Addressing Challenges in Type 2 Diabetes

Postprandial Glucose Levels as a Target for Improving Glycemic Control and Patient Outcomes

Wednesday, April 27, 2011

Anaheim Convention Center
Anaheim, California

Sponsored by pmICME
Session 6: Addressing Challenges in Type 2 Diabetes: Postprandial Glucose Levels as a Target for Improving Glycemic Control and Patient Outcomes

Learning Objectives

1. Identify patients who may benefit from targeted postprandial glucose control based on A1C and blood glucose levels.
2. State the adverse consequences of postprandial hyperglycemia and how effective early intervention may help prevent progression of the disease while lowering risk for cardiovascular complications.
3. Describe 3 insulin regimen strategies that provide postprandial insulin replacement and how they might be utilized in specific patient-case examples.
4. Explain to patients, in a culturally competent way, the need for, and benefits of, prandial insulin control.
5. List 3 strategies that may improve the transfer of care of a hospitalized diabetes patient between the inpatient and outpatient setting.

Faculty

Patrick J. Boyle, MD
Clinical Professor of Medicine
University of New Mexico
Albuquerque, New Mexico

Dr Patrick J. Boyle is a professor of medicine, and former director of the General Clinical Research Center, at the University of New Mexico in Albuquerque, New Mexico.

D. Boyle’s research focuses on type 2 diabetes. His research program has been funded by the National Institutes of Health (NIH) and he is currently the lead physician for the Diabetes Care Management Program at the University of New Mexico. He was also a member of the NIH Steering Committee on Standards and Methods for the Diabetes Control and Complications Trial (DCCT).

Dr Boyle has been an invited speaker at a multitude of national and international scientific meetings. He has been widely published in the clinical literature, including original articles, editorials, reviews, and abstracts in such journals as the New England Journal of Medicine, Proceedings of the National Academy of Science, Diabetes, Diabetes Care, and the Journal of the American Medical Association. He has also written several books and book chapters about type 2 diabetes.

Joseph M. Tibaldi, MD
Assistant Clinical Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Dr Tibaldi is an assistant clinical professor of medicine at Albert Einstein Medical School and director of endocrinology at Flushing Hospital Medical Center, both in New York City. He is also in private practice, specializing in endocrinology, in Queens, New York. Dr Tibaldi received his medical degree from Mount Sinai School of Medicine in New York and completed his residency training in internal medicine at Mount Sinai, followed by a fellowship in endocrinology and metabolism at Montefiore Hospital in the Bronx, New York. He is a fellow of the American College of Physicians. In addition to his clinical practice, Dr Tibaldi dedicates his expertise to teaching medical residents, endocrine fellows, and other health care providers, and he is the author of several recently published papers on insulin therapy. He is a member of the American Diabetes Association, the American Association of Clinical Endocrinology, and The Endocrine Society.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr Boyle reports that he is a speakers bureau member for Amylin, Eli Lilly, and Takeda.

Dr Tibaldi reports that he is a consultant to, and speakers bureau member for, Novo Nordisk Inc.
Education Partner Financial Disclosure Statement
The content collaborators at Global Directions in Medicine have no financial relationships to disclose.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>insulin aspart</td>
<td>NovoLog</td>
<td>metformin</td>
<td>various</td>
</tr>
<tr>
<td>biphasic insulin aspart</td>
<td>NovoLog Mix 70/30</td>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>insulin detemir</td>
<td>Levemir</td>
<td>Sulfonylureas</td>
<td>Diabinese, Glucamide</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>Lantus</td>
<td>chlorpropamide</td>
<td>Glucotrol</td>
</tr>
<tr>
<td>insulin glulisine</td>
<td>Apidra</td>
<td>glipizide</td>
<td>DiaBeta, Glynase, Micronase</td>
</tr>
<tr>
<td>insulin lispro</td>
<td>Humalog</td>
<td>glyburide</td>
<td>Amaryl</td>
</tr>
<tr>
<td>insulin lispro 75/25</td>
<td>Humalog Mix</td>
<td>glimepiride</td>
<td></td>
</tr>
<tr>
<td>insulin human</td>
<td>Humulin 70/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>premixed 70/30</td>
<td>Novolin 70/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin human regular</td>
<td>Humulin, Novolin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suggested Reading List


The Challenges and Risks of Postprandial Hyperglycemia for Patients With Type 2 Diabetes

Patrick J. Boyle, MD
Clinical Professor of Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico

What is your greatest challenge in managing patients with diabetes?
1. Delay in diabetes diagnosis
2. Lack of success with lifestyle interventions
3. Adverse effects associated with antihyperglycemic therapy
4. Lack of durable glycemic control with medications
5. Difficulty in controlling postprandial hyperglycemia

Case Presentation: Charlie
- 59-year-old man with type 2 diabetes for 3 years
- Otherwise healthy; no history of cardiovascular disease (CVD)
- Sedentary office worker; does not exercise during leisure time
- + FH of diabetes and CVD
- Rx: metformin 1000 mg BID, basal insulin analog 46 U QHS
- Findings:
  - BMI: 32 kg/m²
  - BP: 140/90 mm Hg
  - LDL: 120 mg/dL
  - A1C: 7.8%
  - FPG: 120 mg/dL

Pre-Test Question #1
Charlie’s current therapy is focused on which of the following?
1. Fasting plasma glucose (FPG) levels
2. Postprandial plasma glucose (PPG) levels

Pre-Test Question #2
Based on Charlie’s information, what would be your next step?
1. Monitor fasting plasma glucose (FPG) levels and increase basal insulin
2. Monitor postprandial plasma glucose (PPG) levels and initiate therapy to target PPG
3. Encourage better adherence to his medical nutrition therapy and prescribed physical activity
4. Do nothing until the next visit because his A1C is less than 8%
National Diabetes Fact Sheet, 2011
Diabetes affects 25.8 million people; 8.3% of US population
Diagnosed: 18.8 million people
Undiagnosed: 7.0 million people

Among US residents:
- ≥65 years old, 10.9 million (or 26.9%) had diabetes in 2010
- ~215,000 people < 20 years old had diabetes (type 1 or 2) in 2010
- ~1.9 million people ≥ 20 years old were newly diagnosed
- In 2005-2008, based on FPG or A1C levels, 35% of adults ≥ 20 years old had prediabetes (50% of adults ≥ 65 years old)
- Applying this percentage to the entire US population in 2010 yields an estimated 79 million adults with prediabetes
- Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults
- Diabetes is a major cause of heart disease and stroke
- Diabetes is the seventh leading cause of death


Diabetes affects 25.8 million people; 8.3% of US population

Hazard Ratios for Major Causes of Death, According to Baseline Levels of Fasting Glucose

ABCs of Type 2 Diabetes: AACE/ACE 2011 and ADA 2011

Impact of Intensive Therapy in Major Diabetes Clinical Trials

- DCCT/EDIC, UKPDS, ADVANCE & VADT = improved microvascular disease with improved A1C
  - None showed ↓ macrovascular disease during initial trial; benefit seen in long-term follow-up of DCCT/EDIC and UKPDS
- ACCORD = ↓ mortality not for those whose A1C got too low, but rather for those who did not have a reduction in A1C

ADA/AHA/ACC Consensus Recommendations From ACCORD, ADVANCE, and VA Diabetes Trials

- A1C goal for non-pregnant adults in general = < 7.0%
  - Lowering A1C to ~7.0% has been shown to reduce microvascular and neuropathic complications
- For selected individual patients, lower A1C goals may be recommended if goal can be achieved without significant hypoglycemia or other adverse events; eg, patients with:
  - Short duration of diabetes
  - Long life expectancy
  - No significant CVD
- For some patients, less stringent A1C goals may be appropriate; eg, patients with:
  - History of severe hypoglycemia
  - Limited life expectancy
  - Advanced microvascular or macrovascular complications
  - Extensive comorbid conditions
  - Long-standing diabetes for whom goals have not been achieved despite use of optimal medications

A1C Reflects Both Fasting and Postprandial Hyperglycemia

Glycemic Control Recommendations for Type 2 Diabetes: AACE/ACE 2011 and ADA 2011

Target Treatment Goals | AACE/ACE 2011 | ADA 2011
--- | --- | ---
A1C | ≤ 6.5% | < 7.0%
Fasting glucose | Fasting plasma glucose < 110 mg/dL | Preprandial capillary plasma glucose < 70–130 mg/dL
Postprandial glucose | 2-hour postprandial glucose < 140 mg/dL | Peak postprandial capillary plasma glucose < 180 mg/dL

Postprandial Hyperglycemia Antecedes Fasting Hyperglycemia

Factors Affecting PPG
- Gastric emptying
- Carbohydrate absorption
- Incretin effect
- Insulin secretion
- Glucagon secretion
- Hepatic glucose output
- Glucose uptake and metabolism
- Meal
  - Timing
  - Quantity
  - Composition (especially carbohydrates)

Postprandial Glucose Contribution to A1C

Factors Affecting PPG
- Gastric emptying
- Carbohydrate absorption
- Incretin effect
- Insulin secretion
- Glucagon secretion
- Hepatic glucose output
- Glucose uptake and metabolism
- Meal
  - Timing
  - Quantity
  - Composition (especially carbohydrates)

Factors Affecting PPG
- Gastric emptying
- Carbohydrate absorption
- Incretin effect
- Insulin secretion
- Glucagon secretion
- Hepatic glucose output
- Glucose uptake and metabolism
- Meal
  - Timing
  - Quantity
  - Composition (especially carbohydrates)

Factors Affecting PPG
- Gastric emptying
- Carbohydrate absorption
- Incretin effect
- Insulin secretion
- Glucagon secretion
- Hepatic glucose output
- Glucose uptake and metabolism
- Meal
  - Timing
  - Quantity
  - Composition (especially carbohydrates)
**The Primary Function of Insulin Is to Regulate Hepatic Glucose Output**


**Benefit of Early vs. Late Insulin Release**


---

**Overall Impact of Late First Phase Insulin**

IGT = impaired glucose tolerance.


---

**Plasma Glucose Fluctuation?**


---

**Oxidative Stress**

- Related to increase in oxidant generation, decrease in antioxidant protection
- Damage is induced by ROS
  - Free radicals, reactive anions, or molecules containing oxygen atoms that can produce free radicals
  - ROS: hydroxyl, superoxide, hydrogen peroxide, and peroxynitrite
- Intermittent hyperglycemia → ROS overproduction, through a PKC-dependent activation
  - Glucose fluctuation might be involved in the development of oxidative stress and vascular injury

ROS = reactive oxygen species.
PKC = protein kinase-C.

---

**Oxidative Stress Generation: Role of Hyperglycemia**

MDA = malondialdehyde.
TRAP = total radical-trapping antioxidant parameter.
Glycemic Variability: A Hemoglobin A\textsubscript{1c} Independent Risk Factor for Diabetic Complications


Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes


Endothelial Dysfunction Induced by Hyperglycemia

Mean Values of CRP According to 2-Hour Post-Challenge Glucose Category

NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = diabetes mellitus

Unpredictable Insulin Action Contributes to Variable Blood Glucose: Independent Risk Factor for Mortality

![Plot showing the relationship between variability of FPG and CV mortality.](image)

Variability of FPG and CV mortality
10-year survival

- **CV events in epidemiologic studies**
- **Activation of protein kinase-C**
- **Oxidative stress**
- **Inflammatory markers**
- **Endothelial dysfunction**

**Clinical Focus**

**The Effect of Glycemic Variability on the Risk of Microvascular Complications in Type 1 Diabetes**

**Aims**

- Variability in daily QOL ratings was explained by absolute level and the day-to-day variation in BG.
- Both blood glucose (BG) and day-to-day variability, as represented by SD[BG], correlated negatively with M[QOL].
- Variability in daily QOL ratings was explained by absolute level and the day-to-day variation in BG.
- Data provide additional evidence of benefits for maintaining a low and stable glucose profile, and support conducting further studies of BG variability and QOL.
**Impaired PPG Control Increases Cardiovascular Risk**


Key Clinical Studies

*Studies of patients with prediabetes and diabetes.

**The Euro Heart Survey on Diabetes and the Heart: Fasting and Post-Load Glycemia in Patients With CAD and Without Previously Diagnosed Diabetes**

- Number of Patients: 1867

**GAMI Trial**

Time to First Major Cardiovascular Event (Death; Re-MI; Stroke; Hospitalization for Severe Heart Failure)

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Survival Probability</th>
<th>Two-sided P = 0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>55</td>
<td>0.70</td>
</tr>
<tr>
<td>Abnormal</td>
<td>113</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Follow-Up Time (months)

- Patients at risk: Normal 55, Abnormal 113

**Relative Contribution of FPG and PPG to Glycemia**

164 Patients With Baseline A1C ≥ 7.5% on Diet, Oral Agents, or Insulin

3 Months of Forced Titration, Individualized Intensive Treatment

- Baseline A1C
- Final A1C

**Acarbose Treatment and the Risk of CVD in Patients With Impaired Glucose Tolerance**

*Effect of Acarbose on the Probability of Averting Aree of Cardiovascular Disease*
Diurnal Plasma Glucose Profiles Before and After Intensified Therapy Intervention in Subjects Who Did and Did Not Achieve A1C < 7.0%

What medication would you typically add to the regimen of someone like Charlie?

- 59-year-old man with type 2 diabetes for 3 years
  - Otherwise healthy; no history of CVD
  - Sedentary office worker; does not exercise during leisure time
  - + FH of diabetes and CVD
  - Rx: metformin 1000 mg BID, basal insulin analog 46 U QHS
    - BMI: 32 kg/m²
    - BP: 140/90 mm Hg
    - LDL: 120 mg/dL
    - A1C: 7.8%
    - FPG: 120 mg/dL

1. Alpha glucosidase inhibitor
2. DPP-4 inhibitor
3. Glinide
4. GLP-1 agonist
5. Prandial insulin

What medication would you typically add to the regimen of someone like Charlie? (Continued)

1. Alpha glucosidase inhibitor
2. DPP-4 inhibitor
3. Glinide
4. GLP-1 agonist
5. Prandial insulin

Mean Change From Baseline in Fasting and Postprandial Plasma Glucose Levels for Patients Receiving Acarbose

Nateglinide Added to Rosiglitazone Reduces Mealtime Glucose

Further Improvement in Postprandial Glucose Control With Addition of Exenatide or Sitagliptin to Combination Therapy With Insulin Glargine and Metformin: A Proof-of-Concept Study
ADA/EASD Writing Group: Consensus Statement

- If A1C is not at goal after 2 to 3 months and FPG is in target range, add an injection based on pre-meal blood glucose values
  - Elevated pre-lunch: Add rapid-acting insulin at breakfast
  - Elevated pre-dinner: Add NPH at breakfast or rapid-acting insulin at lunch*
  - Elevated pre-bedtime: Add rapid-acting insulin at dinner

*Premixed insulins are not recommended during adjustment of doses, but they can be used before breakfast and dinner if the proportion of rapid-acting and intermediate-acting insulin used is similar to the fixed proportions available.

ADA/EASD Writing Group: Consensus Statement

- Recommended titration:
  - Begin with 4 U and adjust by 2 U/day until blood glucose is in normal range
  - Recheck pre-meal blood glucose levels to determine whether another injection is needed
  - If A1C continues to be out of range, check 2-hour PPG level and adjust rapid-acting insulin

*Premixed insulins are not recommended during adjustment of doses, but they can be used before breakfast and dinner if the proportion of rapid-acting and intermediate-acting insulin used is similar to the fixed proportions available.

Key Takeaway Messages

- Postprandial hyperglycemia deserves greater attention in the management of type 2 diabetes
- PPG plays a critical role in determining overall glycemic control, particularly in patients who are close to achieving glycemic goals
- Several antidiabetic agents that specifically target PPG are available, including alpha-glucosidase inhibitors, glinides, GLP-1 agonists, DPP-4 inhibitors, and rapid-acting insulin analogs
- A more intensive approach to managing PPG may improve the care of patients with diabetes and, ultimately, their outcomes

Post-Test Question #1
Charlie’s current therapy is focused on which of the following?

1. Fasting plasma glucose (FPG) levels
2. Postprandial plasma glucose (PPG) levels
3. More strictly control his diet and encourage exercise
4. Do nothing until the next visit because his A1C is less than 8%

Post-Test Question #2
Based on the description of Charlie, what will be your next step?

1. Monitor fasting plasma glucose (FPG) levels and increase basal insulin
2. Monitor postprandial plasma glucose (PPG) levels and initiate therapy to target PPG
3. More strictly control his diet and encourage exercise
4. Do nothing until the next visit because his A1C is less than 8%

Improving Glycemic Control With Insulin Strategies That Target Postprandial Glucose

Joseph M. Tibaldi, MD
Assistant Clinical Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York
Case Scenario: Transitioning a Patient to Insulin

Maria
- 65-year-old Hispanic woman presents to the ER with a syncopal episode that occurred while cooking at home
- Medical history is notable for diabetes (which began 30 years ago) and well-controlled hypertension (HTN)

Case Presentation: Transitioning a Patient to Insulin

- In the ER, her medications are reviewed; these include:
  - ASA: 81 mg/day
  - Lovastatin: 40 mg/day
  - Lisinopril/HCTZ: 20/12.5
  - Glipizide ER: 10 mg/day
  - Metformin: 1000 mg twice daily
- Relevant laboratory results:
  - A1C = 9.5%
  - Fasting plasma glucose: 222 mg/dL
  - EKG: stable from one completed last year

Pre-Test Question #3
How should Maria’s blood glucose be managed in the hospital setting?
1. Continue oral diabetes medications
2. Stop the oral medications and start basal-bolus insulin
3. Continue the glipizide but stop the metformin

Pre-Test Question #4
What would you recommend to Maria on discharge?
1. Resume previous oral medications and add a DPP-4 inhibitor
2. Resume previous oral medications and add pioglitazone
3. Resume metformin and educate Maria on the use of a basal insulin analog

Insulin Is the Most Appropriate Agent for the Majority of Hospitalized Patients

Scheduled and correction insulin is preferred

Recommended Treatment Strategies on Discharge

Previously diagnosed DM; on oral medications; suboptimal control:
- A1C 7-8%: Consider increasing the dose of home oral agents or adding additional agent, potentially including basal insulin
- A1C 8-9%: Add another agent, probably including basal insulin
- If A1C >9%: Usually discharge on one of the following insulin regimens:
  - QD basal insulin
  - BID premixed insulin
  - Basal-bolus insulin

Adapted from: AACE Inpatient Glycemic Control Center.
Glycemic Goals for Outpatients

• ADA
  - A1C < 7%
  - Pre-meal glucose: 70-130 mg/dL
  - Peak post-meal glucose: <180 mg/dL

• AACE
  - A1C ≤ 6.5%
  - Pre-meal glucose: <110 mg/dL
  - Post-meal glucose (2 hr): <140 mg/dL


Insulin

• The most powerful tool available to control blood glucose
  - A1C reduction potential is limited only by risk of hypoglycemia
    - Patients with type 2 diabetes have a lower risk for hypoglycemia than patients with type 1 diabetes
  - Analog insulins are designed to be more physiologic
    - More rapid onset, more predictable time-action profiles
    - Less weight gain, lower risk of hypoglycemia


Time-Action Profiles of Insulin Products

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 Insulin

• Insulin required to suppress hepatic glucose production overnight and between meals
  - ~ 50% of daily needs
• Advantages:
  - One injection with no mixing
  - Slow, safe, and simple titration
  - Limited weight gain
  - Effective improvement in glycemic control


A1C Reductions With Basal Insulin Analog Once Daily

LOCF = last observation carried forward
 Achievement of ADA-Recommended A1C Target < 7% With Basal Insulin Once Daily

How much basal insulin is enough?

Lack of Coverage of PPG With Basal Therapy Alone

A1C Reflects PPG and FPG

What Is the Effect of Increasing the Dose of Basal Insulin?

- Can obtain a decrease in A1C of approximately 0.5% for each 0.1-U/kg/day increment in insulin dose
  - Up to a threshold of 0.5 U/kg
  - Beyond this dose, the improvement (decrease) in A1C is less substantial and the risk of hypoglycemia increases

When to Intensify Therapy Beyond Titration of Basal Insulin...

- Clinically this occurs when on basal insulin:
  - FBS is at goal
  - A1C is elevated
- The addition or increase in SU dose will not correct the situation and may increase the risk of hypoglycemia
When to Intensify Therapy Beyond Titration of Basal Insulin…

<table>
<thead>
<tr>
<th>Time</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plasma Insulin (μU/mL)

- Mealtime insulin response is missing; high postprandial readings with every meal
- This may lead to hypoglycemia if food changes or meals are missed

When should therapy be intensified beyond basal insulin?

**AACE Recommendation**

- AACE guidelines suggest that, when starting a patient on insulin, some form of prandial insulin should be considered if baseline A1C exceeds 8.5% on oral agents
  - Here, A1C is a surrogate measurement of beta-cell function

**Strategies for Insulin Intensification**

- BASAL
- PREMIXED
- BASAL-BOLUS

**Question for the Patient**

*Would you like the Chevrolet or the Cadillac?*

**Premixed Insulin**

A single injection provides both basal and prandial insulin

<table>
<thead>
<tr>
<th>Premixed Human Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH + regular insulin</td>
</tr>
<tr>
<td>Novolin® 70/30</td>
</tr>
<tr>
<td>Humulin® 50/50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Premixed Insulin Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin aspart protamine suspension + insulin aspart</td>
</tr>
<tr>
<td>NovoLog® Mix 70/30</td>
</tr>
<tr>
<td>Insulin lispro protamine suspension + lispro</td>
</tr>
<tr>
<td>Humalog® Mix 75/25 insulin</td>
</tr>
<tr>
<td>Humalog® Mix 50/50</td>
</tr>
</tbody>
</table>
Premixed Insulin
A single injection provides both basal and prandial insulin

Adapted from product label information approved by the FDA.

---

**Time (hour)**

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>Premixed Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

---

**Change in A1C % (SD)**

<table>
<thead>
<tr>
<th>Change in A1C %</th>
<th>Basal</th>
<th>Premixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>-3</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>-4</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>-5</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

---

**Rate of Hypoglycemia (Events/Patient/Year)**

<table>
<thead>
<tr>
<th>Rate of Hypoglycemia</th>
<th>Analog Basal Insulin</th>
<th>Human Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.8</td>
<td>3.9</td>
</tr>
<tr>
<td>6 months after switch</td>
<td>1.8</td>
<td>1.4</td>
</tr>
</tbody>
</table>

The rate (events/patient/year) of overall hypoglycemia remained relatively constant for patients who switched from analog basal insulin, but it was significantly lower for those who switched from human basal insulin (change from baseline: 3.8; \( P < 0.001 \)).

---

**Mean Daily Insulin Dose (U/kg) for Patients Coming From Basal Insulin**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Study Insulin Dose</th>
<th>Premixed Insulin Aspart 70/30 Dose at Baseline</th>
<th>Premixed Insulin Aspart 70/30 Dose at Final Visit</th>
<th>% of BID Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Basal</td>
<td>0.46</td>
<td>0.50</td>
<td>0.56</td>
<td>73</td>
</tr>
<tr>
<td>Analog Basal</td>
<td>0.34</td>
<td>0.45</td>
<td>0.48</td>
<td>81</td>
</tr>
</tbody>
</table>


**The Plan for Maria (if she chooses premixed insulin)**

- Calculate her total insulin dose, divide it in two, and replace it with that amount of analog premix at breakfast and dinner
- Continue metformin
- Ask Maria to test her glucose level twice daily: before breakfast and before dinner
How often do you allow patients to self-titrate their insulin regimens?

1. Always
2. Often
3. Sometimes
4. Rarely
5. Never

Weekly Adjustment of Premixed Insulin

<table>
<thead>
<tr>
<th>Preprandial Blood Glucose Value</th>
<th>Dose Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.4 mmol/L</td>
<td>&lt; 79 mg/dL</td>
</tr>
<tr>
<td>4.4–6.1 mmol/L</td>
<td>79–110 mg/dL</td>
</tr>
<tr>
<td>6.2–7.8 mmol/L</td>
<td>111–140 mg/dL</td>
</tr>
<tr>
<td>7.9–10.0 mmol/L</td>
<td>141–180 mg/dL</td>
</tr>
<tr>
<td>&gt; 10.0 mmol/L</td>
<td>&gt; 180 mg/dL</td>
</tr>
</tbody>
</table>

Note: Algorithm is from the INITIATE study and the current BiAsp 30/70 EU label.

Maria’s Titration

- Maria left the hospital on 40 units/day of insulin, and went home on 20 units of analog premix twice a day
- The first week, her FBG averaged 155 mg/dL; and she increased her dinnertime insulin by 4 units to 24 units
- The next week, her FBG averaged 132 mg/dL; and she increased her dinnertime insulin by 2 units to 26 units
- She reached the FBG goal and continued on 26 units at dinnertime
- She then started titrating the breakfast dose on a weekly basis, using pre-dinner readings, until she reached goal

Strategies for Insulin Intensification

Basal “Plus” (plus a shot of mealtime insulin)

BASAL-BOLUS

Steps in Transitioning From Basal to Basal-Bolus Insulin Therapy in Type 2 Diabetes

- Above Target: A1C > 7.0%; FPG > 110 mg/dL
  - Weekly Titration based on algorithm
  - All oral agents continued

- Above Target: A1C < 7.0%; FPG < 110 mg/dL

- Basal (long-acting)
- Prandial (rapid-acting)

Optimized Insulin Replacement Regimen: Mimicking Normal Physiology With Basal and Prandial Insulin Analogs

- Basal (long-acting)
- Prandial (rapid-acting)
Premixed vs. Basal-Bolus Insulin

% of Patients Achieving Target A1C (< 7.0)

<table>
<thead>
<tr>
<th></th>
<th>Liebl et al</th>
<th>Hira et al</th>
<th>Rosenstock et al</th>
</tr>
</thead>
</table>

50 60 32 33 54 69

Meal Insulin: Rapid-Acting Analogs (Lispro, Aspart, Glulisine) vs. Regular Insulin

Insulin Activity

Timing of food absorption

Hours


OPAL: Sequential Addition of Bolus Insulin Analog at Mealtime – Study Design

Stratification by Main Meal

Randomization

Breakfast Group: basal + OAD + OD prandial insulin

Main-Meal Group: basal + OAD + OD prandial insulin

Pre-Screening (1–2 weeks) Screening (1–3 weeks) Treatment (24 weeks) Follow-Up (1 week)

Sequential Addition of Bolus Insulin Analog at Mealtime: Change in A1C

Mean Change in A1C From Baseline to Endpoint


Sequential Addition of Bolus Insulin Analog at Mealtime: Change in Daily Insulin Dose

Real-World Choices Depend on the Patient

- Preference for injection frequency
  - Some patients may prefer premixes
- Frequency of glucose self-monitoring
- Variability in lifestyle, including meal timing and carbohydrate content of meals
- Presence of postprandial hyperglycemia
- Patient's ability to follow the prescribed regimen
- Educational and emotional support
**Premixed vs. Basal-Bolus Insulin**

- **Premixed** (1, 2, or 3 injections of the same insulin)
  - Preference for few injections
  - Fixed daily routine
  - Unwilling to self-monitor blood glucose
  - Limited cognitive function
  - Limited healthcare support systems

- **Basal-Bolus** (4 injections; 2 different types of insulin)
  - Variable meal pattern
  - Variable daily routine
  - Postprandial control is an issue
  - Able (and willing) to comply with a more complicated regimen (good cognitive function)
  - Support systems exist

**Glucose Monitoring**

- Medicare allows three measurements per day for patients on insulin
- Consider testing the fasting and “bracketing” one meal with pre- and postprandial measurements daily, on a continual basis

**Simple Algorithm for Intensifying Rapid-Acting Insulin Analogs in Patients With Type 2 Diabetes on Basal Insulin**

- Starting rapid-acting insulin analog dose of 0.1 U/kg at largest meal of the day
- Allow patient to titrate the dose as follows:
  - Patients can also “down-titrate” the dose 1–2 units from baseline if eating a smaller-than-usual meal

**Titration of Basal and Prandial Doses**

- Adjust doses of basal and prandial doses on alternate days (every 3 days)
- Increase prandial dose by 1 unit to achieve target 2-hour post-meal glucose level < 180 mg/dL
- If the patient has persistent postprandial hyperglycemia, consider reducing carbohydrate intake or adjusting the insulin:carbohydrate ratio
- Continue 303 protocol until the target FBG of 80 to 110 mg/dL has been achieved

**Titration of Basal Doses**

<table>
<thead>
<tr>
<th>FPG (mg/dL)</th>
<th>Response</th>
<th>Dose Adjustments Every Third Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80</td>
<td>Reduce dose by 3 units</td>
<td>3</td>
</tr>
<tr>
<td>80–110</td>
<td>No change</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 110</td>
<td>Increase dose by 3 units</td>
<td>3</td>
</tr>
</tbody>
</table>

**Summary**

- Titration of the existing insulin regimen is the first step of the intensification efforts to maintain A1C goals
- Adding prandial insulin to basal insulin regimens provides physiologic coverage of insulin requirements
  - Whether by switching to a premixed insulin analog or by adding a rapid-acting analog at mealtimes

---


Conclusion

A positive attitude toward insulin therapy can be achieved through (1) patient education that focuses on disease pathophysiology and (2) active involvement in treatment that enables patients to manage possible hypoglycemia, weight gain, and injection anxiety.

- Insulin analogs have more physiologic time-action profiles and are more convenient than older human insulins.
- Insulin analogs help achieve glycemic targets with lower hypoglycemia risk and more convenient dosing.
- Titration algorithms provide a straightforward approach for intensifying insulin regimens to improve glycemic control.

Post-Test Question #3

How should Maria’s blood glucose be managed in the hospital setting?

1. Continue oral diabetes medications
2. Stop the oral medications and start basal-bolus insulin
3. Continue the glipizide but stop the metformin

Post-Test Question #4

What would you recommend to Maria on discharge?

1. Resume previous oral medications and add a DPP-4 inhibitor
2. Resume previous oral medications and add pioglitazone
3. Resume metformin and educate Maria on the use of a basal insulin analog

65-year-old Hispanic woman presents to the ER with a syncopal episode that occurred while cooking at home.

- Medical history is notable for diabetes (which began 30 years ago) and well-controlled HTN.
- In the ER, her medications are reviewed; these include:
  - ASA: 81 mg/day
  - Lovastatin: 40 mg/day
  - Lisinopril/HCTZ: 20/12.5
  - Glipizide ER: 10 mg/day
  - Metformin: 1000 mg twice daily
- Relevant laboratory results:
  - A1C = 9.5%
  - Fasting plasma glucose: 222 mg/dL
  - EKG: stable from one completed last year.