COMPLEMENTARY THERAPIES TO IMPROVE GLUCOSE CONTROL IN TYPE 2 DIABETES:

ROLE OF GLP-1 RECEPTOR AGONISTS AND BASAL INSULIN

Dace Trence
MD, FACE
Director, Diabetes Care Center
Professor, Division of Metabolism
Endocrinology and Nutrition
University of Washington Medical Center
Seattle, Washington

Sam Dagogo-Jack
MD, FRCP
Professor of Medicine & Director
Division of Endocrinology, Diabetes & Metabolism
A. C. Mullins Chair in Translational Research
Director, General Clinical Research Center
Director, Endocrinology Fellowship Training Program
University of Tennessee Health Science Center
Memphis, Tennessee

October 16, 2013
9:15 – 10:45am
Donald E. Stephens Convention Center
9301 Bryn Mawr Avenue
Rosemont, IL 60018
Session 2: Complementary Therapies to Improve Glucose Control in Type 2 Diabetes: Role of GLP-1 Receptor Agonists and Basal Insulin

Learning Objectives
1. Apply strategies to individualized therapy in the treatment of patients with type 2 diabetes
2. Incorporate appropriate strategies for timely initiation, selection, titration, and self-management of basal insulin in patients with type 2 diabetes
3. Describe the similarities and differences between individual GLP-1 receptor agonists
4. Summarize the clinical rationale and evidence for combining GLP-1 receptor agonists with basal insulin so as to address various underlying pathophysiologic components of type 2 diabetes

Faculty

Sam Dagogo-Jack, MD, FRCP
Professor of Medicine & Director
Division of Endocrinology, Diabetes & Metabolism
A. C. Mullins Chair in Translational Research
Director, General Clinical Research Center
Director, Endocrinology Fellowship Training Program
University of Tennessee Health Science Center
Memphis, Tennessee

Samuel Dagogo-Jack, MD is the A. C. Mullins Professor in Translational Research, professor of medicine, and chief of the division of endocrinology, diabetes, and metabolism at the University of Tennessee Health Science Center in Memphis. He also serves as director of the endocrinology fellowship training program and director of the General Clinical Research Center at UTHSC. Dr. Dagogo-Jack graduated from the University of Ibadan Medical School in Nigeria, completed his residency training in internal medicine at the Royal Victoria Infirmary, University of Newcastle, UK, and was certified member of the Royal College of Physicians (UK). He underwent research training at the University of Newcastle, earning the master of science and the doctorate in medicine degrees for his work on epidermal growth factor. Dr. Dagogo-Jack completed postdoctoral fellowship training in endocrinology, diabetes, and metabolism at Washington University School of Medicine in St. Louis, Missouri, where he also served on the faculty for several years. He is ABIM board-certified in internal medicine, endocrinology, diabetes, and metabolism.

Dace Trence, MD, FACE
Director, Diabetes Care Center
Professor, Division of Metabolism, Endocrinology and Nutrition
University of Washington Medical Center
Seattle, Washington

Dace L. Trence, MD, FACE, is currently director of the Diabetes Care Center and associate professor of medicine at the University of Washington Medical Center in Seattle. She is also the University of Washington Endocrine Fellowship Program Director and director of Endocrine Days, a medical education program for endocrinologists practicing in the Pacific Northwest. She currently serves on the American Association of Clinical Endocrinologists Board of Directors, chairing the AACE CME committee. She has been on the editorial boards of several journals, including Clinical Diabetes. She has had articles published in JCEM, JAMA, Diabetes Care, and is a co-author of Optimizing Diabetes Care for the Practitioner. Her current interests include improving educational processes in diabetes self-management and clinical training of health care professionals.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr. Dagogo-Jack has served as a consultant for Merk, Novo Nordisk, and Amylin, and is a research grant recipient of Astrazeneca, Novo Nordisk, and Boehringer Ingelheim.

Dr. Trence has no financial relationships to disclose.
Education Partner Financial Disclosure Statement
The content collaborators at Horizon CME have reported the following:

Brian Lee, PharmD, Elizabeth Wilkerson, CHES, Cara Williams, PharmD and Arianna Sunford, BHA, have 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>BG</td>
<td>Blood glucose</td>
<td>OAD</td>
<td>Oral antidiabetic drug</td>
</tr>
<tr>
<td>EP</td>
<td>Education Partner</td>
<td>PPG</td>
<td>Postprandial glucose</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
<td>T2DM</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>GIP</td>
<td>Glucose-dependent insulinotropic polypeptide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suggested Reading List


SESSION 2
9:15–10:45 AM

Complementary Therapies to Improve Glucose Control in Type 2 Diabetes: Role of GLP-1 Receptor Agonists & Basal Insulin

SPEAKER
Dace Trence, MD, FACE
Sam Dagogo-Jack, MD, FRCP

COMPLEMENTARY THERAPIES TO IMPROVE GLUCOSE CONTROL IN TYPE 2 DIABETES: ROLE OF GLP-1 RECEPTOR AGONISTS & BASAL INSULIN

Rosemont, IL – October 16, 2013

Learning Objectives
- Apply strategies to individualize therapy in the treatment of patients with type 2 diabetes
- Incorporate appropriate strategies for timely initiation, selection, titration, and self-management of basal insulin in patients with type 2 diabetes
- Describe the similarities and differences between GLP-1 receptor agonists
- Summarize the clinical rationale and evidence for combining GLP-1 receptor agonists with basal insulin to address the various underlying pathophysiologic components of type 2 diabetes

Drug List

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>US Trade Name</th>
<th>Generic Drug Name</th>
<th>US Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>alogliptin</td>
<td>Nesina</td>
<td>insulin aspart</td>
<td>Novolog</td>
</tr>
<tr>
<td>amlodipine</td>
<td>Norvasc</td>
<td>insulin lispro</td>
<td>Humalog</td>
</tr>
<tr>
<td>atenolol</td>
<td>Tenormin</td>
<td>linagliptin</td>
<td>Tradjenta</td>
</tr>
<tr>
<td>bromocriptine</td>
<td>Parlodel, Cycloset</td>
<td>iragluide</td>
<td>Victoda</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>Invokana</td>
<td>metformin</td>
<td>Glucophage</td>
</tr>
<tr>
<td>saxagliptin</td>
<td>Onglyza</td>
<td>metformin</td>
<td>Glucophage</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
<td>pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td>saxagliptin</td>
<td>Onglyza</td>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>saxagliptin</td>
<td>Onglyza</td>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
</tbody>
</table>

Type 2 Diabetes Epidemiology
The Diabetes Epidemic: 2012
Global Prevalence


World 371 Million 8.3% Prevalence
N. America & Caribbean 38 M 10.5% Prevalence
M = Millions
South & Central America 26 M 4.3% Prevalence
Europe 26 M 6.7% Prevalence
Middle East & N. Africa 34 M 10.9% Prevalence
Africa 132 M 4.3% Prevalence
SE Asia 15 M 8.7% Prevalence
Western Pacific 259 M 8.0% Prevalence

Type 2 Diabetes Pathophysiology

Pathophysiologic Progression of T2DM Vascular Complications

Pathophysiologic Defects of T2DM

The Incretin System: A Regulator of Glucose Metabolism

A1C Goal Setting
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

- Glycemic targets
  - HbA1c < 7.0% (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)

- Individualization is key:
  - Tighter targets (6.0 - 6.5%) - younger, healthier
  - Looser targets (7.5 - 8.0%)+ - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT/EDIC1</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>UKPDS2,3</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD4,5</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ADVANCE6</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VADT7</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials


Type 2 Diabetes Treatment Options

**Primary Sites of Action of Therapeutic Options for T2DM**

- Liver: Glucose Production
  - Metformin1
  - T2Dα
  - SGLT2 (Canagliflozin)
- Pancreas
  - Alpha Cell: Glucagon Secretion
    - GLP-1 Agonists2,6
    - Pramlintide2
  - Beta Cell: Insulin Secretion
    - Sulfonylurias1,2
    - GLP-1 Agonists2,6
- Intestine: Digestion & Absorption
  - GLP-1 Agonists2,6
  - DPP-4 Inhibitors2,3
  - SGLT2 Inhibitors
  - Pramlintide2
- Kidney: Glucosuria
  - Sodium/glucose co-transporter-2 (SGLT-2) inhibitors
    - Canagliflozin
- Brain: Appetite/Metabolic Regulation
  - GLP-1 Agonists2,6
  - Pramlintide2
  - Bromocriptine5
- Muscles & Adipose Tissue: Insulin Resistance
  - Metformin1
  - T2Dα
  - SGLT2 (Canagliflozin)
  - GLP-1 Agonists2,6

Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors

- Canagliflozin
  - SGLT2 inhibition leads to glucosuria in kidneys
  - Works independent of insulin
  - A1C reduction 0.7-1.0%
  - Dosed once daily from 100 mg to 300 mg
  - Contraindicated if CKD (GFR < 45)
  - Causes a small dose-dependent diuretic effect
  - Weight loss from glycosuria (3-4% of body weight)
  - Adverse effects include:
    - Urinary frequency, Candida infections, and UTIs

Leveraging the Incretin Effect –
The Therapeutic Potential of GLP-1 and GIP

GLP-1 Actions on the Alpha and Beta Cells Are 'Glucose-Dependent' in Type 2 Diabetes

Data are mean ± SE.  *P < 0.05

Incretin-Based Therapy for Diabetes
GLP-1 Agonists and DPP-4 Inhibitors

GLP-1 Agonists
- A1C reduction ~0.8%-1.5%
- Significant and sustained weight loss
- Potential GI side effects
- Low rates of hypoglycemia
- ? Improved CV risk factors – lipids, blood pressure, hs CRP, others
- Multiple mechanisms of action
  - ↑ insulin secretion, ↓ glucagon release
  - ↓ food intake, slows gastric emptying
- Injected therapy
- Potential GI side effects
- Low rates of hypoglycemia
- ? Improved CV risk factors – lipids, blood pressure, hs CRP, others
- Multiple mechanisms of action
  - ↑ insulin secretion, ↓ glucagon release
  - ↓ food intake, slows gastric emptying
- Expensive
- Injectable
- Modest A1c efficacy
- Urticaria/angioedema
- May be associated with pancreatitis
- Expensive

DPP-4 Inhibitors
- Gastrointestinal side effects (nausea, vomiting)
- May be associated with pancreatitis
- C-cell hyperplasia/medullary thyroid tumors in rodents
- May be associated with renal insufficiency
- Expensive
- Injectable
- Modest A1c efficacy
- Urticaria/angioedema
- May be associated with pancreatitis
- Expensive

Incretin-based Therapies
Disadvantages/Risks

GLP-1 Receptor Agonists

GLP-1 Agonists
- A1C Reduction
- Elimination Half-life
- Duration of Action
- Comments

Exenatide ~1.0% 2.4 h Short • Avoid use in severe renal dysfunction • Twice daily injection
Linagliptin 1.0-1.5% 13 h Long • Do not use in patients with personal or family history of medullary thyroid cancer • Once daily injection
Exenatide QW 1.0-1.5% 2.4 h Long • Once weekly injection
Linagliptin* ~1.0% 2.4 h Short • Submitted for FDA approval, but file was pulled recently because company wanted to wait for completion of CV study. • Once daily injection
Albiglutide* 1.0-1.5% 6-7 d Long • Submitted for FDA approval • Once weekly injection

*Not FDA approved


GLP-1 Actions on the Alpha and Beta Cells Are ‘Glucose-Dependent’ in Type 2 Diabetes

Data are mean ± SE.  *P<0.05
**Type 2 Diabetes Antihyperglycemic Therapy: General Recommendations**

Consider initial insulin therapy when A1C >10-12%

<table>
<thead>
<tr>
<th>Two drug</th>
<th>Three drug</th>
<th>Dulaglutide</th>
<th>Liraglutide</th>
<th>GLP-1 agonists</th>
<th>GLP-1 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Sulfonylurea</td>
<td>Metformin + Thiazolidinedione</td>
<td>Metformin + DPP-4 inhibitor</td>
<td>Metformin + GLP-1 receptor</td>
<td>Metformin + GLP-1 agonist</td>
<td></td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents


**Starting Insulin**

**Glucose Effect of Short- vs. Long-acting GLP-1 Receptor Agonists**

<table>
<thead>
<tr>
<th>LIRA Baseline</th>
<th>EXN Baseline</th>
<th>EXN Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIRA reduced mean A1C significantly more than EXN, p&lt;0.001</td>
<td>EXN reduced PPG significantly more after breakfast and dinner than LIRA, p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Impact of Exenatide BID Therapy Over 3 Years: Effect on A1c and Body Weight**

Change in A1c (%) and Change in Body Weight (kg)

% Achieving A1c reduction 15-20% in food intake

N = 217, Mean ± SE


**Type 2 Diabetes and Need for Insulin**

UKPDS: at 6 years, more than 50% of patients need insulin to reach target (FPG ≤6.0 mmol/L)

FPG=fasting plasma glucose


**Glucose Effect of Short- vs. Long-acting GLP-1 Receptor Agonists**

<table>
<thead>
<tr>
<th>LIRA Baseline</th>
<th>EXN Baseline</th>
<th>EXN Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIRA reduced mean A1C significantly more than EXN, p&lt;0.001</td>
<td>EXN reduced PPG significantly more after breakfast and dinner than LIRA, p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Impact of Exenatide BID Therapy Over 3 Years: Effect on A1c and Body Weight**

<table>
<thead>
<tr>
<th>Change in A1c (%)</th>
<th>Change in Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Achieving A1c reduction 15-20% in food intake</td>
<td>N = 217, Mean ± SE</td>
</tr>
</tbody>
</table>


**Type 2 Diabetes and Need for Insulin**

UKPDS: at 6 years, more than 50% of patients need insulin to reach target (FPG ≤6.0 mmol/L)

FPG=fasting plasma glucose

Risk of Hypoglycemia Increases as Therapy Intensifies

For all therapies, the significance of differences between levels is \( p < 0.0001 \)

Percentage of patients reporting \( \geq 1 \) hypoglycaemic event per year

- SU=sulfonylurea


Effect of Basal Insulin on HbA\(_{1c}\), Weight, and Hypoglycemia

Pharmacokinetic Profiles of Human Insulins and Analogs

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset</th>
<th>Peak, h</th>
<th>Duration of Action, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro, aspart, glulisine</td>
<td>10-15 min</td>
<td>0.5-1.5</td>
<td>2-4</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human insulin</td>
<td>30-60 min</td>
<td>2-3</td>
<td>3-6</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human NPH insulin</td>
<td>2-4 h</td>
<td>4-10</td>
<td>10-16</td>
</tr>
<tr>
<td>Long-acting (basal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1-2 h</td>
<td>No pronounced peak</td>
<td>24</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1-2 h</td>
<td>Relatively flat</td>
<td>Up to 24</td>
</tr>
<tr>
<td>Ultra long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin degludec*</td>
<td>30-90 min</td>
<td>No peak</td>
<td>&gt; 42</td>
</tr>
</tbody>
</table>

*FDA declined to approve the NDA application in its current form on February 11, 2013.


Strategies for Insulin Selection

- Convenience (once daily vs. twice or three times daily)
- Proven safety
  - Analogs – ORIGIN study showed low hypoglycemic risk, no adverse CV effects, and no cancer risk
  - NPH – a little more hypoglycemic risk than analogs
- Cost
  - NPH $*
  - Analogs $$- $$$
- Insurance coverage
  - Analogs – coverage varies and may require prior authorization

Insulin glargine was associated with 41% risk reduction in hypoglycemia, \( p<0.003 \)

### Sequential Insulin Strategies in T2DM

<table>
<thead>
<tr>
<th>Non-insulin regimens</th>
<th>Number of Regimen injections</th>
<th>Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin only</td>
<td>1</td>
<td>low</td>
</tr>
<tr>
<td>Basal + 1 (meal-time) rapid-acting insulin injection</td>
<td>2</td>
<td>mod.</td>
</tr>
<tr>
<td>Basal insulin + ≥ 2 (meal-time) rapid-acting insulin injection</td>
<td>3+</td>
<td>high</td>
</tr>
</tbody>
</table>

**Flexibility**
- more flexible
- less flexible

### Patient Barriers to Insulin Initiation

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Addressing the Barriers</th>
</tr>
</thead>
</table>
| Sense of failure          | * Insulin is an inevitable step
* Discuss with patients early in the disease about insulin
* Do not use insulin as threat, but as solution                                      |
| Insulin causes complications | * Acknowledge the patient’s fear
* Provide information about the provider’s experiences of the effectiveness of insulin. |
| Loss of independence      | * Empower patient to take control of BG
* Provide self-management education
* Use insulin pens and insulin regimens that offer maximum flexibility               |
| Insulin ineffectiveness   | * Give "limited" trial with appropriate insulin doses
* Monitor for symptom improvement (nocturia, energy level, etc.)                      |

### When To Start Insulin in T2DM

- When combination oral/injectable agents become inadequate
- Unacceptable side effects of other agents
- Patient with advanced hepatic or renal disease
- Special circumstances (e.g., steroids, infection, pregnancy)
- Patient with hyperglycemia in the hospital
- “Severely” uncontrolled diabetes*

*Defined as fasting glucose > 250 mg/dl, random glucose > 300 mg/dl, A1C > 10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) by ADA 2009 Consensus Statement. After glucose controlled, oral agents can be added and insulin withdrawn if preferred.

### Summary of Comparative Insulin Trials

- Any insulin will lower glucose and A1C; the more injections and the higher the dose, the better the control.
- All insulin use results in weight gain and increases the risk of hypoglycemia.
- Generally, insulin analogs reduce the incidence of hypoglycemia over human insulins - but generally do not result in better overall glycemic control.
- Insulin strategies that include prandial dosing (e.g., basal-bolus; premixed) will generally reduce A1c to a greater extent than basal-only, but at the expense of more weight gain, hypoglycemia.

---

**Advancing Basal Insulin**

---

### Patient Barriers to Insulin Initiation

**Barriers**

- Fear of injections
- Fear of hypoglycemia
- Weight gain
- Cost

**Addressing the Barriers**

- * Insulin needles are small (nano-needles)
* Less painful than finger sticks for BG testing
* Have patient give a low dose insulin injection in office
* Insulin pen is less threatening.
- * Incidence is low, especially with basal analogs
* Teach patient to recognize and treat (Rule of 15)
- * Meet with dietitian before initiation of insulin
* More physiologic insulin delivery may minimize weight gain
* Minimize with metformin and GLP-1 receptor agonists
- * Insulin is typically less expensive than using multiple oral medications
* Use premix insulins or less expensive insulins

---


---

**Patient Barriers to Insulin Initiation**

**Barriers**

- Sense of failure
- Insulin causes complications
- Loss of independence
- Insulin ineffectiveness

**Addressing the Barriers**

- * Insulin is an inevitable step
* Discuss with patients early in the disease about insulin
* Do not use insulin as threat, but as solution
- * Acknowledge the patient’s fear
* Provide information about the provider’s experiences of the effectiveness of insulin.
- * Empower patient to take control of BG
* Provide self-management education
* Use insulin pens and insulin regimens that offer maximum flexibility
- * Give “limited” trial with appropriate insulin doses
* Monitor for symptom improvement (nocturia, energy level, etc.)
A Recommendation for Starting and Adjusting Basal Insulin

Bedtime or morning long-acting insulin
OR
Bedtime intermediate-acting insulin

Daily dose: 0.1-0.2 u/kg

Increase dose by 2 units every 3 days until FPG is 70-130 mg/dL.
If FPG is >180 mg/L, increase dose by 4 units every 3 days.

In the event of hypoglycemia or FPG level <70 mg/dL:
Reduce bedtime insulin dose by 4 units, or by 10% if >40 units.

Check FBG daily
Continue regimen and check A1C every 3 months

FBG=fasting blood glucose
FPG=fasting plasma glucose


Patient vs. Physician Adjusted Basal Insulin

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Baseline</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Adjusted</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Physician Adjusted</td>
<td>8.9</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Hypoglycemia

<table>
<thead>
<tr>
<th>Incidence of (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Patient Adjusted</td>
</tr>
<tr>
<td>Physician Adjusted</td>
</tr>
</tbody>
</table>

Severe Symptomatic Nocturnal

When is Basal Alone Not Enough?

When A1C values are still not at target
AND...

- Basal insulin dose titrated to 0.4-0.6 units/kg/day
- Fasting BG levels at or approaching target
- Post-prandial BG values remain above target

BG=blood glucose

Mimicking Physiologic Insulin Secretion: “Basal-Bolus” Insulin Therapy

Endogenous Insulin
- Basal Insulin
- Bolus Insulin

Premixed (Biphasic) Insulin Analogs

- Premixed insulins
  - Humalog 75/25, 50/50 – Intermediate + rapid-acting
  - Novolog 70/30 – Intermediate + rapid-acting
  - Humulin 70/30 – Intermediate + short-acting
  - Novolin 70/30 – Intermediate + short-acting
- Premixed insulin may be appropriate
  - When basal/bolus cannot be used
  - For those with regular lifestyles, who eat similar amounts at similar times each day (similar total calories and similar content for carbohydrate/fat/protein)
  - Those who wish only 2 injections/day

BF = breakfast; D = dinner; hs = at bedtime; L = lunch.

How to Intensify Using the Basal Plus Approach

- Choose the "target" meal to initiate prandial coverage
  - Breakfast or the largest meal of the day
- Start 4-6 units of a rapid-acting insulin analog 10-15 minutes before the meal
- Adjust prandial insulin dose based on
  - 2-h PPG \rightarrow target < 180 mg/dL
  - OR
  - Next pre-prandial or HS BG \rightarrow target < 130 mg/dL
- If A1C remains above target add 2\textsuperscript{nd} prandial dose
  - Usually need about 8-12 units of prandial insulin to cover meal(s)

Summary

- Identify appropriate candidates for intensive diabetes management
- Address barriers to treatment intensification
- Make use of multidisciplinary approach to diabetes management
- Start and optimize basal insulin
  - Involve patient in insulin dose adjustments
- Intensify by adding prandial coverage in a simplified manner

Heine RJ. Ann Intern Med. 2005;143:559-569.

What Do We Know About the Relative Benefits of GLP-1 Agonists vs. Basal Insulin?

**Glucose Effect of Short-acting GLP-1 Receptor Agonist Compared to Basal Insulin**

**Long-acting GLP-1 RA vs. Basal Insulin LEAD-5 Study**

*Significant vs. Glargine (p<0.0001) and placebo (p<0.0001); Mean±2SE

What Do We Know About Combining GLP-1 Receptor Agonists and Basal Insulin?

Potential Benefits of Combining GLP-1-based Therapies with Insulin

GLP-1-based therapies
- Insulin secretion (glucose-dependent)
- Beta-cell preservation
- Glucagon secretion (glucose-dependent)
- Risk of hypoglycaemia
- Body weight
- PPG levels
- Energy intake
- Satiety
- GI tract motility

Basal insulin therapy
- Insulin levels (insulin supplementation)
- Beta-cell rest
- Corrects glucotoxicity
- Relies on endogenous prandial insulin response
- Moderate risk of hypoglycaemia
- Weight gain
- FPG levels

GLP-=glucagon-like peptide-1; GI=gastrointestinal.

Exenatide BID Added to Basal Insulin
Effect on HbA1c and PPG

Adults with T2DM and HbA1c = 7.1% to 10.5% receiving glargine ± metformin ± pioglitazone were randomized to exenatide (10 mcg twice a day) or placebo for 30 weeks.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PB O</th>
<th>EXN BID</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Change</td>
<td>1.0</td>
<td>-1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>1.2</td>
<td>1.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Discontinuation due to Adverse Events</td>
<td>1</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*only 1 reported event of major hypoglycaemia (PBO group)

Exenatide BID Added to Basal Insulin
Effect on Insulin Dose and Weight

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IN Dose U/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine + PBO (n=123)</td>
<td>6</td>
</tr>
<tr>
<td>Glargine + EXN (n=138)</td>
<td>8</td>
</tr>
</tbody>
</table>

Baseline insulin doses = 49.5 and 47 U/day in EXN BID and PBO groups, respectively. Respective changes = 13 and 20 U/day.

Exenatide BID Added to Basal Insulin
Effect on HbA1c and PPG

Adults with T2DM and HbA1c = 7.1% to 10.5% receiving glargine ± metformin ± pioglitazone were randomized to exenatide (10 mcg twice a day) or placebo for 30 weeks.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GLP-1</th>
<th>Basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Change</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Discontinuation due to Adverse Events</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

*only 1 reported event of major hypoglycaemia (PBO group)

Liraglutide with Basal Insulin Improves Glycemic Control with Less Weight Gain in T2DM over 38 Weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PB O</th>
<th>Lira BID</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Change</td>
<td>13</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>1.2</td>
<td>1.4</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Minor hypoglycaemia (EPY)*

EPY = events/patient-year

*No major hypoglycaemia in any group during weeks 12-38. Transient nausea in 21% during weeks 0-12, 4% during weeks 12-38.
Lixisenatide* Combined with Basal Insulin in T2DM over 24 Weeks

![Graph showing efficacy and 2-hour PPG changes](image)

*Not FDA approved, currently under review. PPG=postprandial glucose; SU=sulfonylurea.


### Efficacy

- Change in HbA1c (%)
  - Lixisenatide + Insulin + SU (n = 153)
  - Placebo + Insulin + SU (n = 157)
  - P < 0.0001

- Change in Weight from Baseline (kg)
  - With SU: 0.38
  - Without SU: 0.06

- Nausea (%)
  - Lixisenatide: 39.6
  - Placebo: 4.5

- 2-hour PPG (LS Mean Change (mmol/L))
  - With SU: -7.96
  - Without SU: -8.0
  - P < 0.0001

### Hypoglycemia (Events/pt-yr)

- With SU: 3.54
- Without SU: 1.48

### Key Points

- Combining basal insulin and GLP-1 receptor agonists offers an effective alternative to managing both post-prandial and fasting glucose.
- Majority of clinical experience thus far is with short-acting exenatide.
- Less weight gain observed with combination.
- Lower insulin requirements.
- Significant A1c reduction with minimal increase in hypoglycemia.

### Conclusions

- Type 2 diabetes is marked by progressive beta cell dysfunction and need for progressive therapy.
- GLP-1 agonists offer opportunities for intervention at multiple points in the progression of therapy.
- GLP-1 agonists may have potential advantages over basal insulin as the first injectable added to oral agents.
- Clinicians should initiate basal insulin early in the course of type 2 diabetes when significant hyperglycemia persists or if patient fails to reach the target A1c on other therapies.
- More experience in combining GLP-1 agonists and basal insulin is needed to fully characterize benefits.

### Patient Cases

#### Case 1

- A 54 y.o. woman presents for routine yearly follow-up without specific complaints. She was diagnosed with type 2 DM 9 years ago on a routine annual visit. Her initial A1c was 7.5%.
- She was initially treated with metformin in addition to receiving diabetes education, starting regular exercise and adjusting her diet. HbA1c dropped to 6.6%.
- However, 5 years later her A1c rose to 7.7% and glimepiride was added.

#### Case 1 Continued

- Medical Problems:
  - Type 2 Diabetes
  - Hypertension
  - Hyperlipidemia
  - Postmenopausal
- Medications:
  - Metformin 1000 mg bid
  - Glimepiride 4 mg qd
  - Lisinopril 10 mg qd
  - Simvastatin 20 mg qd
**Case 1 Continued**

- **Social:** Bank officer, married, mother of 3
- **Habits:** non-smoker, exercises 30+ minutes 3-4 days weekly. She is committed to losing weight and has been working with the dietitian recently.
- **PE:**
  - BP = 136/82    Wt = 189 lbs  (BMI = 31.4)
  - Normal exam including fundi and neurological
- **Labs:**
  - Creatinine = 0.95 mg/dl    Electrolytes normal
  - Liver enzymes normal    LDL = 79
  - HbA1c = 8.0 %

**Case 2**

- **A 66 y.o. man was diagnosed with type 2 DM 12 years ago**
- **Medical Problems:**
  - Hypertension
  - Hyperlipidemia
  - CAD (previous CABG)
- **Medications:**
  - Metformin 1000 mg bid
  - Glargine 45 units HS
  - Lisinopril 20 mg
  - Simvastatin 20 mg qd
  - Glipizide 10 mg bid
  - ASA 162 mg qd
  - HCTZ 25 mg qd
  - Atenolol 50 mg qd

**Case 2 Continued**

- **Social:** Married, retired
- **Habits:** nonsmoking; Tries to walk at least 30 minutes 5 times weekly.
- **PE:**
  - BP = 131/82    Wt = 224 lbs  (BMI = 32.4)
  - Decreased vibratory sensation and monofilament
- **Labs:**
  - LDL = 98 mg/dl    HDL = 35    Creatinine = 1.33 mg/dl
  - HbA1c = 8.1 %

**THANK YOU!**