Insulin 101
An Introduction to Insulin Therapy in the 21st Century

April 11, 2012
Anaheim, California
Session 3: Insulin 101:
An Introduction to Insulin Therapy in the 21st Century

Learning Objectives
1. Calculate appropriate insulin doses for initiating basal and basal-prandial insulin regimens in type 2 diabetes mellitus.
2. Demonstrate best practices in insulin injection and self-monitoring of blood glucose (SMBG) techniques to improve treatment adherence and potentially impact patient outcomes.
3. Apply pattern recognition to SMBG data to appropriately titrate insulin doses and adjust insulin regimens to specific patient needs.
4. Summarize the efficacy and safety findings from clinical trials of investigational insulins and the combination of incretin-based therapies with insulin.

Faculty

James R. Gavin III, MD, PhD
Clinical Professor of Medicine
Emory University School of Medicine
CEO and Chief Medical Officer
Healing Our Village, Inc
Atlanta, Georgia

Dr. Gavin is clinical professor of medicine at Emory University School of Medicine in Atlanta, Georgia, and clinical professor of medicine at the Indiana University School of Medicine, Indianapolis, Indiana. He currently serves as chief executive officer and chief medical officer of Healing Our Village, Inc. He served as president and chief executive officer of MicroIslet, Inc, San Diego, California, from January 2006 to July 2007, and was president of the Morehouse School of Medicine in Atlanta from 2002 to 2004. He served as senior scientific officer at the Howard Hughes Medical Institute (HHMI) from 1991 to 2002 and as director of the HHMI–National Institutes of Health Research Scholars Program from 2000 to 2002. Before joining the senior staff of HHMI, Dr. Gavin was professor and chief of the diabetes section, acting chief of the section on endocrinology, metabolism, and hypertension, and William K. Warren Professor for Diabetes Studies at the University of Oklahoma Health Sciences Center, Oklahoma City. He previously served as an associate professor of medicine at Washington University School of Medicine in St. Louis, Missouri.

Dr. Gavin is a member of a number of organizations, including the Institute of Medicine of the National Academy of Sciences, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists, The Endocrine Society, the American Society for Clinical Investigation, the American Association of Physicians, the Alpha Omega Alpha Honor Medical Society, the Sigma Pi Phi leadership fraternity, and the Downtown Atlanta Rotary Club. He is a life member of Alpha Phi Alpha Fraternity, Inc. He is a past president of the ADA and was voted Clinician of the Year in Diabetes by the ADA in 1991. He has served on many advisory boards and on the editorial boards of the American Journal of Physiology and the American Journal of the Medical Sciences. He is on the board of trustees for Emory University and Livingstone College, and is trustee emeritus for the Robert Wood Johnson Foundation. In addition, he is national program director of the Robert Wood Johnson Foundation. He is a member of the national advisory board for the Institute of Medicine’s Health Policy Fellows program. He is also chairman emeritus of the National Diabetes Education Program. He serves as chairman of the data safety monitoring board for the VA Cooperative Diabetes Study. He is chairman of the board of directors for the Partnership for a Healthier America, an independent, nonpartisan foundation formed to support the childhood obesity prevention initiative and the “Let’s Move!” initiative of the First Lady.

Dr. Gavin has published more than 220 articles and abstracts in such publications as Science, Journal of Applied Physiology, Diabetes, and the American Journal of Physiology. He is coauthor of two books: Healing Our Village: A Self-Care Guide to Diabetes Control (written with L. Coleman) and Dr. Gavin’s Health Guide for African Americans (written with S. Landrum). He hosted the Powerpoint health talk-radio shows for public radio station 91.9 FM WCLK, in Atlanta from 2005 to 2006. Among the many honors Dr. Gavin has received is the Daniel Hale Williams Award, the E. E. Just Award, the Herbert W. Nickens Award, the Daniel D. Savage Memorial Science Award, the Emory University Medal for Distinguished Achievement, the Banting Medal for Distinguished Service from the ADA, the Distinguished Alumnus Award from the Duke University School of Medicine, the F. C. Greenwood Award from the RCMI of NCRR at the National Institutes of Health, the Bernardou Houssay Award from the National Minority Quality Forum and the Congressional Black Caucus, and the Internist of the Year Award from the National Medical Association. He was a recipient of the 2009 Living Legend in Diabetes Award from the American Association of Diabetes Educators. He is also a 2010 recipient of the Public Policy Leadership Award from the ADA for contributions to advocacy on behalf of persons with diabetes.
Dr Gavin graduated from Livingstone College (May 1966) in Salisbury, North Carolina, with a degree in chemistry. He earned his PhD in biochemistry from Emory University (December 1970) and his MD from Duke University School of Medicine (December 1975), Durham, North Carolina. He completed his internship, residency, and clinical fellowship training at Barnes Hospital of Washington University in St Louis. He and his wife, Dr Annie Gavin, are the parents of three adult sons.

Donna Rice, MBA, BSN, RN, CDE, FAADE
Past President, American Association of Diabetes Educators
Past President, Diabetes Health and Wellness Institute
Affiliate of Baylor Health Care System
Dallas, Texas

Donna Rice is the recent past president of the Diabetes Health and Wellness Institute, an affiliate of Baylor Health Care Systems, in Dallas, Texas. She is currently the president of Big Picture Health, and serves as a consultant in the areas of diabetes management and care, and business development. Rice is also the 2007 past president of the American Associations of Diabetes Educator (AADE) and currently is the chair of the Diabetes and Education Research Foundation for AADE.

Following completion of her registered nurse diploma at Saint Anne’s Hospital School of Nursing in Chicago, Illinois, Ms Rice earned a BS in nursing at Madonna University in Livonia, Michigan, and later earned her MBA at Baker College of Business in Flint, Michigan.

Ms Rice has more than 20 years’ experience in the area of diabetes and wellness especially as it relates to the business of managing diabetes in today’s environment. An author of numerous peer-reviewed articles, abstracts, and book chapters on these subjects, Ms Rice has also appeared as a guest speaker in radio and television interviews and has developed and co-developed several educational resources and tools for diabetes educators and physicians, including professional DVDs, presentations, and booklets, as well as a hospital database for tracking diabetes outcomes. She is a member of the American Association of Diabetes Educators, the Michigan Organization of Diabetes Educators, and the American Diabetes Association, and currently serves on numerous state and national committees.

Ms Rice is a certified diabetes educator. She is the recipient of the Distinguished Service Award from the American Association of Diabetes Educators, 2009 and the Most Accomplished Award from the Michigan Organization of Diabetes Educators, and was named Diabetes Advocate of the Year by the American Diabetes Association.

Javier Morales, MD
Vice President
Principal Trials Investigator
Advanced Internal Medicine Group, PC
New Hyde Park, New York

Dr Morales is in private practice with the Advanced Internal Medicine Group in New Hyde Park, New York. After graduating from the University of Medicine and Dentistry of New Jersey, he completed residencies at Memorial Sloan-Kettering Cancer Center and North Shore University Hospital, where he served as chief medical resident. Dr Morales serves on multiple committees at St. Francis Hospital in Roslyn, New York. In addition to authoring several publications, he has served as principal investigator for several different studies and clinical trials. He is active in the educational sector and has been a presenter at many Pri-Med symposia. He also serves as a clinical instructor for several nurse practitioner, physician assistant, and internal medicine residency programs at North Shore University Hospital and Winthrop-University Hospital. Dr Morales is an avid musician and percussionist, and he is fluent in Spanish, Italian, and Portuguese.

Faculty Financial Disclosure Statements
The presenting faculty report the following:
James R. Gavin III, MD, PhD, receives honoraria as a consultant and speaker from Eli Lilly and Company and sanofi-aventis U.S. LLC. Dr Gavin is also an advisor for Amylin Pharmaceuticals, Inc.
Donna Rice, MBA, BSN, RN, CDE, FAADE, receives advisory board honoraria from Novo Nordisk Inc. and sanofi-aventis U.S. LLC.

Javier Morales, MD, receives honoraria from Eli Lilly and Company, Novo Nordisk Inc., and Warner Chilcott.

**Education Partner Financial Disclosure Statement**

The content collaborators at the Institute for Medical and Nursing Education, Inc. report the following:

Amy Carbonara, Director of Program Development, has no financial relationships to disclose.

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Steve Weinman, RN, Executive Director, has no financial relationships to disclose.

**Acronym List**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>glycosylated hemoglobin A1C</td>
<td>LIRA</td>
<td>liraglutide</td>
</tr>
<tr>
<td>AACE</td>
<td>American Association of Clinical</td>
<td>LIS</td>
<td>insulin lispro</td>
</tr>
<tr>
<td></td>
<td>Endocrinologists</td>
<td>LM50/50</td>
<td>insulin lispro protamine (50%)/insulin lispro (50%)</td>
</tr>
<tr>
<td>AADE</td>
<td>American Association of Diabetes</td>
<td>LM75/25</td>
<td>insulin lispro protamine (75%)/insulin lispro (25%)</td>
</tr>
<tr>
<td></td>
<td>Educators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>American College of Endocrinology</td>
<td>LY</td>
<td>pegylated insulin lispro</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
<td>MDI</td>
<td>multiple daily injections</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
<td>MET</td>
<td>metformin</td>
</tr>
<tr>
<td>ASP</td>
<td>insulin aspart</td>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>B</td>
<td>breakfast</td>
<td>NDA</td>
<td>New Drug Application</td>
</tr>
<tr>
<td>BBT</td>
<td>basal bolus therapy</td>
<td>NPH</td>
<td>neutral protamine Hagedorn</td>
</tr>
<tr>
<td>BG</td>
<td>blood glucose</td>
<td>NPL</td>
<td>insulin lispro protamine suspension</td>
</tr>
<tr>
<td>Bi-ASP</td>
<td>biphasic aspart</td>
<td>OAD</td>
<td>oral antidiabetes agent</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
<td>OD</td>
<td>once daily</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
<td>PBO</td>
<td>placebo</td>
</tr>
<tr>
<td>CGM</td>
<td>continuous glucose monitoring</td>
<td>PCP</td>
<td>primary care physician</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
<td>PD</td>
<td>pharmacodynamics</td>
</tr>
<tr>
<td>CSII</td>
<td>continuous subcutaneous insulin</td>
<td>PH20</td>
<td>recombinant human hyaluronidase</td>
</tr>
<tr>
<td></td>
<td>infusion</td>
<td>PJO</td>
<td>pioglitazone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK</td>
<td>pharmacokinetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPG</td>
<td>postprandial glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPG UL</td>
<td>postprandial glucose upper limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QHS</td>
<td>every night at bedtime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>recombinant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RA</td>
<td>receptor agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RHI</td>
<td>regular human insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAXA</td>
<td>saxagliptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SITA</td>
<td>sitagliptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SMBG</td>
<td>self-monitoring of blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STeP</td>
<td>Structured Testing Program</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SU</td>
<td>sulfonulary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1DM</td>
<td>type 1 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDD</td>
<td>total daily dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TZD</td>
<td>thiazolidinedione</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U</td>
<td>unit</td>
</tr>
</tbody>
</table>

Session 3
Suggested Reading List


Insulin 101: Course Syllabus

- Part 1: Basal insulin therapy
  - Basics of insulin therapy
  - Currently available basal insulins
  - Initiating basal insulin therapy
  - Optimizing insulin injection techniques

Type 2 Diabetes is Progressive

Daily Plasma Insulin Profiles In Individuals With and Without Type 2 Diabetes

Types of Insulin Therapies
Basal Insulin Therapy in T2DM

- Can be initiated at any point in the T2DM spectrum
  - A1C > 7.5% despite the use of 2 or 3 OADs
  - A1C > 9.0% despite previous T2DM pharmacologic therapy
  - A1C > 9.0% plus symptoms in a newly diagnosed T2DM
- Early initiation is associated with improved β-cell function and a higher probability of attaining A1C < 7%
- Combination with other agents including OADs, prandial insulin, and some incretin-based therapies can improve glycemic control

Insulin 101: Course Syllabus

- Part 1: Basal insulin therapy
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  - Initiating basal insulin therapy
  - Optimizing insulin injection techniques

Currently Available Basal Insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>NPH Insulin</th>
<th>Insulin Glargine</th>
<th>Insulin Detemir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Type</td>
<td>Human; intermediate-acting</td>
<td>Analogue; long-acting</td>
<td>Analogue; long-acting</td>
</tr>
<tr>
<td>Onset</td>
<td>2-4 hours</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Peak</td>
<td>4-10 hours</td>
<td>No pronounced peak</td>
<td>Relatively flat</td>
</tr>
<tr>
<td>Effective Duration</td>
<td>10-16 hours</td>
<td>Up to 24 hours</td>
<td>Up to 24 hours</td>
</tr>
</tbody>
</table>

Time-Action Profiles Illustrate Variability in NPH Insulin vs Basal Insulin Analogues

- Long-acting insulin analogues are preferred over NPH insulin because they:
  - Do not exhibit a pronounced peak in activity
  - Have more predictable time-action profiles and less within/between patient variability
  - Are associated less nocturnal hypoglycemia

Insulin 101: Course Syllabus

- Part 1: Basal insulin therapy
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Insulin Self-Titration Is as Effective and Safe as Physician-Adjusted Dosing

- Safety and efficacy have been demonstrated in 3 trials
  - ATLANTUS (glargine)
  - PREDICTIVE 303 (detemir)
  - INITIATE Plus (biphasic aspart 70/30)
- Anticipated benefits
  - Cost savings
  - Fewer office visits
  - Equivalent or fewer hypoglycemic episodes
  - Greater patient satisfaction (increased autonomy)
- Confirming benefits
  - Patient-centered outcomes study is in progress (Di@log)

AACE and ADA Recommended Glycemic Targets

<table>
<thead>
<tr>
<th>A1C</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6.5%</td>
<td>&lt; 7.0%</td>
</tr>
</tbody>
</table>

SMBG Readings*

<table>
<thead>
<tr>
<th>Glucose</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>70-110 mg/dL</td>
</tr>
<tr>
<td>Preprandial</td>
<td>N/A</td>
</tr>
<tr>
<td>Postprandial</td>
<td>70-140 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>100-140 mg/dL</td>
</tr>
</tbody>
</table>

Both organizations recognize that more or less stringent goals may be appropriate for some individuals

*More than half of the readings should fall within this range.
- ≤ 6-hour PPG reading
- ≥ 6-hour PPG reading
- 1 to 2-hour PPG reading

Ideal Glycemic Control

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Before breakfast</th>
<th>2 h after breakfast</th>
<th>Before lunch</th>
<th>2 h after lunch</th>
<th>Before dinner</th>
<th>2 h after dinner</th>
<th>Before bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPG UL</td>
<td>83</td>
<td>111</td>
<td>79</td>
<td>114</td>
<td>82</td>
<td>118</td>
<td>87</td>
</tr>
<tr>
<td>PPG UL</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
<td>350</td>
<td>400</td>
</tr>
</tbody>
</table>

Glycemic Targets

- Fasting Plasma Glucose:
  - ADA: 70-110 mg/dL
  - AACE: 70-110 mg/dL

Baseline Dose Too Low

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Before breakfast</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>2 h after lunch</th>
<th>Dinner</th>
<th>2 h after dinner</th>
<th>Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before breakfast</td>
<td>175</td>
<td>204</td>
<td>168</td>
<td>199</td>
<td>176</td>
<td>206</td>
<td>183</td>
</tr>
</tbody>
</table>

Basal Dose Too High

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Before breakfast</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>2 h after lunch</th>
<th>Dinner</th>
<th>2 h after dinner</th>
<th>Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before breakfast</td>
<td>52</td>
<td>90</td>
<td>48</td>
<td>90</td>
<td>55</td>
<td>90</td>
<td>65</td>
</tr>
</tbody>
</table>
Insulin 101: Course Syllabus

- Part 1: Basal insulin therapy
  - Basics of insulin therapy
  - Currently available basal insulins
  - Initiating basal insulin therapy
  - Optimizing insulin injection techniques

**Insulin Injection Sites**

- Upper Arm
- Thigh
- Abdomen
- Buttocks

**Lipohypertrophy Can Result from Poor or Improper Site Rotation**

- Results from the growth effects of insulin and induction of local growth factors due to repeated injection
- Often less painful to inject into areas of lipohypertrophy BUT...
  - ...absorption of insulin is altered and can lead to hypo- or hyperglycemia
  - It is recommended that patients do not to inject into these sites
- Prevention:
  - Rotate sites - avoid repeated injection into the same area
  - Use a new needle with every injection

**Encouraging Proper Insulin Injection Technique: Step by Step Instructions**

**Pen**

1. Prime pen to check for flow (a drop of insulin should be visible at the tip of the needle)
2. Ensure dosing dial is set to '0' and dial in dose of insulin to be delivered
3. Insert needle quickly into the SC tissue
4. Fully depress thumb button
5. Count slowly to 10 before withdrawing the needle
6. Following injection, remove needle and discard properly
7. Never leave needles attached to the pen

**Syringe**

1. Draw up equivalent amount of air into syringe and inject into vial prior to drawing up insulin
2. Tap barrel and push plunger to remove air bubbles
3. Insert needle quickly into the SC tissue
4. Depress plunger fully
5. Following injection, remove needle and discard properly
6. Never use syringe needles more than once

**Encouraging Proper Insulin Injection Technique: Step by Step Instructions**

**Syringe**

1. Prime pen to check for flow (a drop of insulin should be visible at the tip of the needle)
2. Ensure dosing dial is set to '0' and dial in dose of insulin to be delivered
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3. Insert needle quickly into the SC tissue
4. Depress plunger fully
5. Following injection, remove needle and discard properly
6. Never use syringe needles more than once

---

*May need longer time when using high doses of insulin.*

**Basal Dose Too High**

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:00 AM</td>
<td>45</td>
</tr>
<tr>
<td>5:00 AM</td>
<td>213</td>
</tr>
<tr>
<td>7:00 AM</td>
<td>144</td>
</tr>
<tr>
<td>9:00 AM</td>
<td>127</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>75</td>
</tr>
<tr>
<td>1:00 PM</td>
<td>100</td>
</tr>
<tr>
<td>3:00 PM</td>
<td>250</td>
</tr>
<tr>
<td>5:00 PM</td>
<td>200</td>
</tr>
</tbody>
</table>


**Tips for Reducing Discomfort From Insulin Injections**

- Ensure injection into subcutaneous tissue, not intramuscularly
- Penetrate skin quickly, but inject slowly
- Allow newly opened insulin to come to room temperature
- If using alcohol, allow to dry before injecting insulin
- Heat/cold is not recommended as it can alter absorption
- Use shorter length needles (4-, 5-, or 6-mm)
  - If longer needles (≥8 mm) are being used, skin-pinch technique should be employed
- Use a new needle with every injection
  - Repeated use blunts needles
  - New needles are coated with silicone lubrication

*Cleaning with soap and water is preferred.*

**Needle Size Consideration**

- Use the shortest needle possible when initiating insulin therapy
- There is no medical reason to use a needle longer than 8-mm

**Conveniences of Insulin Pen Therapy**

- Easy to use/store/carry
- Discreet
- Small needle size

**A Prescriber’s Checklist For Insulin Therapy**

- Insulin prescription should include:
  - Type of insulin
  - Number of units, vials/pens
  - Frequency of dosing
  - Diagnosis code
- Supplies
  - Pen needles or syringe/needles
  - SMBG supplies (lancets, test strips, control solution, log)
- Insulin titration instructions
- Needle disposal - patient resources
- Hypoglycemia treatment protocol
  - Glucagon kit (if patient is at significant risk for hypoglycemia)
- Diabetes education referral

**Basal Insulin Therapy: Summary**

- Basal insulin can be initiated throughout the T2DM spectrum
- Insulin injection is simple and straightforward
  - Always inject into subcutaneous tissue, not muscle
  - Be sure to rotate injection sites
- Analogue basal insulins are often preferred over human insulins (NPH/regular) because of their more physiologic profiles
- Basal insulin is generally initiated at 10 U/day or 0.1-0.2 U/kg/day and titrated to achieve FPG glucose targets
- Proper injection technique should be reinforced periodically and injection sites should be examined regularly
INSULIN 101: BASAL-PRANDIAL INSULIN THERAPY

Javier Morales, MD
St. Francis Hospital
Advanced Internal Medicine Group
New Hyde Park, New York

Insulin 101: Course Syllabus

Part 2: Basal-prandial insulin therapy
- Indications for basal-prandial insulin therapy
- Currently available prandial insulins
- Initiating basal-prandial insulin therapy
- Insulin titration using SMBG data

When Is Prandial Insulin Therapy Indicated in T2DM?

- The individual is not meeting glycemic targets on basal insulin
  - Elevated A1C despite normal FPG (in the absence of available PPG readings) with basal insulin
  - FPG with basal insulin is within targeted range, but PPG is persistently above goal
  - Further increases in basal insulin result in hypoglycemia
- Some patients may only require prandial insulin with their largest meal

Relative Contribution of Postprandial Hyperglycemia to Overall Glycemic Control

The relative contribution of postprandial hyperglycemia to overall glycemia is greater at A1C levels near 7%.

Currently Available Short-Acting Prandial Insulins

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Regular Insulin</th>
<th>Insulin Lispro</th>
<th>Insulin Aspart</th>
<th>Insulin Glulisine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset, h</td>
<td>Human; short-acting</td>
<td>&lt; 0.3-0.5</td>
<td>&lt; 0.25</td>
<td>&lt; 0.25</td>
</tr>
<tr>
<td>Peak, h</td>
<td>2-3</td>
<td>0.5-2.5</td>
<td>0.5-1.0</td>
<td>1-1.5</td>
</tr>
<tr>
<td>Effective duration, h</td>
<td>3-6</td>
<td>3-6.5</td>
<td>3.5</td>
<td>3-5</td>
</tr>
<tr>
<td>Injection: meal timing, m</td>
<td>-30 to -45</td>
<td>-15 to immediately after</td>
<td>-5 to -10</td>
<td>-15 to +20</td>
</tr>
</tbody>
</table>

Insulin 101: Course Syllabus

- Part 2: Basal-prandial insulin therapy
  - Indications for basal-prandial insulin therapy
  - Currently available prandial insulins
  - Initiating basal-prandial insulin therapy
  - Insulin titration using SMBG data

Initiating Basal-Prandial Insulin Therapy: Dosing According to Patient Needs

- Assumptions: patient is already using basal insulin
- Basal-Prandial Dose "Budget":
  - Basal 50% + Prandial 50% divided among meals
  - Initially estimate prandial doses at 1.0-1.5 U/10 g carbohydrate

Basal-Prandial Dose “Budget”: Varying Mealtime Carbohydrate Intake

- Total Daily Dose (TDD) = Basal (50%) + Prandial (50%) divided among meals

Timing of Prandial Insulin Injections Differs Between Human and Analogous Insulins In T2DM

- Regular human insulin needs to be injected 30-45 minutes before meals
- Rapid-acting insulin analogues (aspart, glulisine, lispro) can be injected 0-15 minutes before meals
- Insulin lispro and insulin glulisine can be safely injected immediately after a meal

Method

- Assumes consistent carbohydrate content with each meal

Part

- Dividing the remaining 50% among meals

Initiating Basal-Prandial Insulin Therapy:

- Method: weight-based
  - Total daily dose (TDD) = 0.5-1.0 U/kg/day
  - Basal dose is 50% of TDD
- Method: insulin: carbohydrate ratio-based
  - Initially estimate prandial doses at 1.0-1.5 U/10 g carbohydrate

Insulin 101: Course Syllabus

- Part 2: Basal-prandial insulin therapy
  - Indications for basal-prandial insulin therapy
  - Currently available prandial insulins
  - Initiating basal-prandial insulin therapy
  - Insulin titration using SMBG data

Self-Monitored Blood Glucose Can Improve Glycemic Control In T2DM Patients

- SMBG enables appropriate management of glycemia
  - Detecting/avoiding hyperglycemia
  - Detecting/avoiding hypoglycemia
- SMBG frequency and schedule can be varied to meet individual needs
- Clinician review of SMBG logs is essential
  - Helps assess efficacy and safety of antidiabetic regimen
  - Facilitates provider-patient partnership

Blood Glucose Monitor Features

- Display
  - Large numerical display
  - Backlit display or glow in the dark display
  - Graphing capability
  - Audio reporting of SMBG results
- Computer upload

Comparing Two Methods of Stepwise Prandial Insulin Intensification in T2DM

<table>
<thead>
<tr>
<th>Parameter/Characteristic</th>
<th>SimpleSTEP</th>
<th>ExtraSTEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin titration</td>
<td>Based on average of 3 pre-breakfast PG measurements</td>
<td>Based on pre-meal PG</td>
</tr>
<tr>
<td>Prandial dose addition</td>
<td>• Every 12 wks, if needed</td>
<td>• Every 12 wks, if needed</td>
</tr>
<tr>
<td></td>
<td>• To largest perceived meal</td>
<td>• To meal with highest post-meal PG increase</td>
</tr>
<tr>
<td>Prandial insulin titration</td>
<td>Based on premeal PG</td>
<td>Based on post-meal PG</td>
</tr>
<tr>
<td>SMBG</td>
<td>• 3 X 4-point profiles</td>
<td>• 3 X 6-point profiles</td>
</tr>
<tr>
<td></td>
<td>• Before each meal</td>
<td>• Before each meal</td>
</tr>
<tr>
<td></td>
<td>• Before each meal</td>
<td>• 2 h after each meal</td>
</tr>
<tr>
<td>Participant adjustments?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

SMBG Alone May Not Lead to Improved Glycemic Control

**Patient Education Needs**

- Appropriate glycemic targets (fasting, postprandial)
- When to test
- What the results mean
- When to take action

**Clinician Needs**

- Must review SMBG logs
- Must take action based on SMBG data
- Lack of clinician review/action may render SMBG ineffective
Pattern Recognition and Principles of Insulin Dose Adjustment

<table>
<thead>
<tr>
<th>SMBG Pattern</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>All readings above targets</td>
<td>Increase basal dose</td>
</tr>
<tr>
<td>FPG readings above targets</td>
<td>Add/increase prandial dose</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Decrease insulin dose</td>
</tr>
<tr>
<td>Frequent, unpredictable glycemic fluctuations</td>
<td>May be a pump candidate</td>
</tr>
</tbody>
</table>

If glucose levels are out of target at:
- Adjust this insulin component:
  - Postbreakfast/prelunch: Predawn prandial
  - Postlunch/predinner: Predinner prandial and/or morning basal insulin
  - Midafternoon: Midafternoon basal insulin
  - Postdinner/bedtime: Predinner prandial
  - Early morning: Evening basal insulin

Basal-Prandial Insulin Therapy: Summary

- Prandial insulin can be initiated with basal insulin or when FPG is controlled with basal insulin and A1C or PPG levels remain high.
- Prandial insulin is available in human or synthetic analogue forms.
  - Analogue prandial insulins are often preferred because of their more physiologic profiles compared with human prandial insulin.
- Prandial insulin is initiated as 50% of the TDD of insulin and divided among meals or with an insulin:carbohydrate ratio.
- SMBG plays an important role in determining the efficacy and safety of a patient’s antidiabetic regimen.

INSULIN 101: ELECTIVES

Elective 1: Overcoming Patient Barriers to Insulin Therapy and Pattern Management

Donna Rice, BSN, RN, CDE, FAAD
Past President, American Association of Diabetes Educators
Past President, Diabetes Health and Wellness Institute
Affiliate of Baylor Health Care System
Dallas, Texas

Barriers to Initiating Insulin Therapy Among Privately Insured Patients—New Jersey, 2010

Statistically significant factors influencing insulin use from a survey of privately insured, insulin-naive patients with poorly controlled T2DM; P < .05, not adherent vs adherent for all factors shown.

Facilitating Patient Acceptance of and Adherence to Insulin Therapy

- Educate patients from the beginning of the disease process about
  - The progressive nature of T2DM
  - The complications associated with poor glycemic control
  - The short- and long-term effects of improved glycemic control
- Avoid threatening patients with insulin therapy
- Use a simple insulin regimen to start
- Allow patients to participate in their insulin dose titration
- Patients who receive education about their glycemic goals are more likely to accept insulin therapy

Structured SMBG Reduces A1C in T2DM: SteP Trial Dose Adjustment

- 7-point BG profiles collected over 3 days
- Data used by patient AND provider
- Pattern management priorities:
  1. Hypoglycemia
  2. Fasting/preprandial hyperglycemia
  3. Postprandial hyperglycemia
- Abnormality occurring on 2 of 3 days at the same time of day must be addressed

Prioritize 1 – Correct Hypoglycemia

- AACE/ACE titration and goals recommended
- Basal dose adjustment
  - Initiate at 10 units/day at bedtime
  - ↑ or ↓ 1-2 units every 2-3 days until FBG goals met
- Prandial dose adjustment
  - Initiate at 5 units/meal
  - ↑ or ↓ 2-3 units every 2-3 days until goals met, considering both 2-h FBG and preprandial BG

...But I Really Don’t Have Enough Time to Explain All of This To My Patients...

Strategies to help you communicate this critical information with limited time:

- Utilize the diabetes team to deliver/reinforce your messages
  - Nursing assistants can safely teach insulin use and titration
  - Diabetes educators and comprehensive education can help with initiation and titration of insulin, hypoglycemia awareness, and glucagon use
- Consider group visits
  - Efficient, but optimal group size has not yet been defined
  - May be reimbursed by third-party payors
- Develop or obtain comprehensive handouts for patients and reinforce education in small amounts at each visit

PATTERN MANAGEMENT
Priority 2 – Fix the Fastings ( > 110 mg/dL)

Priority 3 – Postprandial Hyperglycemia

PATTERN MANAGEMENT CASES

Fix the Fasting

Postprandial Hyperglycemia

Hypoglycemia
Premixed/Biphasic Insulin Regimens

- Combination of 2 different types of insulin, usually up to 2 injections/day
- For patients with T1DM or T2DM
  - Requires consistent mealtimes and carbohydrate counting
  - May or may not cause more weight gain than BBT
  - May result in poorer glycemic control than BBT
- For patients with T2DM transitioning from basal-only regimens
  - Premixed/biphasic insulin does not guarantee reduced A1C
  - May increase risk of hypoglycemia
  - May cause more weight gain


Insulin Added to Any Combination of OADs Improves Glycemic Control in Insulin-Naïve Patients With T2DM (DURABLE Study)

- Lispro 75/25 (n = 1045)
- Glargine (n = 1046)


Comparison of Biphasic and Basal – Bolus Therapy: PREFER Study

- Minor hypoglycemia occurred in 31% of patients in the detemir-aspart group and 28% in the biphasic aspart group
- Weight gain was similar in both groups (2.4 kg vs 2.1 kg)

Initiating and Adjusting Premixed/Biphasic Insulin in T2DM – AACE Recommendations, Expert Consensus, and INITIATE Study

AACE
- Administration 2 x 2 times daily
- Dosage at largest meal twice daily
- Adjust basal/bolus dose based on predinner glucose level
- Adjust predinner dose based on predinner fasting glucose level

- Transitioning from once-daily basal insulin to twice-daily premixed/biphasic
- Divide TDD into 2 or 3 components of each insulin (before-breakfast and dinner)
- If meals are not of equal size, larger meal requires a larger proportion of insulin
- Adjust doses according to SMBG and diet history
- Reduce TDD by 20% if there is recurrent hypoglycemia

INITIATE
- Begin 6 units/day of NPH < 180 mg/dL
- OR begin 12 units/day of FPG > 180 mg/dL
- Begin with TDD equally divided for breakfast and dinner
- Administer dose in 30 minutes before meals
- Adjust according to fasting schedule shown in back of program book

Available Premixed/Biphasic Insulins

<table>
<thead>
<tr>
<th>Product</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Effective Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Biphasic Insulin</td>
<td>0.5-1</td>
<td>Dual</td>
<td>10-16</td>
</tr>
<tr>
<td>Analogue Biphasic Insulin</td>
<td>&lt; 0.25</td>
<td>Dual</td>
<td>10-16</td>
</tr>
<tr>
<td>70% NPH/30% regular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% NPL/25% lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% NPL/50% lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% aspart protamine/30% aspart</td>
<td>&lt; 0.25</td>
<td>Dual</td>
<td>15-18</td>
</tr>
</tbody>
</table>

Points for Consideration When Using Premixed Insulin

- Preparation
  - Must be rolled and/or tipped (NOT SHAKEN) for 20 cycles
- Site selection
  - Consideration must be given to injection site when using mixes containing NPH
    - AM injection is best given in the abdomen because of more rapid absorption (coverage for breakfast)
    - PM injection should be given in the buttocks or thigh because of slower absorption (prevention of nocturnal hypoglycemia)

Elective 3: Insulin Therapy in T1DM

James R Gavin, III, MD, PhD – Program Chair
Clinical Professor of Medicine
Emory University School of Medicine
CEO and Chief Medical Officer
Healing Our Village, Inc.
Atlanta, Georgia

Insulin Therapy Considerations in T1DM

- T1DM is characterized by absolute insulin deficiency – insulin administration is required for patient survival
- Glycemic variability tends to be greater in patients with T1DM than in T2DM patients treated with insulin
- The occurrence of hypoglycemia is greater in T1DM patients than T2DM patients
- T1DM demands basal + multiple prandial insulin injections/day
- Experts recommend SMBG measurements 3 times daily in individuals with T1DM

the period covered by the analysis. Singh SR, et al.

Glulisine was not licensed in Canada during

\( P < 0.05 \).

### Basal Prandial (Nutritional)

**Analogue**
- Insulin glargine
- Insulin detemir

**Human**
- NPH

**Analogue**
- Insulin aspart
- Insulin glulisine
- Insulin lispro

**Human**
- Regular

### Efficacy and Safety in T1DM: Basal Insulin Analogues vs NPH

<table>
<thead>
<tr>
<th>Efficacy or Safety Parameter</th>
<th>Weighted Mean Difference (95% CI)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>–0.08 (–0.12 to –0.04)(^a)</td>
<td>Favors analogues</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>–0.63 (–0.86 to –0.40)(^a)</td>
<td>Favors analogues</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>–0.86 (–1.00 to –0.72)(^a)</td>
<td>Favors analogues</td>
</tr>
<tr>
<td>Weight gain</td>
<td>–0.67 (–0.87 to –0.45)(^a)</td>
<td>Favors analogues</td>
</tr>
<tr>
<td>Hypoglycemia Odds Ratio</td>
<td>1.08 (1.02 to 1.14)</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Any</td>
<td>0.93 (0.8 to 1.08)</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Severe</td>
<td>0.73 (0.61 to 0.87)(^a)</td>
<td>Favors analogues</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>0.70 (0.63 to 0.79)(^a)</td>
<td>Favors analogues</td>
</tr>
</tbody>
</table>

\(^a\) Data may vary depending on whether patient is a child or adult and on patient's clinical situations.

### Calculating Insulin Dose for Adult Patient With T1DM

1. Obtain patient weight in kg
2. Calculate total daily dose (TDD) as 0.2-0.4 U/kg/day\(^a\)
3. Choose the dosing schedule
   - Give 50% of TDD as basal insulin
   - Give 50% of TDD as bolus (premeal) insulin
4. Adjust according to results of BG monitoring

\(^a\) Results based on 23 studies in adults with T1DM, 3872 on basal insulin analogues, 2915 on NPH insulin.

### Efficacy and Safety in T1DM: Rapid Insulin Analogues vs RHI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trials (N)</th>
<th>Adults With T1D (N)</th>
<th>Change in A1C % (95% CI)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart</td>
<td>7</td>
<td>3035</td>
<td>–0.13 (–0.20 to –0.07)(^a)</td>
<td>Favors analogue</td>
</tr>
<tr>
<td>Lispro</td>
<td>22</td>
<td>6021</td>
<td>–0.09 (–0.16 to –0.02)(^a)</td>
<td>Favors analogue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trials (N)</th>
<th>Adults With T1D (N)</th>
<th>Severe Hypoglycemia % Relative Risk Ratio (95% CI)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart</td>
<td>4</td>
<td>1814</td>
<td>0.83 (0.65 to 1.04)</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Lispro</td>
<td>10</td>
<td>4502</td>
<td>0.80 (0.67 to 0.96)</td>
<td>Favors analogue</td>
</tr>
</tbody>
</table>

\(^a\) Results based on 23 studies in adults with T1DM, 3872 on basal insulin analogues, 2915 on NPH insulin.

### Analogues Are Associated With Lower Hypoglycemia Rates Than Human Insulins for the Same Degree of Control in T1DM

- Lispro
- Glulisine
- Aspart
- NPH insulin

### Adjusting Insulin Dose for Adult Patient With T1DM

1. Obtain patient weight in kg
2. Calculate total daily dose (TDD) as 0.2-0.4 U/kg/day\(^a\)
3. Choose the dosing schedule
   - Give 50% of TDD as basal insulin
   - Give 50% of TDD as bolus (premeal) insulin
4. Adjust according to results of BG monitoring

\(^a\) Results based on 23 studies in adults with T1DM, 3872 on basal insulin analogues, 2915 on NPH insulin.
Insulin Pump Therapy

- Up to 40% of T1DM patients in the US utilize continuous subcutaneous insulin infusion (CSII)1,2
- CSII uses rapid-acting insulin to deliver both basal and bolus therapy1
- Advantages of pump therapy in T1DM include:1,2,3,4,5
  - Improved glycemic control
  - A reduction in hypoglycemia
  - Improved quality of life
  - Reduced frequency of diabetic ketoacidosis
- CSII can be paired with continuous glucose monitoring (CGM):4,5
  - To provide more frequent glucose readings
  - To reduce the incidence of hypoglycemia
- CGM does not replace SMBG2

Prerequisites for CSII

- Motivated to improve glycemic control
- Intellectually and physically able to manage insulin pump therapy
- Experience with frequent SMBG
- Fluency in carbohydrate counting and insulin correction
- Willingness to communicate with the diabetes team

Insulin in T1DM: Summary

- Insulin therapy considerations differ for patients with T1DM and patients with T2DM
- Similarly to T2DM, insulin analogues are preferred in the treatment of T1DM due to their more physiologic profile
- The time-action profiles of insulins may differ in individuals with T1DM compared to T2DM
- Insulin pump therapy can contribute to improved glycemic control and less hypoglycemia in T1DM
- Insulin pump therapy requires a motivated, compliant patient willing to communicate with the diabetes team

Insulin 201: Course Syllabus

- New Insulin Combinations
  - Insulin + DPP-4 inhibitors
  - Insulin + GLP-1 receptor agonists
- Investigational Insulins
  - Limitations of current insulins and future needs
  - Investigational basal insulins
  - Investigational prandial insulins

*Some of the agents and/or combinations to be discussed are not US FDA-approved at this time.
**US FDA-Approval Status for DPP-4 Inhibitor Combinations**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approval Status for Combination with Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Approved for use in combination with insulin³</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Approved for use in combination with insulin³</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Not approved for use in combination with insulin² Clinical trials in progress²</td>
</tr>
</tbody>
</table>


---

**DPP-4 inhibitors as Add-On Therapy to Insulin: Glycemic Efficacy**

**DPP-4 inhibitors as Add-On Therapy to Insulin: Hypoglycemia**

**DPP-4 inhibitors as Add-On Therapy to Insulin: Effect on Body Weight**

**US FDA-Approval Status for Insulin-GLP-1 RA Combinations**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approval Status for Combination with Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Approved in combination with insulin glargine¹</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Not yet approved in combination with insulin NDA filed in 2011 - awaiting response from the US FDA²</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>Not yet approved in combination with insulin¹ Clinical trials in progress²</td>
</tr>
</tbody>
</table>

---

**Exenatide BID Added to Insulin Glargine**

**Similar rates of minor hypoglycemia in EXN BID (25%) and PBO (29%) groups**

More discontinued due to AEs in EXN BID (5%) vs PBO (7%) group (P < .01).  
**Insulin 201: Course Syllabus**

- **New Insulin Combinations**
  - Insulin + DPP-4 inhibitors
  - Insulin + GLP-1 receptor agonists

- **Investigational Insulins**
  - Investigational basal insulins
  - Investigational prandial insulins

---

**Milestones in Insulin Development**

1920: Insulin discovered
1922: Insulin developed
1936: Insulin protamine developed
1952: Insulin zinc developed
1965: Insulin Lente developed
1978?: Insulin lispro approved in US
1979: Insulin Glargine approved in US
1981: Insulin aspart approved in US
1996: Inhaled insulin approved in US
2000: Insulin detemir approved in US
2004: Insulin liraglutide approved in US
2010: Insulin albiglutide approved in US

Withdrawn:
- Inhaled insulin

---

**Glargine and Detemir Time-Action Profiles Are Dose-Dependent**

Glargine and Detemir Action Profiles for Clinically Relevant Doses in Patients With T2DM

---

**Insulin Detemir Added to Liraglutide**

- **Study**:
  - Patients not achieving A1C < 7% randomized to study treatments
  - 26-week study + 26-week extension
  - Added insulin detemir or nothing
  - Mean starting A1C = 7.6%

**Time Action Profile of Basal Insulins**

- GLAR added to EXN BID (n = 30)
- EXN BID added to GLAR (n = 166)

- Weight decreased significantly (-2.5 kg) in the EXN BID to GLAR group
- Weight remained unchanged in the GLAR added to EXN BID group

---

**Does Order of Initiation Matter? Insulin and Exenatide BID**

- Study on order of addition (chart review, 24-mo treatment)

---

*P < .005 vs baseline.*

Are Current Basal Insulins True 24-Hour Therapies?


Morning 21%
Evening 43%
Twice daily 36%

Why Do We Need New Insulins?
Characteristics of An Ideal Basal Insulin

• Flat, peakless time-action profile
• Low variability within and between individuals
• Long duration of action
• Low risk of hypoglycemia

Late-Stage Investigational Basal Insulins

<table>
<thead>
<tr>
<th>Insulin Administration</th>
<th>Status</th>
<th>Peak</th>
<th>Effective Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro protamine suspension (ILPS)</td>
<td>Once or twice daily</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Degludec (NN1250)</td>
<td>Once daily, thrice weekly</td>
<td>Filed for approval</td>
<td>Peakless &gt; 24 h</td>
</tr>
</tbody>
</table>

Insulin Degludec Time-Action Profile

Once-Daily Degludec<sup>a</sup> vs Once-Daily Glargine in Insulin Naive Patients With T2DM

Phase 2 trial
- 16 weeks
- DEG (n = 61) vs GLAR (n = 62), all receiving OADs
- BL A1C: 8.6% - 8.7%
- Similar A1C changes
  - DEG: -1.3%
  - GLAR: -1.5%

Once-Daily Degludec<sup>a</sup> vs Once-Daily Glargine With Mealtime Aspart in T2DM: 1-Year Data<sup>b</sup>

BL A1C: 8.3%
ΔA1C: -1.2% -1.3%
P = NS

Patients Attaining A1C < 7%
Confirmed Overall
Nocturnal

Once-Daily Degludec<sup>a</sup> vs Once-Daily Glargine With Mealtime Aspart in T1DM: 1-Year Data<sup>b</sup>

BL A1C: 7.7%
ΔA1C: -0.4% -0.4%
P = NS

Patients Attaining A1C < 7%
Confirmed Overall
Nocturnal

---

<sup>a</sup> Degludec is currently not FDA approved.
<sup>b</sup> N = 992; all with mealtime aspart and MET ± PIO.
Hypoglycemia, plasma glucose < 56 mg/dL or severe per ADA definition. Hollander PA, et al. Diabetologia. 2011;54 (suppl 1):1035.

<sup>1</sup> Nosek L, et al. AHA 71st Annual Scientific Sessions. 2011; 49-LB.
ILPS, Detemir, and Glargine PK/PD in T2DM


Time (hours)

2 4 6 8 10 12 14 20 22 24

GIR (mg/min/kg)

5
4
3
2
1
0

ILPS (0.8 U/kg; n = 28)
DET (0.8 U/kg; n = 32)
GLAR (0.8 U/kg; n = 29)

Insulin 201: Course Syllabus

• New Insulin Combinations
  - Insulin + DPP-4 inhibitors
  - Insulin + GLP-1 receptor agonists

• Investigational Insulins
  - Investigation basal insulins
  - Investigational prandial insulins

Pharmacokinetics of Rapid-Acting Analogs vs Regular Human Insulin

Rapid-acting analog

Insulin Lispro

Insulin Aspart

Insulin Glulisine


Insulin Glulisine

0 60 120 180 240 300 360

140
120
100
80
40
20
0

Free Serum Insulin, mU/L

20 60

Time (min)

0

0 2 4 6 8 10 12 14 20 22 24

Hyaluronidase Accelerates Insulin Pharmacokinetics

Adding Hyaluronidase To Insulin Accelerates Subcutaneous Insulin Absorption

Hyaluronan

- Naturally occurring space-filling gel-like substance
- Major component of normal soft connective tissue such as skin

Hyaluronidase

- A naturally occurring enzyme
- Temporarily degrades hyaluronan and facilitates penetration of drugs at the injection site
- Natural and synthetic hyaluronidase formulations are available
- US FDA-approved as adjuvants to increase the dispersion and absorption of injected drugs
- Transient locally acting permeation enhancers

Girish KS, Kemparaju K. Life Sci. 2007;80(21):1921-1943; Drugs@FDA. Hyaluronidase.


Hyaluronidase Accelerates Insulin Pharmacokinetics

Adding Hyaluronidase To Insulin Accelerates Subcutaneous Insulin Absorption

Insulin, μIU/mL

20
60

Time (min)

0 60 120 180 240 300 360

80
70
60
50
40
30
20
10
0

Rapid-acting analog

Regular human insulin

Rapid-onset

Quick peak

Short-duration of action

Low risk of hypoglycemia

Why Do We Need New Insulins?
Characteristics of An Ideal Prandial Insulin

Investigational Very Rapid-Acting Subcutaneous Insulins

<table>
<thead>
<tr>
<th>Insulin</th>
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<th>Clinical Trial Phase</th>
<th>Peak</th>
<th>Effective Duration</th>
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<tbody>
<tr>
<td>Human insulin with hyaluronidase</td>
<td>With meals</td>
<td>2</td>
<td>45-120 min</td>
<td>&lt; 5 h</td>
</tr>
<tr>
<td>Analogue insulin with hyaluronidase</td>
<td>With meals</td>
<td>2</td>
<td>30-90 min</td>
<td>&lt; 5 h</td>
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* None of these insulins are US FDA approved.

Other Investigational Insulins

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<td>Once daily</td>
<td>filed for approval</td>
<td>Yes</td>
<td>&gt; 24?</td>
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<td>Thrice daily</td>
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<td>3</td>
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<td></td>
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Twice-Daily Degludec Plus Aspart vs Twice-Daily Biphasic Aspart in T2DM: Efficacy and Hypoglycemia at 16 Weeks

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Inhaled Prandial Insulin Plus Basal Insulin Glargine vs Biphasic Aspart in T2DM

- 52-week non-inferiority trial
  - IHP (3 X daily, at meals, with basal insulin glargine; n = 323)
  - BIASP (2 X daily, n = 331)
- Similar A1C changes
  - IHP: -0.59%
  - BIASP: -0.71%
- Significantly fewer hypoglycemic events with IHP
  - IHP: 0.43 events per patient-month
  - BIASP: 0.61 events per patient-month
- Significantly less weight gain with IHP (0.9 kg) vs BIASP (2.5 kg; P = .0002)
- Adverse events
  - Withdrawals due to AEs: 9% in IHP group vs 4% in BIASP group (P < .05)
  - More reported cough with IHP (32%) vs BIASP (4%)

BIASP, biphasic insulin aspart; IHP, inhaled prandial insulin.

Insulin 201: Summary

- GLPL-1 RAAs or DPP-4 inhibitors combined with insulin can improve glycemic control, with weight loss or no appreciable weight gain, in patients with T2DM
- Investigational basal insulin analogues have the potential to improve insulin therapy by providing relatively peakless time-action profiles and lower rates of hypoglycemia
- Prandial insulins with more rapid onset and offset than current prandial analogues are in development


QUESTION AND ANSWER