Insulin Therapy in Type 2 Diabetes:
When and How Do We Start?
When Do We Add?
How do The Guidelines Guide Us?

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Professor of Medicine
Emory University School of Medicine

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%</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%</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%</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>


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

External Industry Relationships *

| Equity, stock, or options in biomedical industry companies or publishers | None |
| Board of Directors or officer | None |
| Royalties from from external entity | None |
| Industry funds to Emory for my research | Sanofi-Aventis, Merck, Investigator-Initiated Research Projects |

*Consulting, scientific advisory board, industry-sponsored CME, expert witness for company, FDA representative for company, publishing contract, etc.
**Hypoglycemia Frequency, Not Severity, Before Enrollment in ACCORD, Increased Risk of Mortality**

<table>
<thead>
<tr>
<th>Mortality rate (% per year)</th>
<th>Hazard ratio for no previous event vs at least 1 event, stratified by glycemia arm (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>1.2% (1.02 to 1.46)</td>
</tr>
<tr>
<td>Standard</td>
<td>1.0% (0.88 to 1.30)</td>
</tr>
</tbody>
</table>

*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, use of sulfonylurea, intervention, enrolled in lipid intervention, enrolled in BP trial, intensive BP control group, and fibrate.

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

**Approximate A1C Targets Determined by Clinical Characteristics**

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration of diabetes (years)</th>
<th>Macrovascular complications</th>
<th>Microvascular complications</th>
<th>Treatment Intensity (A1C Target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45</td>
<td>Any Established and/or Advanced</td>
<td>Most intensive (~7.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-65</td>
<td>Any Established and/or Advanced</td>
<td>Less intensive (~7.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>Any Established and/or Advanced</td>
<td>Not intensive (~7.0%)</td>
<td></td>
<td></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)**

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

<table>
<thead>
<tr>
<th>Tier 1: Well-controlled normoglycemia—the intervention should be changed if A1C is ≥7.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highly motivated, adherent, knowledgeable, recommend lifestyle interventions and comprehensive support systems</td>
</tr>
<tr>
<td>• Hypoglycemia risk Moderate</td>
</tr>
<tr>
<td>• Patient age: 65-75</td>
</tr>
<tr>
<td>• Disease duration: 10-15 years</td>
</tr>
<tr>
<td>• Other comorbid conditions None</td>
</tr>
<tr>
<td>• Established vascular complications None</td>
</tr>
<tr>
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</tbody>
</table>

**Considerations based on UKPDS, ACCORD, ADVANCE, and VADT:**

**Type 2 Diabetes Oral Medication Choices**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Year</th>
<th>Efficacy as monotherapy (% in HbA1c)</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>Glitazones</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>0.5-1.0</td>
</tr>
<tr>
<td>DPP-IV Inhibitors</td>
<td>Oral</td>
<td>2005</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Closelastim</td>
<td>Oral</td>
<td>2008</td>
<td>0.5</td>
</tr>
<tr>
<td>Bromosopine mesylate</td>
<td>Oral</td>
<td>2009</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>

**Glycemic Control Declines Over Time With Traditional Monotherapy**

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

<table>
<thead>
<tr>
<th>Patients (%) With</th>
<th>A1C &gt;7%</th>
<th>3y</th>
<th>5y</th>
<th>9y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequately controlled and treated with metformin*</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>*Overweight drug-naive patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight and overweight drug-naive patients</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*UKPDS: Progressive Deterioration in Glycemic Control Over Time*

- **HbA1c level**
  - Median A1C (%)
  - B-cell function (%)

- **Years from diagnosis**
Effects of Metformin on HbA1c in Glyburide-Treated Patients

-2.5 -2 -1.5 -1 -0.5 0 0.5
Mean Change from Baseline HbA1c (%) Weeks

*P =0.001
N=632


Treatment Paradigm

Secondary Failure of Oral Combination Therapy
Lab: FPG >150 mg/dL, HbA1c >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

Profiles of Long-Acting Human Insulins

Basal Insulin Therapy – Concept and Physiology

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
Starting With Basal Insulin
Bedtime NPH + Oral Agents

Reduction in A1C at 12 mo

Baseline A1c affects results of basal insulin treatment

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

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**

![Graph showing cumulative number of hypoglycemic events over time for Glargine and NPH.](Image)


**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 (56%). Baseline A1c 8.6% n = 582

![Graph showing HbA1c levels and weight change for Glargine and Detemir.](Image)


**Less Hypoglycemia with Insulin Glargin vs NPH**

![Graph showing hypoglycemia events per 100 patient-years for NPH vs Glargin.](Image)

Basal Insulin Therapy with Glargin versus Degludec in T2DM

![Graph showing HbA1c levels and weight change for Glargin vs Degludec.](Image)


Heise et al. Diabetes Care 34:669-674, 2011
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-naive T2DM patients (n=110) failed on oral agents
• HbA1c 9.5 ± 0.1%
• OHAs
  - Insulin glargine + metformin
  - NPH insulin + metformin

Insulin glargine + metformin

NPH insulin + metformin

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>
<th>Study</th>
<th>N</th>
<th>Duration (mo)</th>
<th>BMI Basal (%)</th>
<th>HbA1c Basal (%)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yasumine et al [21]</td>
<td>10</td>
<td>7-11</td>
<td>35±0.4</td>
<td>7.6±0.5</td>
<td>75±4</td>
</tr>
<tr>
<td>Otsu et al [22]</td>
<td>15</td>
<td>6-8</td>
<td>30±0.5</td>
<td>7.8±0.6</td>
<td>74±4</td>
</tr>
<tr>
<td>Siroky et al [23]</td>
<td>20</td>
<td>6-8</td>
<td>33±0.5</td>
<td>7.9±0.5</td>
<td>73±4</td>
</tr>
<tr>
<td>Wautelet et al [24]</td>
<td>14</td>
<td>8</td>
<td>32±0.7</td>
<td>7.8±0.4</td>
<td>75±4</td>
</tr>
</tbody>
</table>

What if Basal Insulin is Not Enough?

- Insufficiency of oral + basal insulin treatment
  - 50% of patients with basal insulin do not reach HbA1c target at initiation, with titration of the dose

Insufficiency of oral + basal insulin treatment

- 50% of patients with basal insulin do not reach HbA1c 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

Monnier et al. Diab Metab 2006.


Progressive Loss of β-Cell Function in Type 2 Diabetes

- Basal and meal replacement
- Late type 2, type 1


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

- 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

Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 5-10

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

![Graph showing blood glucose profile before and after treatment](image1)

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

![Graph showing blood glucose profiles](image2)

Insulin Glargine vs 70/30 Premixed Insulin in OHA Failures

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

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Twice-daily premixed insulin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5%</td>
<td>7.2%</td>
<td>0.0003</td>
</tr>
<tr>
<td>7.7%</td>
<td>5.7%</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

*Confirmed symptomatic hypoglycemia (blood glucose <60 mg/dL <3.3 mmol/l)
Hypoglycemia

Documented Hypoglycemic Episodes (<56 mg/dL)

- **Hypoglycemia**

<table>
<thead>
<tr>
<th>Episodes per patient year</th>
<th>P&lt;0.05</th>
<th>3.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Glargine</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>PreMix</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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

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

2. **STEP 2 Add insulin**
   - Above target: A1C >7.0%, FPG >110 mg/dL
   - Main Meal

3. **STEP 3 Add insulin**
   - Above target: A1C <7.0%, FPG <110 mg/dL
   - Largest Meal

4. **STEP 4 Add insulin**
   - Above target: A1C <7.0%, FPG <110 mg/dL
   - Last Meal

Maintain treatment regimen with monitoring of FPG and A1C


**Premix insulins**

- Efficient on HbA1c, but very few clinical studies available
- Mainly to simplify the protocols ++
- Many disadvantages with:
  - Lack of flexibility
  - Risk of hypos
  - Poor reproducibility

**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 OMDs using Telecare system</td>
<td>Lantus® + Met + 1 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</td>
<td>Efficacy of Basal Plus strategy in persons with T2DM + T2Ds</td>
<td>Lantus® + T2D + 1x Apidra® vs Lantus® + T2D + 2x Apidra® vs Lantus® + T2D + 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® + 1,2,3 Apidra® vs Met + 2 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 is more effective than premixed insulin</td>
<td>Lantus® + 1,2,3 Apidra® vs 2 premix</td>
<td>% subjects HbA1c &lt;7%</td>
<td>USA</td>
</tr>
</tbody>
</table>
Stepwise Intensification: 1-2-3 Study Design

Poorly controlled on OADs (n=343)
Switched to GLAR for 14 weeks
A1C >7.0%

Group 1: GLAR + OADs + 1×GLU
Group 2: GLAR + OADs + 2×GLU
Group 3: GLAR + OADs + 3×GLU

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

Randomization and 24 week F/U
- Insulin glulisine was administered 0–15 minutes before greatest glycemic index meal
- Initial glulisine dose was 1/10th of the glargine dose at randomization
- Weekly titration to target PPG 70–109 mg/dL and HS level 70–129 mg/dL

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

Matching treatment to disease progression using a stepwise approach

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

Progressive deterioration of β-cell function

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

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>
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<tbody>
<tr>
<td>DPP-4 inhibitors¹</td>
<td>Sitagliptin, Saxagliptin</td>
</tr>
<tr>
<td>GLP-1 RAs²</td>
<td>Exenatide BID, Liraglutide</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>- 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.

14
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

$P < .001$

**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$^1$</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>NDA filed in 2011; awaiting response from the US FDA$^2$</td>
</tr>
<tr>
<td>Lixisenatide$^*$</td>
<td>Not FDA approved; studied in combination with insulin glargine$^1$</td>
</tr>
</tbody>
</table>

$^*$Not FDA approved.


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

**Efficacy**

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

Hypoglycemia threshold not defined.


**Hypoglycemia**

- Percent of Patients
  - Overall: 16.4 vs 6.3 ($P < .001$)
  - Confirmed: 19.0 vs 2.3

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 ($P < .01$).

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.

Δ Weight from baseline (kg)

Nausea

P < .0001

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

Efficacy

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

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%

Δ A1C Change (Δ)

P < .0001

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%

Δ A1C Change (Δ)

P < .0001

Lifestyle changes plus metformin
(± other agents)

Basal
Add basal insulin and titrate

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)
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 plus DPP4-inhibitors or GLP1 Analogs

Milestones in Insulin Development

- Insulin discovered (1921)
- NPH insulin developed (1946)
- Synthetic human insulin developed (1965)
- Recombinant human insulin developed (1979)
- Insulin detemir approved in US (2005)
- Insulin lispro approved in US (1996)
- Inhaled insulin developed (2006)
- Insulin aspart and insulin glulisine approved in US (2000)
- Insulin pen developed (1981)
- Insulin pump developed (1978)
- Lente (zinc) insulins developed (1952)
- Protamine and protamine zinc insulins developed (1936)
- First human treatment with bovine insulin (1922)
- Insulin lispro approved in US (1996)
- Insulin detemir approved in US (2005)
- Insulin aspart and insulin glulisine approved in US (2000)