Diabetes Update: Intensifying Insulin Therapy
Nuts, Bolts and Other Items

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PRIMARY CARE CONFERENCE
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Objectives

Following today’s presentation, the provider should be able to:

• Understand WHY patients need therapeutic intensification after basal insulin.
• Identify WHEN therapeutic intensification is indicated.
• Learn HOW to target post-prandial hyperglycemia using several different strategies including:
  – GLP-1 receptor agonists
  – Subcutaneous rapid acting insulin
  – Inhaled technosphere insulin
• Have time for questions (and avoid tangents)
Introduction
The Cost of Hyperglycemia

- 29.1 million people in the US have been diagnosed with diabetes.
- 37% of US adults >20 years old have pre-diabetes.
- The annual cost of health care for diabetes is ~$245 billion.
- Diabetes is the leading cause of dialysis and non-traumatic lower-limb amputations.
- Diabetes is the 7th leading cause of death in the US.

Natural History of Type 2 Diabetes

Adapted from International Diabetes Center, Minneapolis MN.
Why intensify therapy after basal insulin?
Percent of Your Patients Achieving HbA1c <8% in One Year

42%
This means 58% of patients are NOT achieving their glycemic targets.
Medications for Type 2 Diabetes: General Recommendations

If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

- Initial drug monotherapy
  - Efficacy (i-HbA1c)
  - Hypoglycemia

- Two-drug combinations
  - Efficacy (i-HbA1c)
  - Weight
  - Major side effect(s)

- Healthy eating, weight control, increased physical activity

- Metformin
  - High
  - Low risk

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:

Inzucchi S E et al. Dia Care 2012;35:1364-1379
Failure to Intensify = Clinical Inertia

- Clinical inertia: lack of treatment intensification in a patient not at evidence-based goals.
When to intensify after basal insulin?
Daily Insulin Requirements

- 0.5 units/kg (~50 units)
- 0.75 units/kg (~75 units)
- 1 unit/kg (100 units)

*Approximately* 0.5 units/kg (50 units)
Natural History of Type 2 Diabetes

Adapted from International Diabetes Center, Minneapolis MN.
OVERBASALIZATION = Hypoglycemia and Weight Gain

- Increasing basal insulin without addition of prandial coverage requires the patient to eat for the insulin.
- The ideal basal dose should allow a patient to fast for 24 hours without hypoglycemia
When to Add Prandial Coverage?

- When basal insulin dose is about 0.5 units/kg/day

- OR -

- HbA1c is not at goal despite appropriate fasting blood glucose values.
HOW to Intensify After Basal Insulin?
Options for Post-Prandial Coverage

(To Be Covered Today)

• Subcutaneous GLP-1 Receptor Agonist
• Subcutaneous Rapid Acting Insulin
• Inhaled Rapid Acting Insulin
Post-prandial Hyperglycemia: Option 1
GLP-1 Receptor Agonists
Glucagon Like Protein 1 Receptor Agonists (GLP-1 RAs)
GLP-1 RA: New Alternative to Prandial Insulin*

- When studied as add-on to basal insulin compared to rapid acting insulin analogues, GLP-1RAs demonstrated:
  - Comparable HbA1c reductions
  - Weight loss instead of weight gain
  - Fewer hypoglycemic events
  - Possible improvement in patient quality of life

*Diamant et al. Diabetes Care 2014; 37: 2763-73
# GLP-1 RA Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Increments</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta (exenatide)</td>
<td>5-10 mcg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Bydureon (exenatide)</td>
<td>2 mg</td>
<td>Weekly</td>
</tr>
<tr>
<td>Victoza (liraglutide)</td>
<td>0.6-1.8 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Tanzeum (albiglutide)</td>
<td>30-50 mg</td>
<td>Weekly</td>
</tr>
<tr>
<td>Trulicity (dulaglutide)</td>
<td>0.75-1.5 mg</td>
<td>Weekly</td>
</tr>
</tbody>
</table>
Contraindications

- Severe gastroparesis
- History of pancreatitis not attributable to gallstones
- Personal or family history of medullary thyroid carcinoma
- MEN Type 2
- Severe GI disease
- Creatinine clearance <30 mg/dl
Practical Considerations: HOW to Add GLP-1 RA to Basal Insulin

- Discontinue sulfonylurea
- If HbA1c <8%, ↓ basal insulin by 10-20% until maximal tolerated dose achieved.
- Start with lower dose. Titrate weekly as tolerated.
- THEN titrate basal insulin.
- Nurse/MA should provide face-to-face education about dose administration.
- TIP: Providing discount co-pay cards and ensuring that you prescribe the GLP-1RA preferred by patient insurance augments adherence.
Post-prandial Hyperglycemia: Option 2
Rapid Acting Insulin
Rapid Acting Insulin Analogue

- Humalog (lispro)
- Novolog (aspart)
- Apidra (glulisine)

**Fig 1. Pharmacokinetic Profile of Insulin Analogues**

- Action begins faster
- Peak is higher
- Disappears faster
Basal Plus Approach

**Basal–Plus 1**
Addition of 1 injection of rapid-acting insulin at the main meal to basal insulin

**Basal–Plus 2**
Basal + 2 prandial

**Basal–Plus 1**
Basal + prandial insulin at main meal

**Basal**
Add basal insulin and titrate

**Oral monotherapy and/or combinations**

**Lifestyle changes**

**Progressive deterioration of β-cell function**
Intensification Strategy with SQ RAIA

Add 3-4 units RAIA at largest meal of day and continue with basal insulin

Add 1 extra unit RAIA every week if post-prandial BG >180 mg/dl

Continue titration until post-prandial BG <180 mg/dl

If HbA1c is not at goal after 3 months, add 2nd injection RAIA at 2nd largest meal of the day
Approach to starting and adjusting insulin in type 2 diabetes.

**Add 1 rapid insulin* injection before largest meal**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose. If HbA1c <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.

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**Basal insulin**

(usually with metformin +/- other noninsulin agent)

- **Start:** 10 U/day or 0.1–0.2 U/kg/day
- **Adjust:** 10–15% or 2–4 U once-twice weekly to reach FBG target.
  - **Hypo:** Determine and address cause; lose by 4 U or 10–20%.

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**Add ≥2 rapid insulin* injections before meals ("basal–bolus")**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose/meal.
  - If HbA1c <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
Post-prandial Hyperglycemia: Option 3
Inhaled Prandial Insulin
Physiologic Insulin Replacement

Adapted from ADA’s Clinical Education Program “Insulin Therapy for the 21st Century.”
Inhaled Technosphere Insulin (TI) vs SQ RAIA

Technosphere Insulin

- Is a dry powder human oral insulin inhaler.
- Indicated for pre-meal time, rapid insulin delivery for type 1 and type 2 diabetes.
  - Must be used in combination with long-acting agent for patients with type 1-diabetes.
- Should be avoided in smokers, patients with chronic pulmonary and patients with increased risk of lung cancer.
- Has a $t_{\text{max}}$ of 12-15 minutes and a duration of 28-39 minutes.
- Comes in 4-unit and 8-unit dose packs and cartridges.
- Common side effects include hypoglycemia, cough, throat irritation/pain and a decline in FEV$_1$. 
pH < 6

- Reproducible, well controlled process
- Insulin adsorption onto particle

Blood Vessel

pH > 6

- Rapid dissolution
Intensification Strategy with Inhaled Prandial Insulin

Add 4 unit dose before each meal

Increase to 8 unit dose if subsequent pre-prandial BG >220 mg/dl for a week*

Continue to titrate 4 units every week until subsequent pre-prandial BG is <180 mg/dl*

Theoretically could start in basal plus fashion – has not been studied.*

* These recommendations are based on presenter’s opinion and interpretation of the literature.
## Mealtime Dose Conversion

<table>
<thead>
<tr>
<th>Subcutaneous Insulin Dose</th>
<th>Technosphere Insulin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 4 units SQ</td>
<td>4 units inhaled</td>
</tr>
<tr>
<td>5-8 units SQ</td>
<td>8 units inhaled</td>
</tr>
<tr>
<td>9-12 units SQ</td>
<td>12 units inhaled</td>
</tr>
<tr>
<td>13-16 units SQ</td>
<td>16 units inhaled</td>
</tr>
<tr>
<td>17-20 units SQ</td>
<td>20 units inhaled</td>
</tr>
<tr>
<td>21-24 units SQ</td>
<td>24 units inhaled</td>
</tr>
</tbody>
</table>
In Summary
Intensification of Therapy for Type 2 Diabetes is Important

- Therapy should be intensified when basal insulin dose is approximately 0.5 units/kg OR a patient is not achieving target HbA1c despite appropriate FBG.
- There are several options for intensification. Selection thereof should be individualized for each patient.
- GLP-1RA can be dosed BID, QD or Qweek, is associated with weight loss, less hypoglycemia, and typically reduced basal insulin dose.
- Subcutaneous RAIA can be started once daily prior to largest meal and titrated as needed to achieve glycemic goals.
- Inhaled TI is a new prandial insulin dosed in 4-8 unit increments prior to each meal for patients without COPD, asthma or current tobacco use.
## Comparison of 3 Different Strategies for Insulin Intensification

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 RA</th>
<th>SQ RAIA</th>
<th>Inhaled TI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose schedule</strong></td>
<td>QD, BID, Qweek</td>
<td>QD, BID, TID</td>
<td>TID</td>
</tr>
<tr>
<td><strong>HbA1c Reduction</strong></td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Medullary thyroid cancer, Pancreatitis, Cr/Cl &lt;30 mg/dl</td>
<td>NA</td>
<td>COPD, Asthma, Current tobacco abuse</td>
</tr>
</tbody>
</table>
## Advantages and Disadvantages of Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Receptor Agonist</td>
<td>Hypoglycemia ↓ weight ↓ post-prandial glucose excursion ↓ some CV risk factors</td>
<td>GI side effects (n/v/d) ↑ HR ? Pancreatitis C-cell hyperplasia/medullary TC (rats) Injectable</td>
</tr>
<tr>
<td>SQ Rapid Acting Insulin</td>
<td>Nearly universal response Theoretically unlimited efficacy ↓ microvascular risk (UKPDS)</td>
<td>Hypoglycemia Weight gain Injectable Patient reluctance</td>
</tr>
<tr>
<td>Inhaled Technosphere Insulin</td>
<td>Less hypoglycemia Less weight gain Avoidance of injections</td>
<td>Decreased FEV1 Cough Not for COPD/Asthma No long-term data</td>
</tr>
</tbody>
</table>
Questions?

CHANGE

Never doubt that a small group of thoughtful, concerned individuals can change the world. Indeed, it's how we got stuck with the IRS, the Federal Reserve, and the Mafia.