Current Basal Insulin-based Treatment Strategies and the Potential Impact of Emerging Options on Patient Outcomes

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NRG Center
Houston, Texas

Education Partner
Global Directions in Medicine
Session 4: Current Basal Insulin-based Treatment Strategies and the Potential Impact of Emerging Options on Patient Outcomes

Learning Objectives

1. Describe the clinical benefits and practical aspects of timely, appropriate initiation and intensification of insulin therapy in patients with T2DM
2. Implement strategies that can be used to reduce the risk of hypoglycemia in patients with T2DM that are treated with insulin
3. Review the safety, efficacy, and tolerability of incretin mimetics (i.e., GLP-1 RAs, DPP-4 inhibitors) as add-on therapies to basal insulin for glucose control
4. Compare profiles of traditional and emerging basal insulin agents, based on clinical evidence and patient-relevant features

Faculty

Richard E. Pratley, MD
Samuel E. Crockett MD, Chair in Diabetes Research
Director, Florida Hospital Diabetes Institute
Senior Scientist, Florida Hospital Sanford|Burnham Translational Research Institute
Adjunct Professor, Sanford|Burnham Medical Research Institute
Orlando, Florida

Dr. Pratley is an internationally recognized expert in diabetes and is board certified in internal medicine. He received his medical degree from Wayne State University in Detroit, and completed fellowships in geriatric medicine and gerontology at the University of Michigan, John Hopkins University, and the National Institute on Aging. As a member of the American Diabetes Association, the European Association for the Study of Diabetes and The Obesity Society, Dr. Pratley continues his active involvement in the professional community. He is a member of the editorial boards of The Journal of Diabetes and its Complications and the Journal of Clinical Endocrinology and Metabolism, and acts as an ad hoc reviewer for many other journals. Dr. Pratley regularly presents at national and international meetings, has conducted numerous research studies on the pathogenesis, prevention and treatment of diabetes, and has published over 190 peer-reviewed articles on diabetes. His research interests include the prevention of diabetes, improving the care for older persons with diabetes, developing new drugs to treat and prevent diabetes and its complications, and understanding the role of the fat cell in increasing the risk of diabetes and heart disease.

Javier Morales, MD
Clinical Professor of Medicine
Hofstra Northshore – LIJ School of Medicine at Hofstra University
Hempstead, New York

Dr. Morales is in private practice with the Advanced Internal Medicine Group in New Hyde Park, NY, and is Associate Clinical Professor of Medicine for the North Shore-LIJ Hofstra School of Medicine. After having graduated from UMDNJ-NJ Medical School, his medical training included residencies at Memorial Sloan-Kettering Cancer Center and North Shore University Hospital where he served as Chief Medical Resident. He serves on multiple committees at St. Francis Hospital in Roslyn, N.Y. and in addition to several publications, has served as principal investigator for several different studies and clinical trials. He is active in the educational sector having presented at many Pri-Med symposiums. He also serves as clinical instructor for several nurse practitioner programs, physician assistant programs, in addition to the internal medicine residency program at North Shore University Hospital and Winthrop University Hospital. In addition to being an avid musician and percussionist, Dr. Morales is fluent in Spanish, Italian and Portuguese. He is a member of the American Medical Association, American College of Physicians, American Society of Clinical Pathologists, National Hispanic Medical Association, Nassau County Medical Society, American Academy of Family Physicians, American Association of Clinical Endocrinologists, and is a fellow of the Interamerican College of Physicians and Surgeons.
Faculty Financial Disclosure Statements
The presenting faculty reported the following:
Javier Morales, MD: Speakers Bureau for Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc. Medical Advisory Board for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; Novo Nordisk Inc.; and sanofi-aventis U.S. Consultant for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; and Novo Nordisk Inc.
Richard E. Pratley, MD: No financial relationships to disclose.

Education Partner Financial Disclosure Statements
The content collaborators at Global Directions in Medicine have reported the following:
Anne Sendaydiego, PharmD, Medical Director, has no financial relationships to report.
Deanna Schuly, President, has no financial relationships to report.

Suggested Reading List
Garber AJ. Will the next generation of basal insulins offer clinical advantages? Diabetes Obes Metab. 2014;16(6):483-491.
12:30 – 1:45 pm

Current Basal Insulin-based Treatment Strategies and the Potential Impact of Emerging Options on Patient Outcomes

SPEAKERS
Javier Morales, MD
Richard E. Pratley, MD

Drugs Cited

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Albglutide</td>
<td>Tanzeum®</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Norvasc®</td>
</tr>
<tr>
<td>Exenatide bid</td>
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</tr>
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<td>Glimepiride</td>
<td>Amaryl®</td>
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<td>IDegLira</td>
<td>Xultophy (in Europe)</td>
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<tr>
<td>Insulin degludec</td>
<td>Tresiba®</td>
</tr>
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<td>Insulin detemir</td>
<td>Levmir®</td>
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<td>Insulin glargine</td>
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<tr>
<td>(U100, U300)</td>
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Drugs Cited (cont’d)

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<td>Neutral protamine</td>
<td>Hagedorn</td>
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<tr>
<td>Pioglitazone</td>
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Learning Objectives

• Describe the clinical benefits and practical aspects of timely, appropriate, initiation and intensification of insulin therapy in patients with T2DM
• Implement strategies that can be used to reduce the risk of hypoglycemia in patients with T2DM that are treated with insulin
• Compare and contrast the attributes of basal insulin products, including traditional and emerging agents, based on clinical evidence and patient-relevant features
• Review the safety, efficacy, and tolerability of incretin mimetics (ie, GLP-1 RAs and DPP-4 inhibitors) as add-on therapies to basal insulin for glucose control

Patient Challenges With Insulin Therapy

Introducing Therapy, Simplifying Dosing and Administration, Empowering Patients, Calming Concerns

Presenter Disclosure Information

The following relationships exist related to this presentation:

► Javier Morales, MD: Speakers Bureau for Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc. Medical Advisory Board for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; Novo Nordisk Inc.; and sanofi-aventis U.S. Consultant for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; and Novo Nordisk Inc.

► Richard E. Pratley, MD: No financial relationships to disclose.

Off-Label/Investigational Discussion

► In accordance with proCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
**Prevalence of Diabetes and Prediabetes in the United States**

- Diabetes: 9.3% of US population
- Prediabetes: 37% of US population

**Projected Prevalence of Diabetes in the United States: 1990 to 2050**

**Long-term Complications of Diabetes**

**Consequences of Sustained Hyperglycemia**

- Diabetic Retinopathy: leading cause of blindness in working-age adults
- Diabetic Neuropathy: leading cause of nontraumatic lower-extremity amputations
- Stroke: 2-fold to 4-fold increase in CV events and mortality

**Benefits of Appropriate Glucose Control**

UKPDS: Legacy Effect of Earlier Glucose Control

**Impact of Intensive Therapy for Diabetes**

**Summary of Major Clinical Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>Cardiovascular</th>
<th>Mortality</th>
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<td>UKPDS**†**</td>
<td><img src="downArrow" alt="" /></td>
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<td>ACCORD†</td>
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<tr>
<td>VADTER‡</td>
<td>![downArrow]</td>
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<td>![downArrow]</td>
</tr>
</tbody>
</table>

**Eventual Need for Insulin in T2DM**

UKPDS: At 6 years, more than 50% of patients (newly diagnosed at start of study) need insulin to reach target (FPG ≤ 6.0 mmol/L).
**Identify and Address Patient-related Barriers to Initiation of Insulin Therapy**

<table>
<thead>
<tr>
<th>Identify the Barrier</th>
<th>Address the Barrier</th>
</tr>
</thead>
</table>
| Ask patients, listen, and confirm answers | *"What is the hardest thing about taking care of your diabetes?"*  
*"What concerns or worries do you have about using insulin to treat your diabetes?"* |

**Barrier**  
**Fear of injections**  
- Have patient give a dry injection in the office  
- Insulin pen is less threatening  
- Insulin needles are small

**Fear of hypoglycemia**  
- Residence is low, especially with basal insulin analogs  
- Teach patients to recognize and treat

**Fear of weight gain**  
- Have patient meet with dietician before starting insulin  
- More physiologic insulin delivery may minimize weight gain

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**Changes in A1C Levels and Glycemic Burden**

*Most Patients Have 8–10 Years of Poor Glucose Control Before Insulin Is Started*

- **Mean A1C and Cut-Off Test (%)**
  - 7.0%
- **Time Elapsed Since Initial Diagnosis (yr)**
  - 2.5
- **8.2 Years**
- **Initiation of insulin**

**Potential Barriers to Starting Insulin: HCPs and Patients**

- **Possible Reasons Given to Not Use Insulin Treatment**
  - HCPs
  - Patients who are insulin-naive

**Ultimately, the Choice to Start Insulin Should Be a Shared Decision Between Patient and Provider**

**Tips for Shared Decision Making**

- Insure patients to participate  
- Present options  
- Provide information on benefits and risks  
- Assist patients in evaluating options based on their goals and concerns  
- Facilitate deliberation and decision making  
- Assist patients to follow through on their decision

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**Multiple Basal Insulin Agents Are Available**

- NPH
- Detemir
- Glargine U100
- Glargine U300

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**Why and When Should We Introduce Insulin to T2DM Management?**

**Indications for Insulin Treatment in Patients With T2DM**

**Strong indications**

- New diagnosis or long-term diabetes with symptoms of hyperglycemia (rescue treatment)  
- Ketoacidosis  
- Non-insulin hypoglycemic treatments not tolerated or contraindicated  
- Acute medical events (eg, infection or myocardial infarction) or major surgery  
- Concomitant disease such as pancreatitis, cirrhosis, or chronic steroid treatment  
- Failure of non-insulin treatments (replacement treatment)

**Potential indications**

- Glycemic control not achieved with diet, exercise, non-insulin drugs (augmentation treatment), and latent autoimmune diabetes  
- Women with diabetes who are pregnant or planning a pregnancy  
- Patients admitted to hospital and unable to take their usual drug regimen or during enteral or parenteral nutrition  
- Increasingly flexible lifestyle or unplanned eating behavior (elderly patients)

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**Lancet**  
**2015;7:267–282.**

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**Cahn et al.**  
**Lancet Diabetes Endocrinol.**  
**2015 Jan 6 [Epub ahead of print].**
Glycemic Control With Basal Insulin

- Meta-analysis of 22 studies
- Subjects: T2DM receiving insulin glargine or detemir
  - Baseline A1C levels: 8.1% to 9.8% (glargine) and 8.6% to 9.1% (detemir)

A1C change from baseline

<table>
<thead>
<tr>
<th></th>
<th>Glargine</th>
<th>Detemir</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔA1C (%)</td>
<td>~0.3% to ~2.36%</td>
<td>~0.8% to ~1.8%</td>
</tr>
</tbody>
</table>

1.4% mean change for both insulins

Multiple Consensus-based Guidelines Regarding the Initiation and Intensification of Insulin Exist

- ADA/EASD Position Statement on the Management of Hyperglycemia
- AACE Algorithm for Adding/Intensifying Insulin

ADA/EASD Algorithm for the Management of Hyperglycemia in T2DM

Summary—Patient Challenges With Insulin Therapy: Introducing Therapy, Simplifying Dosing and Administration, Empowering Patients, Calming Concerns

- Appropriate and early treatment of hyperglycemia reduces the risk for micro- and macrovascular complications
- Insulin is a core treatment strategy to achieve glycemic control in patients with T2DM
- Many patients can benefit from early initiation of insulin therapy
- It is not a “treatment of last resort”
- Multiple basal insulin agents are available
- The ADA and AACE provide sample algorithms to help guide insulin initiation
Mark: 52-year-old Man With 8-year History of T2DM (cont’d)

- Diet—trying; has lowered carbohydrate intake and stopped post-supper snacking
- Exercise—about 3 months ago, started walking his dog ~1 mile most nights of the week
- Social history
  - Does not smoke; occasional alcohol
- Family history
  - Father: (+) CVD; 1 brother with obesity
  - Marketing director for a Midwest food distribution company
    - He is married and has 2 children in college

Normal Insulin Secretion Profile

Currently Available Basal Insulin Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Time for onset of action</th>
<th>Time of peak action</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>1–2 h</td>
<td>4–12 h</td>
<td>12–16 h</td>
</tr>
<tr>
<td>Detemir</td>
<td>1–2 h</td>
<td>4–8 h</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>1–2 h</td>
<td>10–14 h</td>
<td>18–26 h</td>
</tr>
<tr>
<td>Glargine U300</td>
<td>1–2 h</td>
<td>None</td>
<td>Up to 36 h</td>
</tr>
</tbody>
</table>
**Basal Analog Insulin Therapy**

- **Breakfast**
- **Lunch**
- **Dinner**

**NPH Insulin at Bedtime**

- **Breakfast**
- **Lunch**
- **Dinner**

**NPH Insulin Twice Daily**

- **Breakfast**
- **Lunch**
- **Dinner**

**Treat-to-Target: Insulin Glargine vs NPH Added to Oral Therapy**

- **No Difference in A1C Level But Lower Rate of Hypoglycemia**
  - **Study**
    - N = 756
    - Currently on stable doses of OADs
    - A1C level >7.5%
    - Randomized to insulin glargine or NPH at bedtime added to existing oral therapy for 24 weeks
    - Weekly titration of insulin to target FPG ≤100 mg/dL
  - **Results**

**Treat-to-Target: Insulin Detemir vs NPH Added to Oral Therapy**

- **No Difference in A1C Level But Lower Rate of Hypoglycemia**
  - **Study**
    - N = 476
    - Currently on 1 or 2 oral agents for at least 4 months
    - A1C level = 7.5%–10.0%
    - Randomized to twice-daily insulin detemir or twice-daily NPH added to existing oral therapy for 26 weeks
    - Titration of insulin to target pre-breakfast/pre-dinner PG ≤108 mg/dL
  - **Results**

**Head-to-Head Comparison of Glargine vs. Detemir in T2DM**

- **52-week, randomized, open-label, treat-to-target trial in insulin-naive adults with T2DM (n = 582, A1C level = 8.5%, BMI ≤0.0 kg/m²)**
  - Once-daily glargine or detemir, could be titrated to twice-daily detemir
  - 55% of patients on insulin detemir were titrated to twice-daily injections
  - All patients on insulin glargine received only 1 injection per day
  - Average daily doses:
    - Detemir once daily 0.52 U/kg
    - Detemir twice daily 1.04 U/kg
    - Glargine once daily 0.44 U/kg
    - 3.9 kg weight gain with glargine vs. 3.0 kg with detemir (P = 0.012)
  - No difference between glargine and twice-daily detemir

**References**

Advantages of Traditional Basal Insulin Analogs Over Human Insulin

- Longer-acting (≥24 hours)
- Less variability from day to day
- Better flexibility in time of administration
- Flatter biological activity (less peak)
  - Lower risk of nocturnal and overall hypoglycemia
- Less weight gain (insulin detemir)

New Basal Insulin Analog—
Glargine U300 (300 U/mL)

- Contains the same molecule as glargine U100, but in a lower volume
- Smaller depot surface area leading to a reduced rate of absorption
- Steady state is 4 days
- Duration of action ≤36 hours

When to Use Glargine U300 In Clinical Practice?

- Therapeutic option for patients on high doses/high volumes of insulin

Appropriate Titration Is Critical to the Success of Insulin Therapy

ADA/EASD consensus algorithm for the initiation and adjustment of a basal insulin regimen is indicated as follows:

- Basal Insulin (usually with metformin +/- other noninsulin agent)
  - Start: 10 U/day or 0.1-0.2 U/kg/day

- Check fasting glucose daily and increase dose by 10%-15% or 2-4 U once/twice weekly to reach HbA1c target (7.0-7.5%)

- For hypos: Determine and address cause; ↓ dose by 4 U or 10%-20%

Office-based vs. Patient-based Titration of Insulin Therapy

For 6 months, patients in the experimental group took daily fasting glucose measurements, and adjusted insulin dosage every third day based on the mean FPG.

303 titration algorithm

Fasting plasma glucose (3 day mean)

+80 mg/dL, reduce 3 units
80–110 mg/dL, no change
>110 mg/dL, increase 3 units

In the control group, titration was done by physicians based on physicians’ standards of care.

Insulin Glargine Added To Metformin +/- SU: Impact on Hypoglycaemia

- Pooled analysis of 11 prospective randomized clinical trials (n=2,371 adults with uncontrolled T2DM) initiating insulin glargine following a specific titration algorithm
- Despite higher insulin doses, those taking MET alone had less hypoglycemia than those taking SU or MET + SU

Meta-Analysis of Log Odds Ratio of Symptomatic Hypoglycaemia vs OAD Use (MET vs MET/SU)

<table>
<thead>
<tr>
<th>Glargine</th>
<th>Log odds ratio and 95% CI</th>
<th>SE</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>1.03 (0.93–1.14)</td>
<td>0.07</td>
<td>0.88</td>
<td>1.19</td>
<td>0.355</td>
</tr>
<tr>
<td>MET/SU</td>
<td>1.00 (0.89–1.12)</td>
<td>0.07</td>
<td>0.84</td>
<td>1.16</td>
<td>0.960</td>
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</table>

Insulin-naive Patients: Similar Results for Self-directed vs. Physician-directed Insulin Titration

Glycemic Control

Hypoglycemia

Risk Factors for Hypoglycaemia

- Clinical Scenarios
  - Excessively/ill-timed insulin doses
  - Missed meals or overnight fast
  - Ingestion of alcohol
  - Physical activity
  - Malnutrition
  - Increased insulin sensitivity
  - Weight loss
  - Improved glycemic control
  - Decreased insulin clearance
  - Renal insufficiency
  - Chronic liver disease
  - Hypothyroidism

Risk Factors for Severe Hypoglycaemia

- Age/duration of diabetes treatment
- Intensive glycemic control
- Hypoglycaemia unawareness
- Sleep
- Antecedent hypoglycaemia
- History of severe hypoglycaemia

Hypoglycemic Risk Reduction

- Patient education and empowerment
  - Symptom recognition
    - Older/elderly patients with hypoglycemia may experience nontraditional symptoms of hypoglycemia
    - Response time of older/elderly patients is generally diminished
  - Frequent self-monitoring of BG
  - Appropriate and flexible insulin (and other drug) regimens
  - Individualized glycemic goals
  - Ongoing professional guidance and support

Mark: 24 Months Later

- You started Mark on a basal insulin analog 17 units at bedtime and asked him to up-titrate his dose to reach FPG <50 mg/dL.
- At most recent visit
  - A1C level = 7.8%
  - BP = 135/90 mm Hg
  - Wt = 89.6 kg (gained 3.2 kg over last 24 months)
- Current medications
  - 48 units basal insulin analog at bedtime
  - Glimepride 2 mg od
  - Metformin 1g bid
- BG diary as follows:

<table>
<thead>
<tr>
<th>M</th>
<th>Tu</th>
<th>W</th>
<th>Th</th>
<th>F</th>
<th>Sat</th>
<th>Sun</th>
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<tr>
<td>AM</td>
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<td>110</td>
<td>105</td>
<td>100</td>
<td>103</td>
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<td>Before lunch</td>
<td>180</td>
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<td>170</td>
<td>197</td>
<td></td>
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<tr>
<td>Before supper</td>
<td>190</td>
<td>208</td>
<td>208</td>
<td>208</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before bedtime</td>
<td>175</td>
<td>190</td>
<td>170</td>
<td>197</td>
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Combination of Basal Insulin With a GLP-1 RA Has Scientific Logic

![Diagram showing the combination of basal insulin with a GLP-1 receptor agonist with scientific logic](image)

**Summary of Clinical Trial Data**

<table>
<thead>
<tr>
<th>GLP-1 RAs and Basal Insulin Combined: GLP-1 RA added to basal insulin in T2DM</th>
<th>Hypoglycemia and Insulin Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypoglycemia (% of patients)</strong></td>
<td></td>
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<tr>
<td>Minor</td>
<td>25</td>
</tr>
<tr>
<td>Major nocturnal</td>
<td>17</td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
</tr>
<tr>
<td><strong>Change in Insulin Doses</strong></td>
<td></td>
</tr>
<tr>
<td>Units/day</td>
<td>12</td>
</tr>
<tr>
<td>Units/kg</td>
<td>0.15</td>
</tr>
</tbody>
</table>

**Notes:**
- 7% (0.001) for between-group comparisons (error bars are confidence intervals).
- N = 233 adults with T2DM (HbA1c > 7% to <10%) who were receiving insulin glargine plus metformin or pioglitazone.

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**GLP-1 RAs and Basal Insulin Combined: Summary of Clinical Trial Data**

<table>
<thead>
<tr>
<th>Treatment Goal</th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C level (%)</td>
<td>&lt;7</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>80–130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>80–130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Postprandial glucose (PPG) (mg/dL)</td>
<td>&lt; 180*</td>
<td>&lt;140*</td>
</tr>
</tbody>
</table>

*Peak FPG; *2-hour PPG

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**GLP-1 RA Added to Basal Insulin in T2DM**

**Hypoglycemia and Insulin Doses**

<table>
<thead>
<tr>
<th>Hypoglycemia (% of patients)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Major nocturnal</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Change in Insulin Doses**

| Units/day | 12 | 22 |
| Units/kg | 0.15 | 0.25 |

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**GLP-1 RAs and Basal Insulin Combined: Summary of Clinical Trial Data**

<table>
<thead>
<tr>
<th>Baseline A1C level</th>
<th>7.0%</th>
<th>8.5%</th>
<th>8.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean A1C change</td>
<td>−1.13%</td>
<td>−1.74%</td>
<td>−0.82%</td>
</tr>
<tr>
<td>Patients achieving A1C goal</td>
<td>44%</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Baseline weight</td>
<td>95.5 kg</td>
<td>95.4 kg</td>
<td>92.7 kg</td>
</tr>
<tr>
<td>Mean weight change</td>
<td>−4.7 kg</td>
<td>−1.8 kg</td>
<td>−0.73 kg</td>
</tr>
<tr>
<td>Minor hypoglycemia</td>
<td>0%</td>
<td>25%</td>
<td>25%*</td>
</tr>
</tbody>
</table>

*Any hypoglycemic event.
Summary—T2DM and Basal Insulin Therapy: The Evolution of Efficacy and Safety

- Many T2DM patients will require insulin for glycemic control
- Insulin works!
- Basal insulin analogs have several advantages over human insulin products
  - When FPG is at goal but A1C level is elevated, PPG needs to be assessed
    - Multiple options for addressing elevated PPG
  - Clinical trials demonstrate benefit of adding basal insulin to a GLP-1 RA or vice versa
    - Effective glucose control; control of FPG and PPG
    - Lower risk for/no weight gain
    - Low risk for hypoglycemia
- Ultimately many patients may require prandial insulin

Rationale for Development of Modern Basal Insulin Analogs

- Desire to prevent complications of diabetes
  - Improve adherence
- More options regarding dosing times; fewer injections
  - Bring closer to normoglycemia
- Most patients do not achieve target A1C goals in clinical practice
- Concerns related to basal insulin therapy
  - Hypoglycemia and weight gain
  - Often delay insulin use
  - Inability to coadminister with other injectable agents

Investigational, Second-Generation Basal Insulin Analogs

- Insulin degludec
  - Approved in over 50 countries
  - US: Phase 3 completed
- Basal insulin peglispro (LY2605541)
  - Phase 3

Basal Insulins: Current and Investigational

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Onset (h)</th>
<th>Peak Onset (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1–2</td>
<td>4–12</td>
<td>12–16</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determir</td>
<td>1–2</td>
<td>6–8</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>1–2</td>
<td>No peak</td>
<td>20–26</td>
</tr>
<tr>
<td>Glargine U300</td>
<td>1–2</td>
<td>No peak</td>
<td>Up to 36 h</td>
</tr>
<tr>
<td>Ultra long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec*</td>
<td>30–90 min</td>
<td>No peak</td>
<td>&gt;42 h</td>
</tr>
<tr>
<td>Peglispro*</td>
<td>N/A</td>
<td>No peak</td>
<td>&gt;36 h</td>
</tr>
</tbody>
</table>

*Investigational agent.

Emerging Basal Insulin Options for the Treatment of T2DM Latest Updates

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Long-acting Basal Insulin Degludec*
Pharmacodynamic Profile in Steady State (T2DM)

- Investigational.


**IMAGINE-2: Hypoglycemia Risk With Basal Insulin Peglispro**

- **Total Hypoglycemia**
  - Peglispro: 1.56 %
  - Glargine: 1.23 %
  - Peglispro vs. Glargine: *P* < 0.001
- **Nocturnal Hypoglycemia**
  - Peglispro: 0.3%
  - Glargine: 0.4%
  - Peglispro vs. Glargine: *P* = 0.01

*Investigational.

**DUAL I: IDEglira* in Insulin-naive T2DM Patients—Glycemic Control Over Time**

- **A1C Level (%)**
  - IDEglira vs. Liraglutide: *P* < 0.001
  - IDEglira vs. Insulin Degludec: *P* < 0.001
  - IDEglira vs. glargine: *P* < 0.001

*Investigational.

**Hepatic Safety With Basal Insulin Peglispro (Phase 3)**

- **ALT Change**
  - Peglispro Glargine: 2.3 units
  - IDEglira Glargine: 1.3 units

*Investigational.

**Dosing Regimen of IDEglira*: Fixed-ratio Combination of Insulin Degludec and Liraglutide**

- **1 dose step:**
  - 1 unit insulin degludec
  - 0.036 mg liraglutide

*Investigational.

**DUAL I: IDEglira* in Insulin-naive T2DM Patients—Change in Body Weight Over Time**

- **Change in Weight (kg)**
  - IDEglira vs. Liraglutide: *P* < 0.001
  - IDEglira vs. Insulin Degludec: *P* < 0.001
  - IDEglira vs. glargine: *P* < 0.001

*Investigational.
Summary—Emerging Basal Insulin Options for the Treatment of T2DM: Latest Updates

• Novel ultra–long-lasting basal insulins have been developed
  — Flat, stable glucose-lowering profile
  — Lower intrapatient variability in glucose-lowering effect
  — Similar A1C reduction vs. traditional basal insulins
  — Lower overall and nocturnal hypoglycemia vs. traditional basal insulins
  — Elevations in liver enzymes with peglispro not fully understood
• Combinations/coformulations of novel basal insulins also in development
  — IDegLira demonstrates
  • Better A1C control vs. IDeg or Lira; less hypoglycemia than IDeg; less weight gain than Lira

Program Conclusions

1. To improve outcomes and reduce the risk of T2DM-related complications, more intensive management of glycemia is warranted, including the option of introducing insulin therapy earlier than the current widely practiced substandard of care
2. Advantages of basal insulin analogs over basal human insulin exist, primarily a longer duration of action, less intra-patient variability, and less weight gain

Program Conclusions (cont’d)

3. Basal insulin is recommended by multiple consensus-based guidelines as part of 2- and 3-drug combinations
  • Using a GLP-1 RA in combination with basal insulin can help achieve PPG control, reduce the risk for hypoglycemia, reduce insulin-associated weight gain, and reduce overall insulin requirements
4. Multiple second-generation basal insulin analog are in development (eg, insulin degludec, peglispro) or have recently been made available (glargine U300)
  • Provide similar reductions in A1C level to traditional basal insulin agents, but with less risk for hypoglycemia
  • Greater variability in drug administration that may help improve patient satisfaction and adherence