Initiation and Titration of Insulin in Diabetes Mellitus Type 2

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Disclosure

I have no actual or potential conflicts of interest in relation to the content of this lecture.
Objectives

• Timing of insulin administration in type 2 diabetes
  – Basal insulin
  – Bolus insulin
  – Biphasic insulin

• Insulin choice
  – Insulin analogs
  – Human insulin

• Patient preference and values
Glycemic Recommendations for Nonpregnant Adults with Diabetes

The first step in the treatment of patients with type 2 diabetes is setting glycemic targets. The current standard of care involves individualizing these targets on the basis of patient characteristics. Ultimately, the goal of any treatment should be to provide the patient with the greatest possible improvement in both short- and long-term quality of life.
Glycemic Recommendations for Nonpregnant Adults with Diabetes

- **A1C** <7.0%
- **Preprandial capillary plasma glucose** 80–130 mg/dL
- **Peak postprandial capillary plasma glucose** <180 mg/dL

*Goals should be individualized.*
†Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.
Goals should be individualized based on

- Duration of diabetes
- Age/life expectancy
- Comorbid conditions
- Known CVD or advanced microvascular complications
- Hypoglycemia unawareness
- Individual patient considerations
  - psychologic
  - economic
  - support systems
  - social functioning
Glycemic Recommendations for Nonpregnant Adults with Diabetes

Less stringent A1C goals (such as <8%) may be appropriate for patients with

- History of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions

- Those with longstanding diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin
Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>PATIENT / DISEASE FEATURES</th>
<th>more stringent</th>
<th>A1C 7%</th>
<th>less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>A1C 7%</td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></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 attitude and expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capacities</td>
<td>less motivated, nonadherent, poor self-care capacities</td>
<td></td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

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Recommendations: Pharmacological Therapy For Type 2 Diabetes

Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes.

If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or insulin.

In patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy (with or without additional agents).
Recommendations: Therapy for Type 2 Diabetes

A *patient-centered approach* should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences.

Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
# Antihyperglycemic Therapy in Type 2 Diabetes

## Therapy Algorithm

### Healthy eating, weight control, increased physical activity, and diabetes education

### Monotherapy
- **Efficacy**: high  
- **Hypo risk**: low  
- **Weight**: neutral/loss  
- **Side effects**: GI/lactic acidosis  
- **Costs**: low

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- **Metformin + Thiazolidinedione**
  - **Efficacy**: high/moderate  
  - **Hypo risk**: low  
  - **Weight**: gain  
  - **Side effects**: edema, HF, fxs  
  - **Costs**: low

- **Metformin + DPP-4 inhibitor**
  - **Efficacy**: high/intermediate  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: rare  
  - **Costs**: high

- **Metformin + SGLT2 inhibitor**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: loss  
  - **Side effects**: GU, dehydration  
  - **Costs**: variable

- **Metformin + GLP-1 receptor agonist**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: gain  
  - **Side effects**: hypoglycemia  
  - **Costs**: variable

- **Metformin + Insulin (basal)**
  - **Efficacy**: highest  
  - **Hypo risk**: high  
  - **Weight**: gain  
  - **Side effects**: hypoglycemia  
  - **Costs**: variable

### Dual therapy
- **Metformin + Sulfonylurea**
  - **Efficacy**: high  
  - **Hypo risk**: moderate  
  - **Weight**: gain  
  - **Side effects**: hypoglycemia  
  - **Costs**: low

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- **Metformin + Thiazolidinedione + TZD**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: reduced  
  - **Costs**: variable

- **Metformin + DPP-4 inhibitor + GLP-1-RA**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: variable  
  - **Costs**: variable

- **Metformin + SGLT2 inhibitor + GLP-1-RA**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: variable  
  - **Costs**: variable

- **Metformin + GLP-1 receptor agonist + Insulin (basal)**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: variable  
  - **Costs**: variable

### Triple therapy
- **Metformin + Thiazolidinedione + TZD + DPP-4 inhibitor**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: reduced  
  - **Costs**: variable

- **Metformin + Thiazolidinedione + TZD + SGLT2 inhibitor**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: variable  
  - **Costs**: variable

- **Metformin + Thiazolidinedione + TZD + GLP-1 receptor agonist**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: variable  
  - **Costs**: variable

- **Metformin + Thiazolidinedione + TZD + Insulin (basal)**
  - **Efficacy**: high  
  - **Hypo risk**: low  
  - **Weight**: neutral  
  - **Side effects**: variable  
  - **Costs**: variable

### Combination injectable therapy
- **Basal insulin + Mealtime Insulin or GLP-1-RA**

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2.
Insulin Therapy in Type 2 Diabetes: Lessons Learned from Outcome Studies

• UKPDS
  – Intensive glycemic control in *newly* diagnosed patients led to a 25% reduction in overall microvascular complications

• UKPDS
  – Patients randomized to intensive therapy showed a significant reduction for any diabetes related endpoint and for MI at 10 years

• ADVANCE, VADT
  – Intensive glycemic control yielded no benefit in cardiovascular disease outcomes

• ACCORD
  – Intensive glycemic control led to a significant increase in mortality including an increase in cardiovascular mortality
Insulin Therapy in Type 2 Diabetes: Lessons Learned from Clinical Trials

• Patients can successfully titrate basal insulin to treatment targets
• Basal insulin *analogs* are associated with fewer episodes of nocturnal hypoglycemia than NPH
• Supplementation with basal insulin is associated with improvements in both first and second phase prandial insulin secretion
• Basal insulin compared to prandial or biphasic insulin initiation is associated with fewer hypoglycemic episodes and less weight gain
• *After 3 years, the majority (> 80%) of patients started on basal insulin are also taking prandial insulin*
Insulin Therapy in Type 2 Diabetes

- **Basal:** Simple to use, low injection frequency, well tolerated. Establishes patient confidence in insulin. Relatively low risk of hypoglycemia. May facilitate “beta cell rest” leading to some recovery of prandial insulin release.

- **Prandial:** Demanding, with need for carbohydrate counting and multiple injections. Higher hypoglycemia risk.

- **Premix (biphasic):** Simple way of supplementing both basal and prandial insulin. Fixed dose ratio, titration not straightforward.
When to Initiate Insulin Therapy in Type 2 Diabetes

• **Entry** hemoglobin A1c
  - > 9%
    - Basal insulin
      - TDD 0.2-0.3 units/kg
  - > 11%
    - Basal-bolus insulin (or biphasic insulin)
      - TDD 0.3-0.5 units/kg

• **On-treatment** hemoglobin A1c
  - < 8%
    - Basal insulin
      - TDD 0.1-0.2 units/kg
  - > 8%
    - Basal insulin
      - TDD 0.2-0.3 units/kg
Fasting Glucose and HbA1c Values Following Introduction of Basal Insulin

Diabetes Care 2003:26;3080
Cumulative Hypoglycemic Events Following Introduction of Basal Insulin

*Diabetes Care* 2003:26;3080
Distribution of Hypoglycemia Following Introduction of Basal Insulin

Diabetes Care 2003:26;3080
Basal Insulin

• Usually in combination with metformin +/- other non-insulin agent
• Total daily dose based on A1c level
• Titrate to fasting glucose target
  – Increase by 10-15% or 2-4 units once or twice weekly until fasting glucose level attained or total dose 50 units
  – Decrease by 4 units or 10-20% for hypoglycemia
Approach To Starting and Adjusting Insulin in Type 2 Diabetes

Diabetologia 2012:55;1577

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Adding/Intensifying Insulin Algorithm

Endocr Pract 2013:19;327
Beyond Basal Insulin

• If target fasting glucose attained but daytime control suboptimal, or if total daily basal insulin dose is 50 units, consider:
  – Adding GLP1 RA (or DPP4-i)
  – Adding RAI analog
    • Stop sulfonylurea, continue metformin
    • 10% of basal dose before largest meal (A1c < 8%?)
    • 10% of basal dose before each meal (A1c > 8%?)
    • Titrate weekly (usually with provider follow-up)
  – Switching to biphasic insulin
    • Stop sulfonylurea, continue metformin
    • TDD 2/3 AM, 1/3 PM
    • TDD 1/2 AM, 1/2 PM
    • Titrate weekly (usually with provider follow-up)
Basal Bolus vs. Biphasic Insulin

Diabet Med 2015:32;585

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Severe Insulin Resistance

• Patients who require more than 200 units of insulin daily are considered to have severe IR
• Large insulin volumes can cause injection site discomfort and the need for multiple injections to deliver a single dose
• Large subcutaneous insulin depot may impede insulin absorption and result in delayed hypoglycemia
Concentrated Regular Insulin

- In type 2 diabetes, the dose response at the target level is markedly attenuated and much higher doses of insulin are required to achieve goals.
- With U-500 insulin, not only can larger doses be administered but peaks of concentration and action profile are blunted and the effect of the peak is prolonged, with a duration of action similar to U-100 NPH.
Clinical Trials of U-500 Regular Insulin

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Mean duration (months)</th>
<th>Mean baseline HbA1c (%)</th>
<th>Mean HbA1c reduction (%)</th>
<th>Mean baseline TDD (units)</th>
<th>Mean TDD change (units)</th>
<th>Mean weight change (kg)</th>
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</thead>
<tbody>
<tr>
<td>Studies using MDI (n = 310)</td>
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<tr>
<td>Garg et al. (24)</td>
<td>16</td>
<td>24</td>
<td>11.34</td>
<td>3.29</td>
<td>313</td>
<td>-31</td>
<td>6.5</td>
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<td>Neal et al. (22)</td>
<td>20</td>
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<td>9.59</td>
<td>1.76</td>
<td>221</td>
<td>-7</td>
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<tr>
<td>Wafa et al. (20)</td>
<td>15</td>
<td>12</td>
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<td>116</td>
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<td>Nayyar et al. (21)</td>
<td>81</td>
<td>30</td>
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<td>1.1</td>
<td>311</td>
<td>57</td>
<td>5.1</td>
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<td>Davidson et al. (17)</td>
<td>11</td>
<td>26</td>
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<td>Dailey et al. (23)</td>
<td>40</td>
<td>12</td>
<td>9.4</td>
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<td>240</td>
<td>97</td>
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<td>Boldo et al. (25)</td>
<td>53</td>
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<td>10.1</td>
<td>1.5</td>
<td>225</td>
<td>69</td>
<td>6.8</td>
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<td>Ziesmer et al. (27)</td>
<td>53</td>
<td>20</td>
<td>9.1</td>
<td>1.0</td>
<td>391</td>
<td>24</td>
<td>2.0</td>
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<tr>
<td>Quinn et al. (26)</td>
<td>21</td>
<td>12</td>
<td>9.51</td>
<td>1.8</td>
<td>297.5</td>
<td>57.5</td>
<td>-0.35</td>
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<tr>
<td>Overall effect (95% CI)</td>
<td></td>
<td></td>
<td>1.59</td>
<td>(1.26–1.92)</td>
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</tbody>
</table>
U-500R initiation

- HbA1c >10% → Increase TDD by 10%
- HbA1c 8–10% → Maintain same TDD
- HbA1c <8% → Decrease TDD by 10–20%

<table>
<thead>
<tr>
<th>TDD  150–300 units</th>
<th>Twice daily injections (60/40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Three daily injections (40/30/30, 45/35/20, 40/40/20, or 33/33/33)</td>
</tr>
<tr>
<td>TDD  300–600 units</td>
<td>Three daily injections (as above)</td>
</tr>
<tr>
<td></td>
<td>Four daily injections (30/30/30/10)</td>
</tr>
<tr>
<td></td>
<td>CSII (50% as basal infusion and 50% as bolus)</td>
</tr>
<tr>
<td>TDD &gt;600 units</td>
<td>Four daily injections (25/25/25/25 or 30/30/30/10)</td>
</tr>
<tr>
<td></td>
<td>CSII</td>
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</tbody>
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## The “Fair Cost” of Insulin
Feb 1, 2016

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Price</th>
<th>Volume</th>
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</thead>
<tbody>
<tr>
<td>Lantus SoloStar Pen</td>
<td>$381</td>
<td>15 ml</td>
</tr>
<tr>
<td>Levemir FlexTouch Pen</td>
<td>$412</td>
<td>15 ml</td>
</tr>
<tr>
<td>Humalog KwikPen</td>
<td>$472</td>
<td>15 ml</td>
</tr>
<tr>
<td>Novolog FlexPen</td>
<td>$466</td>
<td>15 ml</td>
</tr>
<tr>
<td>Toujeo SoloStar Pen</td>
<td>$349</td>
<td>4.5 ml</td>
</tr>
<tr>
<td>Tresiba FlexTouch Pen</td>
<td>$536</td>
<td>9 ml</td>
</tr>
<tr>
<td>U500 R vial</td>
<td>$&gt;1500 (?)</td>
<td>20 ml</td>
</tr>
<tr>
<td>Novolin R vial</td>
<td>$136</td>
<td>10 ml</td>
</tr>
<tr>
<td>Novolin N vial</td>
<td>$135</td>
<td>10 ml</td>
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<tr>
<td>Novolin 70/30 vial</td>
<td>$136</td>
<td>10 ml</td>
</tr>
<tr>
<td>Relion/Novolin R vial</td>
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</tr>
<tr>
<td>Relion/Novolin N vial</td>
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</tr>
<tr>
<td>Relion/Novolin 70/30 vial</td>
<td>$24.88</td>
<td>10 ml</td>
</tr>
</tbody>
</table>
In Summary...

- Insulin therapy is ultimately required in most patients with long-standing type 2 diabetes.
- For most, basal insulin is effective initial treatment and dose titration can be successfully accomplished by the properly educated patient.
- Glycemic targets must be individualized for all patients with diabetes, particularly in those with long-standing type 2 diabetes and comorbidities, limited self-care capacity and limited resources.
- The majority of patients initiated on basal insulin replacement will require additional treatment strategies within a few years.
- In patients with severe insulin resistance, use of concentrated regular insulin can improve overall glycemic control.
- Insulin is costly.