Navigating New Insulins
Diana Isaacs, PharmD, BCPS, BC-ADM, CDE
Clinical Pharmacy Specialist
Cleveland Clinic Diabetes Center

Objectives
• Compare and contrast currently available insulin products.
• Determine the factors that guide insulin selection based on individualized patient characteristics.

Disclosures
• Diana Isaacs has nothing to disclose.

Diabetes: The Stats
• Cases of diabetes
  - 29.1 million people in the U.S. (9.3% population)
• New cases: 1.4 million Americans/year
• On insulin: 28.7%

Normal Insulin Release
Individuals without diabetes

History of Insulin

So Much Insulin...

- Regular insulin
  - Novolin R, Humulin R
- Neutral protamine hagedorn (NPH) insulin
  - Novolin N, Humulin N
- Long-acting insulin
  - Glargine (Lantus®, Basaglar®), Detemir (Levemir®), Degludec (Tresiba®)
- Rapid-acting insulin
  - Lispro (Humalog®), Aspart (Novolog®), Glulisine (Apidra®)
- Pre-mixed insulin
  - Lispro 70/30, 70/25, 50/50
  - Aspart 70/30,
  - Ryozideg 70/30
- Inhaled insulin
  - Afrezza®
- Concentrated insulin
  - Humulin R U-500
  - Glargine U-300 (Toujeo®)
  - Degludec U-200 (Tresiba®)
  - Lispro U-200 (Humalog®)
- Lispro U-200 (Humalog®)
- Aspart 70/30
- Ryzodeg 70/30

ADA Treatment Algorithm

Choice of Basals

- NPH
- Levemir
- Lantus
- Toujeo
- Tresiba U-100
- Tresiba U-200

Choice of Bolus

- Novolog
  - Humalog U-100
  - Apidra
  - Afrezza
  - Regular

Insulin/GLP-1 RA Combos

- Lixisenatide + insulin glargine in a fixed-ratio pen (Soliqua®)
  - Daily dose range: 10-60 units corresponding to lixisenatide 5-20mcg

- Liraglutide + insulin degludec in a fixed-ratio pen (Xultophy®)
  - Max dose 50 units corresponding to liraglutide 1.8mg
New Drug Approvals 2015-2016

- Long-acting insulin
  - Insulin degludec (Tresiba U-100®)
  - Insulin degludec/aspart 70/30 (Ryzodeg®)
  - Insulin glargine U-100 (Basaglar®)

- Concentrated insulin
  - Insulin degludec (Tresiba® U-200)
  - Insulin glargine U-300 (Toujeo®)
  - Humulin R U-500 Kwipen
  - Insulin lispro U-200 (Humalog® U-200)

Insulin Degludec (Tresiba®)

- Mechanism of action
  - After injection, Ideg dihexamers join together creating long, soluble multidexamer chains that prolong duration of action

- Available in U-100, U-200, and Insulin aspart 70/30 combo (Ryzodeg®) kwip pens
  - Ryzodeg® not available in U.S.

Tresiba® Clinical Data

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Intervention</th>
<th>Results: Efficacy</th>
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| 52 weeks, randomized, controlled, open-label, multinational, parallel design, treat-to-target, non-inferiority trial | Adults with T2DM randomized to insulin degludec (n=773) or insulin glargine (n=257) both in combination with metformin. | • Insulin degludec and insulin glargine decreased mean A1C by 1.06 and 1.19%, respectively (95% CI –0.04 to 0.22%), meeting criteria for non-inferiority.
• Nocturnal hypoglycemia and severe hypoglycemia occurred less with degludec (p < 0.05). |

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| 52 weeks, randomized, controlled, open-label, treat-to-target, multinational, non-inferiority trial | Adults with T2DM randomized to insulin degludec (n = 755) or insulin glargine (n=251) both in combination with aspart before meals, +/- metformin and/or pioglitazine. | • Insulin degludec and insulin glargine decreased mean A1C by 1.10 and 1.18%, respectively (95% CI –0.05 to 0.21%), meeting criteria for non-inferiority.
• Rates of overall hypoglycemia and nocturnal hypoglycemia were lower with insulin degludec. |

Tresiba® Vs. Lantus®

- Insulin degludec
  - Longer half-life
  - More forgiving if a dose is missed
  - True once daily dosing
  - Ability to mix with insulin aspart
  - No vial available
  - Both available in combo with GLP-1 RA

- Insulin glargine
  - Easier to treat hypoglycemia
  - Quicker to make dose adjustments
  - Max 80 (pen) to 100 units (vial) per injection
  - More years of experience
  - Cheaper alternative basaglar available

Insulin Glargine U-300 (Toujeo®)

- Offers a smaller depot surface area, leading to a reduced rate of absorption
- Provides flatter and prolonged PK and PD profiles and more consistency
- Structurally identical to insulin glargine
- May need higher doses than Lantus®
- Longer half-life
- Longer duration of action
- Limited to 80 units/dose via pen, no vial

Toujeo® Clinical Data
**Insulin Glargine U-100 (Basaglar®)**
- Identical amino acid sequence to insulin glargine (Lantus®)
- Different excipients
- Demonstrated non-inferiority to Lantus®
- Available in 3mL Kwikpen, no vial
- Not technically approved as a biosimilar
  - “Follow on” abbrev approval process
- Cheaper price

**Basaglar® Clinical Data**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Intervention</th>
<th>Results: Efficacy/Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Element 1</td>
<td>Adults with T1DM randomized to Lantus® (n=267) or Basaglar (n=257) both in combination with insulin lispro.</td>
<td>Lantus® and insulin basaglar decreased mean A1C by 0.46% and 0.35%, respectively (95% CI -0.002 to 0.219, P&gt;0.05%), meeting criteria for non-inferiority.</td>
</tr>
<tr>
<td>Element 2</td>
<td>Adults with T2DM randomized to insulin Lantus® (n=380) or Basaglar (n=376) both in combination with 2 or more oral anti-diabetes agents.</td>
<td>Mean A1c change in both groups was 1.3% (CI: -0.70 to 0.0175, P&gt;0.05) meeting criteria for non-inferiority.</td>
</tr>
</tbody>
</table>

**Humulin R U-500**
- Pen FDA approved Jan, 2016
- 5x insulin concentration compared to U-100
- Delivers up to 300 units in a single injection
- Acts like intermediate acting insulin
- Most ideal for patients with insulin resistance
  - Patients injecting >200 units/day
- Unlike the vial, no dosing conversions
- Vial is still available
- New U-500 syringe now available

**Inhaled insulin**

**Afrezza®**
- Insulin human inhalation power
- Onset: 12-15 minutes, Peak: 1 hour, DOA: 3 hours
- Available in prepackaged blister packs containing 15 insulin cartridges
- Each blister pack, once opened, is good for 10 days
- Inhaler must be changed everyday
- Warnings
  - Acute bronchospasm in patients with asthma or COPD
  - Contraindicated with chronic lung diseases
  - Before initiating, perform a detailed medical history, physical exam and spirometry
  - Side effects: hypoglycemia, cough, throat pain

**Fiasp®**
- Meal time insulin aspart formulation with niacinamide (vitamin B3)
  - Faster absorption
  - Quicker onset
- Inject 2 min before start of meal up to 20 min after
- Duration of action 10% shorter vs. Novolog®
- Available in Canada (not U.S.)
**Insulin Profiles**

**Long-Acting Insulin Comparison**

<table>
<thead>
<tr>
<th>Property</th>
<th>Glargine (U-300)</th>
<th>Glargine (U-100)</th>
<th>Degludec (U-100)</th>
<th>Degludec (U-200)</th>
<th>Humulin R U-500 KwikPen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>300 units/mL</td>
<td>100 units/mL</td>
<td>100 units/mL</td>
<td>200 units/mL</td>
<td>500 units/mL</td>
</tr>
<tr>
<td>Onset</td>
<td>6 hours</td>
<td>4-5 hours</td>
<td>24 hours</td>
<td>24 hours</td>
<td>30 min</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>24-36 hours</td>
<td>24 hours</td>
<td>&gt; 42 hours</td>
<td>&gt; 42 hours</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>~ 19 hours</td>
<td>~ 12 hours</td>
<td>25 hours</td>
<td>25 hours</td>
<td>4.5 hours</td>
</tr>
<tr>
<td>Time to Steady State</td>
<td>5 days</td>
<td>1 day</td>
<td>3 days</td>
<td>3 days</td>
<td>1 day</td>
</tr>
<tr>
<td>Units per pen</td>
<td>450 units in 1.5mL</td>
<td>300 units in 3mL</td>
<td>300 units in 3mL</td>
<td>600 units in 3mL</td>
<td>1500 units in 3mL</td>
</tr>
<tr>
<td>Max units injected/dose</td>
<td>80 units</td>
<td>80 units</td>
<td>80 units</td>
<td>160 units</td>
<td>300 units</td>
</tr>
<tr>
<td>Dial</td>
<td>Pen</td>
<td>Pen/visol</td>
<td>Pen/visol</td>
<td>Pen/visol</td>
<td>Pen/visol</td>
</tr>
<tr>
<td>Expiration</td>
<td>42 days</td>
<td>28 days</td>
<td>56 days</td>
<td>56 days</td>
<td>28 days pen/40 days visol</td>
</tr>
</tbody>
</table>

**Rapid-Acting Insulin Comparison**

<table>
<thead>
<tr>
<th>Property</th>
<th>Insulin Lispro Humalog®</th>
<th>Insulin Lispro Humalog® (U-200)</th>
<th>Insulin Aspart Novolog®</th>
<th>Insulin Glulisine Apidra®</th>
<th>Insulin Inhaled Afrezza®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>15-30 min</td>
<td>15-30 min</td>
<td>10-20 min</td>
<td>25 min</td>
<td>12-15 min</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>3-6.5 hours</td>
<td>3-6.5 hours</td>
<td>3-5 hours</td>
<td>4-5.3 hours</td>
<td>160 min</td>
</tr>
<tr>
<td>Next Timing</td>
<td>SC up to 15 min before meal</td>
<td>SC up to 15 min before meal</td>
<td>SC 5-10 min before meal</td>
<td>SC within 15 min before meal</td>
<td>Inhaled at beginning of meal</td>
</tr>
<tr>
<td>Units per pen</td>
<td>300 units in 3mL</td>
<td>600 units in 3mL</td>
<td>300 units in 3mL</td>
<td>300 units in 3mL</td>
<td>NA</td>
</tr>
<tr>
<td>Max units injected/dose</td>
<td>60 units</td>
<td>60 units</td>
<td>60 units</td>
<td>80 units</td>
<td>6,8,12 unit cartridges</td>
</tr>
<tr>
<td>Pen or Vial</td>
<td>Pen/visol</td>
<td>Pen/visol</td>
<td>Pen/visol</td>
<td>Pen/visol</td>
<td>NA</td>
</tr>
<tr>
<td>Expiration</td>
<td>28 days</td>
<td>28 days</td>
<td>28 days</td>
<td>28 days</td>
<td>3 days</td>
</tr>
</tbody>
</table>

**Insulin Tips and Tricks**

- Long-acting with rapid-acting (or insulin pump) best for T1DM or insulin-dependent T2DM
- NPH-great for pregnancy and steroid induced diabetes
- Regular, NPH, Novolin 70/30 are available OTC and cheap
  - Co-pay cards available for the newer insulins
- 70/30 and other combs good for limiting to 2 injections/day, but less dose flexibility
- All insulin can cause weight gain and hypoglycemia
Which of the following insulins are available in a U-300 formulation?

A. Insulin detemir  
B. Insulin glargine  
C. Insulin regular  
D. Insulin degludec

Key Points

- New insulins offer more treatment options
- The goal is to mimic the body’s natural production of insulin (basal/bolus)
- Several factors guide insulin selection including side effect profile, onset/duration of action, volume of injection, and patient preferences

Which of the following insulins are available in a vial?

A. Humulin R U-500  
B. Insulin degludec U-100 (Tresiba®)  
C. Insulin glargine U-200 (Toujeo®)  
D. Insulin glargine (Basalgar®)

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isaacsd@ccf.org