Timely Insulinization In Type 2 Diabetes, When and How

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Current Control and Targets
Treatment Guidelines for Diabetes

- **American Diabetes Association**
  - A1C < 7.0%
  - Preprandial BG 90-130 mg/dL (5.0-7.2 mmol/L)
  - Postprandial BG <180 mg/dL (<10 mmol/L)
- **American Association of Clinical Endocrinologists**
  - A1C ≤ 6.5%
  - Preprandial BG <110 mg/dL (<6.1 mmol/L)
  - Postprandial BG <140 mg/dL (<7.8 mmol/L)
- **International Diabetes Federation**
  - A1C < 6.5%
  - Preprandial BG <100 mg/dL (<5.5 mmol/L)
  - Postprandial BG <140 mg/dL (<7.8 mmol/L)

Current Treatment Targets Are Not Being Achieved!!
Insulinization in Type 2 Diabetes
Philip Raskin, MD

Current Control And Targets

The Proportion Of Patients Reaching HbA$_1$c Targets

- NHANES 1988–1994: 44.5%
- NHANES 1999–2000: 35.8%
- NHANES 2003–2004: 56.8%

Koro et al. Diabetes Care 27:17, 2004

Insulin Use in the US Remains Low Despite Poor Control

Koro CE et al. Diabetes Care 27:17, 2004
Clinical Inertia

Current Control And Targets
Glycemic Control Is Poor Even Among Insulin-using Type 2 Diabetic Patients

Mean = 8.4%  Median = 8.1%

N=3,658 Insulin-users In UK And Germany

78.0% ≥ 7.0%
32.3% ≥ 9.0%
18.2% ≥ 10.0%

Insulin Resistance Starts in the Doctor’s Office

Insulin Treatment in Type 2 Diabetes

When????
As Early as Possible in the Course of Diabetes

- **Metabolic Memory**: Beneficial effects of good diabetes control have long lasting benefits

- Intensive diabetes control in older diabetic individuals with long standing diabetes and well established microvascular and macrovascular complications can result in bad outcomes (Accord, etc)

### Lasting Benefits of Early, Intensive Intervention: UKPDS “Legacy” Effect

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Any Diabetes Endpoint</td>
<td>0.029</td>
<td>0.0099</td>
<td>0.040</td>
<td>0.001</td>
</tr>
<tr>
<td>Microvascular Disease</td>
<td>0.052</td>
<td>0.44</td>
<td>0.14</td>
<td>0.007</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.0099</td>
<td>0.014</td>
<td>0.007</td>
<td>0.001</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>0.001</td>
<td>0.007</td>
<td>0.007</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Insulin Treatment in Type 2 Diabetes

How??????

Indications To Initiate Insulin Therapy in Type 2 Diabetes

• Significant hyperglycemia at presentation

• Hyperglycemia despite diet, exercise and maximal doses of oral agents
Significant Hyperglycemia At Presentation

- Two daily injections of a mix of intermediate and short acting insulin
- Often 70/30 insulin for starters
- Metformin (unless specific contraindication)
- Add pioglitazone as needed to achieve target
- Change insulin dose / type / number of injections as needed

Insulin As Initial Therapy in Type 2 Diabetes

Study Design

- 63 treatment naive individuals with Type 2 diabetes for less than 2 months
- Ages 21 to 70 Years old
- Initiation of treatment with 70/30 twice daily (0.2U/kg) plus metformin 500 mg per daily
- Insulin dose titrated upward based on targets (FPG 70 - 110mg/dl, PPG <140 mg/dl)
- Weekly dose escalations of metformin of 500mg to target of 1000 mg BID
- Study duration was 3 months

Initial Insulin Treatment in Type 2 Diabetes
HbA1c Results

* P<.0001 vs baseline


Insulin As Initial Therapy in Type 2 Diabetes
Side Effects

Hypoglycemic events
Weight gain

Initial Insulin Treatment in Type 2 Diabetes

HbA1c Results

Indications To Initiate Insulin Therapy in Type 2 Diabetes

- Significant hyperglycemia at presentation

- Hyperglycemia despite diet, exercise and maximal doses of oral agents
**Hyperglycemia Despite Maximal Oral Treatment**

- Begin at 0.4-0.7 units/kg/day
- Continue insulin sensitizers especially metformin but often the thiazolidinedione
- Discontinue secretagogues and α-glucosidase inhibitors
- Bedtime Insulin (Glargine, detemir or NPH)
- Two daily injections of a mixture of intermediate and short acting Insulin
- Often 70/30 for starters
- Change insulin dose/ type/ number of injections as needed to achieve glycemic targets

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"Insulin is Better Than No Insulin!"
What To Do When There is Basal Insulin Failure

In No Particular Order

- Intensify using two or even three daily injections of Pre-mixed (70/30, 75/25) insulin
- Add a GLP-1 agonist
- Use a stepwise approach using pre-meal insulin before the largest meal. If that doesn’t work, add insulin before the second largest meal. When all else fails add pre-meal insulin before all meals
- Switch to basal bolus therapy
How Often is There “Basal Insulin” Failure???

• In studies with either insulin glargine or insulin detemir 50%-60% of subjects achieve a HbA1c of < than 7.0 % when a single daily injection of basal insulin is added to oral hypoglycemic agents
• Thus, there is close to a 50% basal insulin failure rate

“Two Shots of Insulin are Better Than One!”
Comparison of Glargine + Metformin vs BID Analog Premix 75/25 + Metformin

Study Design

- 91 individuals with poorly controlled Type 2 diabetes on tablets
- Age 30 to 80 years
- HbA1c between 1.3 and 2.0 times upper level of normal (average 8.7%)
- 8 week lead in with metformin titrated to 1500 – 2550 mg plus NPH insulin at bed (FBG target 90 – 126mg/dl)
- Random assignment to metformin plus either Lispro 75/25 twice daily or glargine once daily
- Treatment crossover after 16 weeks
- FBG target 100 mg/dl


Comparison of Glargine + Metformin vs BID Insulin Lispro 75/25 + Metformin

![Graph showing A1C levels over weeks of study for Glargine and BID Insulin Lispro 75/25 + Metformin treatments.](Image)

The Initiate Study

Study Design
- 233 subjects with Type 2 diabetes with inadequate glycemic control on oral hypoglycemic agents
- HbA1c ≥ 8.0%
- BMI ≤ 40 kg/m²
- Four week run-in: stop secretagogues and alpha glucosidase inhibitors, optimize metformin ≥1500 mg/day, switch rosiglitazone to 30 mg pioglitazone
- Random assignment to either glargine 10 or 12 U at bed or 70/30 pre-breakfast (5 or 6 U) and pre-dinner (5 or 6 U)
- Follow insulin titration schedule
- Study duration 28 weeks

Raskin, et al Diabetes Care 28: 260, 2005

<table>
<thead>
<tr>
<th></th>
<th>BIAsp 30</th>
<th>Glargine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>-2.79 ± 0.11</td>
<td>-2.36 ± 0.11</td>
<td>0.0057</td>
</tr>
<tr>
<td>Subjects with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c ≥ 8.5%</td>
<td>-3.13 ± 1.63</td>
<td>-2.60 ± 1.50</td>
<td>0.0026</td>
</tr>
<tr>
<td>HbA1c &lt; 8.5%</td>
<td>-1.40 ± 0.55</td>
<td>-1.42 ± 0.59</td>
<td>&gt;0.05</td>
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</tbody>
</table>

Raskin, et al Diabetes Care 28: 260, 2005
INITIATE
Comparison of Biphasic Insulin Aspart 70/30 and Glargine in Achieving Glycemic Targets

![Graph showing comparison]

**HbA1C Target**

- **HbA1C < 7.0%**
- **HbA1C ≤ 6.5%**

Patients reaching target at Week 28 (%)

<table>
<thead>
<tr>
<th>Biphasic Insulin Aspart 70/30 (BIAsp 30)</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>p = 0.0002</strong></td>
<td></td>
</tr>
<tr>
<td>42%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>p = 0.0356</strong></td>
<td></td>
</tr>
</tbody>
</table>

**HbA1C < 7.0%**

- Diabetes Care 28: 260, 2005

**HbA1C ≤ 6.5%**

- Diabetes Care 28: 260, 2005

**1–2–3 Study**

**Study Design**

**Phase 1**

- **QD**
  - Pre-dinner x 16 wks
  - Start with 12 U at dinner
  - A1C ≤ 6.5%
  - End of Study

- If A1C > 6.5%, go to BID, d/c secretagogues

**Phase 2**

- **BID**
  - Pre-breakfast & dinner x 16 wks
  - Add 3 U at breakfast if FPG ≤ 110
  - Add 6 U at breakfast if FPG > 110
  - A1C ≤ 6.5%
  - End of Study

- If A1C > 6.5%, go to TID

**Phase 3**

- **TID**
  - TID x 16 wks
  - Add 3 U at lunch

Garber AJ et al, Diabetes Obes Metab. 2006; 8: 58-66
**1–2–3 Study**

**Achievement of A1C Targets**

<table>
<thead>
<tr>
<th>A1C ≤ 6.5%</th>
<th>A1C &lt; 7.0%</th>
</tr>
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<tbody>
<tr>
<td>% of patients</td>
<td>% of patients</td>
</tr>
<tr>
<td>QD</td>
<td>BID</td>
</tr>
<tr>
<td>28.4</td>
<td>66.2</td>
</tr>
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</table>

Garber AJ et al, Diabetes Obes Metab. 2006; 8: 58-66

**Stepwise Approach to Insulin Therapy in Patients with Type 2 Diabetes and Basal Insulin Failure**

- **Screening** (N=1232) +2 or 3 OADs
  - **Run-in** (n=785) + Insulin glargine + 2 or 3 OADs
  - **A1C > 7.0%**
    - Insulin glulisine 1x/d (n=115)
    - **Insulin glulisine 2x/d** (n=113)
    - **Insulin glulisine 3x/d** (n=115)
      - + Insulin glargine + Sensitizer(s) Discontinue SU

Davidson, Raskin et al, Endocrine Practice 17:395, 2011
Stepwise Approach to Insulin Therapy in Patients with Type 2 Diabetes and Basal Insulin Failure

<table>
<thead>
<tr>
<th>Patients (%) Achieving A1C &lt;7.0% at Week 24</th>
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<tbody>
<tr>
<td>Step 1</td>
</tr>
<tr>
<td>30%</td>
</tr>
<tr>
<td>Step 2</td>
</tr>
<tr>
<td>33%</td>
</tr>
<tr>
<td>Step 3</td>
</tr>
<tr>
<td>46% *</td>
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</table>

* = P< 0.05 vs 1 and 2 injections


GLP-1 Agonists Added to Basal Insulin

A New Idea!!!!
Addition of Exenatide to Basal Insulin Treated Patients with Type 2 Diabetes

Study Design
- 259 type 2 diabetic individuals receiving insulin glargine alone or in combination with metformin and/or pioglitazone
- HbA1c between 7.1 and 10.5%
- Random assignment to receive either exenatide or placebo injections, twice daily
- Insulin glargine could be titrated upwards using an algorithm designed to have the FBG <100 mg/Dl after the first 5 weeks
- Prospective randomized masked trial
- Study duration was 30 weeks


Addition of Exenatide to Basal Insulin-Treated Patients with Type 2 Diabetes

* = p < 0.001 vs. Placebo

Additional Tools To Reach The Target

Insulin Analog

Insulin produced by technology that uses recombinant DNA to produce an insulin molecule that is slightly different from human insulin in structure as well as pharmacokinetic/pharmacodynamic properties.
### Insulin Preparations

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
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<tbody>
<tr>
<td>Human Insulin</td>
<td>Regular, NPH</td>
</tr>
<tr>
<td>Insulin Analogs</td>
<td>Insulin aspart, insulin glulisine, insulin lispro, insulin glargine, insulin detemir</td>
</tr>
<tr>
<td>Premixed Insulin</td>
<td>Human 70/30, 50/50</td>
</tr>
<tr>
<td>Premixed Insulin Analogs</td>
<td>Insulin Lispro 75/25, 50/50</td>
</tr>
<tr>
<td></td>
<td>Biphasic insulin aspart 70/30</td>
</tr>
</tbody>
</table>

### Time Action Profiles of Insulin Products

![Graph showing plasma insulin levels over time for different types of insulin preparations](image)

- **Insulin Aspart, Insulin Glulisine, Insulin Lispro**: 4–6 hours
- **Regular**: 6-8 hours
- **NPH**: 12–20 hours
- **Insulin Glargine, Insulin Detemir**: up to 24 hours

Basal Bolus Therapy

Basal/Bolus

Using Analog Insulin

Insulin uU/mL

Breakfast  Lunch  Supper

Lispro/Aspart/Glulisine

Less potential for nocturnal hypoglycemia; improved FPG

Bed

Glargine/Detemir

Time
Insulin Pumps

Basal/Bolus Using an Insulin Pump

Breakfast  Lunch  Supper
Lispro  Aspart  Glulisine

Insulin U/mL

Basal Insulin
Comparison of Insulin Pump and Multiple Daily injection Treatment in Type 2 Diabetes

Results

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Baseline: 8.2 ± 1.4</td>
<td>Baseline: 8.0 ± 1.1</td>
</tr>
<tr>
<td>Δ HbA1c (%)</td>
<td>-----</td>
<td>0.62 ± 1.1</td>
</tr>
<tr>
<td>Body Weight(Kg)</td>
<td>96.4 ± 17</td>
<td>98.1 ± 18.1</td>
</tr>
<tr>
<td>Hypoglycemic (% of subjects)</td>
<td>-----</td>
<td>54</td>
</tr>
<tr>
<td>Rate (episode/subject)</td>
<td>-----</td>
<td>0.8 ± 1.6</td>
</tr>
<tr>
<td>Nocturnal (% of subjects)</td>
<td>16</td>
<td>-----</td>
</tr>
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</table>


Conclusions

- Type 2 diabetes is a disease of progressive beta cell failure
- Insulin treatment is usually inevitable and should be started sooner rather than later
- Insulin sensitizers, especially metformin are helpful adjuncts to insulin treatment
- Premixed insulin is a simple (for the patient and the health care provider) therapy and is effective in having patients achieve their targets 60 to 70% of the time
- Multiple daily injection therapies as well as insulin pumps can be used when targets are not being achieved with less complicated regimens