs

Lifestyle changes plus metformin
(± other agents)
Milestones in Insulin Development

- Insulin discovered (1921)
- Synthetic human insulin developed (1965)
- Recombinant human insulin developed (1979)
- Insulin lispro approved in US (1996)
- Insulin detemir approved in US (2005)
- Insulin aspart and insulin glargine approved in US (2000)
- Lente (zinc) insulins developed (1952)
- Insulin pump developed (1981)
- Insulin pen developed (1981)
- Insulin detemir approved in US (2005)
- NPH insulin developed (1946)
- Protamine and protamine zinc insulins developed (1936)
- First human treatment with bovine insulin (1922)