This presentation will:

• Explain the pathophysiological aspects of T2DM, and how defects can be addressed with injectable therapies.

• Outline incretin-based injectable therapies for T2DM and obesity management and discuss evidence from clinical trials.

• Describe established and newly available insulin therapies for treatment of T2DM.

• Describe how to intensify insulin regimens to achieve glycemic targets.
Injectable Therapies for T2DM and Obesity

GLP-1 RA

Insulin

GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.
IN testinal SeCRETion of INsulin
INCRETIN
The Incretin Effect in Healthy Subjects


Plasma Glucose (mg/dL)

- Oral Glucose
- Intravenous (IV) Glucose

n = 6; mean (SE); *P≤0.05
The Incretin Effect

Control subjects (n=8)

Type 2 diabetes (n=14)

GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Beta-cells: Enhances glucose-dependent insulin secretion

Brain promotes satiety and reduces appetite

Alpha cells: ↓ Glucose-dependent postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

GLP-1 = glucagon-like peptide-1.

Metabolism of GLP-1 and GIP

Dipeptidyl Peptidase-4 (DPP-4)
- Ubiquitous, specific protease
- Cleaves N-terminal dipeptide
- Inactivates > 50% of GLP-1 in ~1 min
  > 50% of GIP in ~7 min

Active hormones
GLP-1 [7-36NH₂]
GIP [1-42]

Inactive metabolites
GLP-1 [9-36NH₂]
GIP [3-42]

DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotrophic peptide; GLP-1 = glucagon-like peptide-1.
GLP-1 RA Increases Active Incretin Levels

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Umpierrez et al. Endocrine Practice 2014
GLP-1 Receptor Agonists

- Exenatide BID (twice daily)
- Liraglutide (once daily)
- Exenatide ER (weekly)
- Albiglutide (weekly)
- Dulaglutide (weekly)
- Lixisenatide (once daily)

BID = twice daily; ER = extended release; GLP-1 = glucagon-like peptide-1.
# Marketed GLP-1 RAs

<table>
<thead>
<tr>
<th></th>
<th>Exenatide BID</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Byetta®</td>
<td>Victoza®</td>
<td>Bydureon®</td>
<td>Tanzeum™ (US)</td>
<td>Trulicity®</td>
<td>Adlyxin™ (US)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eperzan (EU)</td>
<td></td>
<td>Lyxumia (EU)</td>
</tr>
<tr>
<td>Description</td>
<td>Synthetic exendin-4, a peptide identified in H. suspectum that activates GLP-1 and is resistant to DPP-4 degradation</td>
<td>GLP-1 modified&lt;sup&gt;a&lt;/sup&gt; to be resistant to DPP-4 degradation</td>
<td>Exenatide contained in a hydrolyzable polymer microspheres for extended release</td>
<td>An albumin fusion protein made of 2 copies of modified human GLP-1</td>
<td>A fusion protein with 2 disulfide-linked human GLP-1 analog sequence chains, connected by a small peptide linker to human immunoglobulin G4 (IGG4)</td>
<td>A peptide containing 44 amino acids, amidated at the C-terminal amino acid (position 44)</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.4 hours</td>
<td>13 hours</td>
<td>&gt; 1 week</td>
<td>5 days</td>
<td>5 days</td>
<td>3 hours</td>
</tr>
<tr>
<td>Dosing</td>
<td>2X daily, before meals</td>
<td>1X daily, any time</td>
<td>1X weekly</td>
<td>1X weekly</td>
<td>1X weekly</td>
<td>1X daily, before 1st meal</td>
</tr>
</tbody>
</table>

<sup>a</sup> Amino acid substitution and addition of acyl chain.

**BID** = twice daily; **DPP-4** = dipeptidyl peptidase-4; **ER** = extended release; **E.U.** = European Union; **GLP-1** = glucagon-like peptide-1; **IGG4** = human immunoglobulin; **U.S.** = United States.
Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)

- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
  - Binds to known human GLP-1 receptors on β cells *in vitro*
  - Resistant to DPP-4 inactivation
- Administered twice daily

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Exenatide ER

- 2 mg SC every 7 days, with or without food
- Reconstituted w/ diluent; 23G x 5/16” needle
- Microsphere release; steady state: 6-7 wks
- A1C reduction vs BID exenatide: ~0.7%
- No GLP1 Rx is recommended as first-line Rx
- Add on to MET, SU, TZD, or combination
- Less nausea vs exenatide BID
- ↑ weight loss vs exenatide BID: 3.53 lbs vs 1.98 lbs at 24 wks

A1C = glycated hemoglobin; BID = twice daily; ER = extended release; lbs = pounds; MET = metformin; Rx = prescription; SC = subcutaneously; SU = sulfonylurea; TZD = thiazolidinedione.

Liraglutide

• Injected SC once-daily
• Acylated GLP-1(C-16 fatty acid, palmitic acid, on position 26)
• Liraglutide is extensively bound to plasma protein (greater than 98%)
• 97% homology to GLP-1
• Endogenously metabolized without specific organ as major route of elimination

GLP-1 = glucagon-like peptide-1; SC = subcutaneously.

Liraglutide

• Liraglutide: 0.6 mg SC QD x 1 week then 1.2 mg SC QD increase to 1.8 mg SC QD if needed
• Supplied as pen
• Use: 2-3 pens per month

QD = once daily; SC = subcutaneously.

Liraglutide 3mg

• Approved 2010 for treatment of overweight/obesity
• Indications: adults with BMI ≥ 30 or BMI ≥ 27 kg/m² with one CV risk factor: hypertension, type 2 diabetes mellitus, hypercholesterolemia
• Approved with REMS: follow up and registry for MTC, breast cancer, CV safety
• Supplied as 3 mL pen, 6mg/mL (5 pens/mo)
• Dose titration: 0.6mg daily SC x 7 d; 1.2mg daily x 7 d; 1.8mg daily x 7 d; 2.4mg daily x 7 d; 3mg daily maintenance

BMI = body mass index; CV = cardiovascular; MTC = medullary thyroid cancer; REMS = Risk Evaluation and Mitigation Strategies; SC = subcutaneously.
Liraglutide 3mg

• Phase 3
• 56-week trials
• Proportion of patients achieving weight loss:

<table>
<thead>
<tr>
<th></th>
<th>≥ 5%</th>
<th>≥ 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 3mg</td>
<td>62.3</td>
<td>33.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>34.4</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Albiglutide

- 30 mg SC QWK
- Increase to 50 mg SC QWK if needed
- Supplied as single-dose prefilled pen

QWK = every week; SC = subcutaneously.

Albiglutide – Efficacy

• Albiglutide is an GLP-1 agonist
  - Approved by the U.S. FDA on April 15, 2014
• The Harmony program, consisting of 8 phase III studies, evaluated safety and efficacy
  - Albiglutide causes significant reductions in A1C in patients with T2DM when used alone or as add-on therapy with combinations of metformin, pioglitazone, and glimepiride, with decreases from baseline A1C ranging from -0.75% to -0.91%
  - Additionally, albiglutide produced superior A1C control to mealtime insulin lispro at 26 weeks
• Albiglutide use results in moderate weight loss

A1C = glycated hemoglobin; FDA = Food and Drug Administration; GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus.

Dulaglutide

- 0.75 mg SC QWK
- Increase to 1.5 mg SC QWK if needed
- Supplied as single-dose prefilled pen or prefilled syringe

QWK = every week; SC = subcutaneously.

Dulaglutide – Efficacy

• Dulaglutide is a GLP-1 agonist
  - Approved by the U.S. FDA on September 18, 2014
• Six phase III clinical trials evaluated the safety and efficacy of dulaglutide as monotherapy or in combination with other diabetes medications
  - Dulaglutide causes significant reductions in A1C in patients with T2DM when used alone or as an add-on therapy with metformin, metformin + sulfonylurea, and metformin + thiazolidinedione
  - Additionally, dulaglutide produced superior A1C control to insulin glargine at 26 weeks
• Dulaglutide use results in moderate weight loss; up to 3.1% of body weight

A1C = glycated hemoglobin; FDA = Food and Drug Administration; GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus.

Semaglutide

• Not FDA approved as of 11/2016
• Under investigation in the SUSTAIN phase 3 clinical trial program
• Long-acting GLP-1, once-weekly dosing
• Structurally similar to liraglutide

FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; SC = subcutaneously; SUSTAIN = Trial To Evaluate Outcomes with Semaglutide in Subjects with Type 2 Diabetes.
**Semaglutide – Efficacy**

- **Semaglutide** is a long-acting GLP-1 agonist
  - Not approved by the FDA as of 11/2016

- **Six phase III clinical trials (the SUSTAIN phase III clinical trial program)** examined semaglutide for safety and efficacy
  - Semaglutide causes significant reductions in A1C in patients with T2DM compared to sitagliptin, exenatide ER, and insulin glargine
  - Semaglutide reduced the risk of major CV events by 26% compared to placebo in patients with T2DM at high CV risk
  - In SUSTAIN 6, A1C was significantly lower in the semaglutide vs placebo group
  - Results confirmed semaglutide noninferiority

- **Semaglutide** use results in moderate weight loss; up to 5.3% of body weight

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A1C = glycated hemoglobin; ER = extended release; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; SUSTAIN = Trial To Evaluate Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM = type 2 diabetes mellitus.

Safety: Nausea

• Most frequent adverse effect of GLP-1 RAs is nausea, which occurs in up to one-third of patients and is usually self-limiting, although some patients cannot tolerate these agents.
• Nausea may be diminished by avoiding overeating and slowing the titration.
• Administering exenatide BID closer to mealtime can also decrease nausea.

BID = twice daily; GLP-1 RA = glucagon-like peptide-1 receptor agonist.
Safety: Medullary Thyroid Cancer Risk

- All GLP-1 RAs are contraindicated in patients with a personal or family history of MTC or MEN2 because of the occurrence of c-cell tumors in rodents.
- The c-cell tumor risk in humans is unknown, because human relevance could not be determined in clinical trials.
- The value of routine calcitonin and/or ultrasound monitoring is uncertain.
- Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist.
- To monitor potential associations, report MTC to state cancer registry, regardless of treatment.

GLP-1 RA = glucagon-like peptide-1 receptor agonist; MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer.

Safety: Renal Impairment

• Renal impairment affects the clearance of exenatide BID & ER, but not that of liraglutide, albiglutide or dulaglutide.

• Hypovolemia due to nausea and vomiting may worsen renal function.

• Renal impairment with GLP-1 RAs has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration.

BID = twice daily; ER = extended release; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Safety: Pancreatitis

- Pancreatitis has been reported with all incretin-based therapies, although no causal relationship has been established.
- Patients should know signs and symptoms of pancreatitis and stop taking incretin-based therapies if signs and symptoms occur.
- If pancreatitis is confirmed, therapy should not be restarted.

Type 2 Diabetes and Pancreatitis Risk

- 2.8-fold increased risk of pancreatitis among patients with type 2 diabetes

Incidence per 100,000 patient-years

Summary: GLP-1 Receptor Agonists

- Good glycemic efficacy, glucose-dependent action
- Complement the actions of oral antihyperglycemic agents
- Can be used as monotherapy if MET is contraindicated and in combination with other oral agents and/or insulin
- Favorable weight effects and low hypoglycemic risk
- Consider patient risk factors and educate patients about potential risks and/or adverse effects (eg, nausea, history of thyroid tumors, pancreatitis)
  - No increased risk of pancreatitis relative to other antihyperglycemic agents
  - Potential for gastrointestinal side effects
  - Cardioprotective (LEADER trial)

GLP-1 = glucagon-like peptide-1; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; MET = metformin.
Antihyperglycemic Monotherapy
Maximum Therapeutic Effect, Dependent Upon Initial A1C

A1C = glycated hemoglobin; GITS = gastrointestinal therapeutic system.

When To Start Insulin in T2DM

- When combination oral/injectable agents become inadequate
- Unacceptable side effects of oral/injectable agents
- Patient wants more flexibility
- Special circumstances (i.e. steroid use, infection, pregnancy)
- Patients with hepatic or renal disease,
- Patients with CAD, $\uparrow$ TG

CAD = coronary artery disease; T2DM = type 2 diabetes mellitus; TG = triglycerides.

Current Basal Insulins

- **Human insulins (intermediate-acting)**: U-100 NPH
- **Analogues (long-acting)**:
  - U-100 glargine
  - U-100 detemir
  - U-100 biosimilar glargine
- **Analogues (ultra-long-acting)**:
  - U-300 glargine
  - U-100 degludec
  - U-200 degludec

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**Blue boxes indicate FDA Approval**

- Approved by the US FDA in December, 2016.
- Approved by the US FDA in September 2015.
- Not currently approved by the US FDA.

**FDA** = U.S. Food and Drug Administration; **NPH** = neutral protamine hagedorn.
Insulin Therapy in Type 2 Diabetes: Current Strategies

- **Basal insulin therapy**
  - Long-acting insulin analog once daily
  - Intermediate-acting NPH at bedtime

- **Human or analog insulin (prandial or premixed w/ intermediate)**
  - Once daily at largest meal
  - Twice daily (breakfast and dinner)
  - Three times daily (with each meal)

- **Intensive insulin therapy**
  - Basal +
  - Rapid-acting analog insulin
    - Once daily at largest meal
    - Twice daily at meals
    - Three times daily (with each meal)

- **Insulin pump therapy**

NPH = neutral protamine hagedorn.

## Comparison of Available Insulins
(Per Prescribing Information)

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin (R)</td>
<td>30-60 min</td>
<td>2-5 hrs</td>
<td>5-8 hrs</td>
</tr>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin lispro U-200</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>10-20 min</td>
<td>40-50 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>20-30 min</td>
<td>30-90 min</td>
<td>1-2.5 hrs</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 hrs</td>
<td>4-12 hrs</td>
<td>18-24 hrs</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1-1.5 hrs</td>
<td>relatively flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td>6 hrs</td>
<td>flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Biosimilar insulin glargine</td>
<td>6 hrs</td>
<td>relatively flat</td>
<td>Up to 24 hrs</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1-2 hrs</td>
<td>relatively flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insuline degludec</td>
<td>1 hr</td>
<td>3-4 days</td>
<td>up to 42 hours</td>
</tr>
<tr>
<td><strong>Premixed Insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular/NPH insulin 70/30</td>
<td>30 min</td>
<td>2-12 hrs</td>
<td>14-24 hrs</td>
</tr>
<tr>
<td>Lispro protamine 75/25, 50/50</td>
<td>15 min</td>
<td>0.5-2.5 hrs</td>
<td>16-20 hrs</td>
</tr>
<tr>
<td>Biphasic insulin aspart 70/30</td>
<td>10-20 min</td>
<td>1-4 hrs</td>
<td>up to 24 hrs</td>
</tr>
</tbody>
</table>

NPH = neutral protamine hagedorn.
Oral agents plus **Basal** Insulin at Bedtime

- Continue oral agent(s) at same dosage
- Add single, evening BASAL insulin dose (10 U or 0.2/kg)
- Adjust dose by SMBG - goal FBS < 130 mg/dl

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FBS = fasting blood sugar; NPH = neutral protamine hagedorn; SMBG = self-monitoring of blood glucose.
Simple Way to Start Basal Insulin

Bedtime or morning: long-acting insulin OR
Bedtime: intermediate-acting insulin
Daily dose: 10 units or 0.2 units/kg

Check FBG Daily

Increase dose by 2 units every 3 days until FBG is 70–130 mg/dL

If FBG is >180 mg/dL, increase dose by 4 units every 3 days

Continue regimen and check A1C every 3 months

In the event of hypoglycemia or FBG level <70 mg/dL
Reduce bedtime insulin dose by 4 units, or by 10% if >60 units

A1C = glycated hemoglobin; FBG = fasting blood glucose.

When Basal is Not Enough
Optimizing Insulin Therapy For Glycemic Control

Basal insulin titration every 2 – 3 days to reach glycemic goal:
• Add 2 U
or
• FBG > 180 mg/dL: 20%
• FBG 140-180 mg/dL: 10%
• FBG 110-139 mg/dL: add 1 U

Consider prandial coverage if:
• A1C not at goal on total daily basal insulin dose > 0.3 U/kg
Increase prandial insulin when:
• 2h postprandial or next premeal glucose BG consistently 140-180 mg/dL

Lifestyle changes plus metformin
(±1, ±2, ±3 agents)

A1C = glycated hemoglobin; BG = blood glucose; FBG = fasting blood glucose.
Intensify (Prandial Control)

Add GLP-1 RA
Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3
- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 5 units

Basal Bolus
- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- Start: 50% of TDD in three doses before meals

DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT = sodium-dependent glucose cotransporters; TDD = transdermal drug delivery.

New Basal Insulin Formulations

Glargine U-300
Degludec U100 and U 200
High Concentration Glargine (U300)

- U300 insulin glargine offers a smaller depot surface area leading to a reduced rate of absorption
- Provides a flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
- Half-life is ~23 hours
- Steady state in 4 days
- Duration of action ≤36 hours

**U300 Glargine vs U100 Glargine in Type 2 Diabetes**

**Mean change in A1C for both treatment groups**

-0.83%

**No difference in A1C change**

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**Lower rate of severe or confirmed hypoglycemia, particularly overnight**

<table>
<thead>
<tr>
<th>Time period</th>
<th>U100</th>
<th>U300</th>
<th>RR with U300</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>Nocturnal</td>
<td>57.5%</td>
<td>44.6%</td>
<td>0.78</td>
</tr>
<tr>
<td>9 weeks – 6 mo</td>
<td>Nocturnal</td>
<td>46.0%</td>
<td>36.1%</td>
<td>0.79</td>
</tr>
<tr>
<td>0-6 months</td>
<td>24 hours</td>
<td>87.8%</td>
<td>81.9%</td>
<td>0.93</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; CI = confidence interval; LOCF = last observation carried forward; RR = rate ratio.

Insulin Degludec

• desB30 insulin acylated (16 carbon fatty acid chain) at LysB29
• Duration of action > 42 hours
• Half-life ~25 hours
  – Detectable for at least 5 days
• Steady state in 2-3 days
• FDA approved

FDA = U.S. Food and Drug Administration.

Degludec vs Glargine in Type 2 Diabetes

A1C = glycated hemoglobin.

Flexible vs Fixed Degludec Once-Daily Dosing in Adults with T2DM: Efficacy and Hypoglycemia at 26 Weeks

Efficacy

BL A1C: 8.5% 8.4%
-1.3 -1.1

Hypoglycemia

Event Rate (EPY)

Confirmed Overall Nocturnal Severe (episodes)
3.6 3.6 0.6 0.6 2 2

ΔA1C (%)

N = 457; DEG +/- OADs (not specified). FIXED, administered with evening meal daily; FLEX, administered 8-40 hours apart; Hypoglycemia, plasmaglucose < 56 mg/dL or severe per ADA definition.
A1C = glycated hemoglobin; BL = baseline; DEG = insulin degludec; EPY = events per year; OAD = oral anti-diabetic; QD = once daily; T2DM = type 2 diabetes mellitus.

New Insulin and Insulin + GLP-1 Receptor Agonist Combinations: Application and Therapeutic Efficacy

GLP-1 = glucagon-like peptide-1.
Postprandial Hyperglycemia Persists After Basal Therapy

164 patients with baseline A1c ≥7.5% on diet, oral agents, or insulin. Mealtime hyperglycemia persists after 3 months of intensive treatment.

A1C = glycated hemoglobin.

Use of Twice-Daily Exenatide in Basal Insulin-Treated Patients with T2DM

A1C = glycated hemoglobin; BID = twice daily; EXE = exenatide; GLAR = glargine; MET = metformin; PIO = pioglitazone; PBO = placebo; T2DM = type 2 diabetes mellitus.

Insulin Detemir Added to Liraglutide

A1C = glycated hemoglobin; LIRA = liraglutide; MET = metformin.

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

No major hypoglycemia in any group during weeks 12-38. Transient nausea in 21% during weeks 0-12, 4% during weeks 12-38.

A1C = glycated hemoglobin; DET = insulin detemir; EPY = events per year; LIRA = liraglutide; MET = metformin; T2DM = type 2 diabetes mellitus.

Rosenstock J, et al. *Diabetes*. 2011;60(suppl 1):A76 [abstr 276-OR].
Lixisenatide Combined with Basal Insulin Improves Glycemic Control with Less Weight Gain in T2DM Over 24 Weeks

A1C = glycated hemoglobin; INS = insulin; LIXI = lixisenatide; PBO = placebo; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Results reported as available from 7 RCTs and 15 clinical practice or observational studies including at least 30 patients with T2DM. A1C = glycated hemoglobin; GLP-1 RA = glucagon-like peptide-1 receptor agonist; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus.

IDegLira: A Fixed Ratio Combination of Insulin Degludec\(^a\) and Liraglutide

- 1663 T2DM patients on MET ± PIO; 26 week open-label trial
- Patients achieving A1C <7%
  - IDegLira: 81%
  - DEG: 65%
  - LIRA: 60%
- IDegLira vs DEG
  - Weight change: -2.22 kg; \(P < .001\)
  - Hypoglycemia: RR 0.68; \(P < .002\)
- IDegLira vs LIRA
  - Weight change: 2.44 kg; \(P < .001\)
  - Hypoglycemia: RR: 7.6; \(P < .001\)

A1C = glycated hemoglobin; DEG = insulin degludec; FDA = U.S. Food and Drug Administration; LIRA = liraglutide; MET = metformin; PIO = pioglitazone; RR = ratio risk; T2DM = type 2 diabetes mellitus.

\(^a\) IDegLira and insulin degludec are not FDA approved for clinical use.

Lixisenatide + Glargine: A1C

A1C = glycated hemoglobin; FDA = U.S. Food and Drug Administration; LOCF = last observation carried forward.

FDA approved combinations of basal insulin and GLP 1 agonist

• Insulin glargine and lixisenatide (Soliqua)
  • (100 units glargine insulin/ml and 33mcg lixisenatide/ml)

• Insulin degludec and liraglutide (Xultophy)
  • (100 units insulin degludec/ml and 3.6 mg liraglutide/ml)
Key Points: Insulin Initiation

• Diabetes is a progressive disease and many individuals with T2DM eventually need insulin to control their blood glucose.

• There are cultural taboos and misconceptions regarding insulin therapy; it is important to understand and acknowledge patients' specific concerns and design individualized treatment plans that fit their needs.

• Start with a simple regimen, such as a once-daily basal insulin analog, and up-titrate the dose based on FPG; if A1C remains high when FPG is in the target range, add a DPP-4 inhibitor, a GLP-1 RA, or mealtime insulin.

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.

2. Peragallo V. Diabetes Educ. 2007;33:60S–65S.
Summary

- Many patients on basal insulin therapy will ultimately require treatment intensification
- Current options include:
  - Addition of mealtime control via addition of prandial insulin, leading to multiple daily insulin therapy
  - Switch to premix insulin
  - Add a DPP-4 inhibitor or a GLP-1 agonist

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Hypoglycemia: Clinical Consequences

**Acute**
- Symptoms (sweating, irritability, confusion)
- Accidents
- Falls

**Long-term**
- Recurrent hypoglycemia and hypoglycemia unawareness
- Refractory diabetes
- Dementia (elderly)
- Cardiovascular events
  - Cardiac autonomic neuropathy
  - Cardiac ischemia
  - Fatal arrhythmia
  - Angina

Hypoglycemia: Risk Factors

Patient Characteristics

• Older age
• Female gender
• African American ethnicity
• Longer duration of diabetes
• Neuropathy
• Renal impairment
• Previous hypoglycemia

Behavioral & Treatment Factors

• Missed meals
• Elevated A1C
• Insulin or sulfonylurea therapy

A1C = glycated hemoglobin.

The Basal-Bolus Insulin Concept

• **Basal insulin**
  – Controls glucose production between meals and overnight
  – Nearly constant levels
  – 50% of daily needs

• **Bolus insulin (mealtime or prandial)**
  – Limits hyperglycemia after meals
  – Immediate rise and sharp peak at 1-hour postmeal
  – 10% to 20% of total daily insulin requirement at each meal

• **For ideal insulin replacement therapy**, each component should come from a different insulin with a specific profile

Starting Basal/Bolus Therapy

• **Starting insulin dose** is based on weight
  = 0.3-0.5 units/kg

• **Basal dose** (glargine/detemir/NPH)
  = 50% of starting dose at bedtime

• **Bolus dose** (meal dose)
  = 50% of starting dose divided between meals
  (rapid-acting analog or Regular insulin)

NPH = neutral protamine hagedorn.

Reasons Patients Avoid Insulin

- Lack of knowledge
- Cultural taboos and family beliefs
- Fear of needles or injection pain
- Fear of hypoglycemia and/or weight gain
- Inconvenience
- Sense of personal failure
- Diabetes seen as worse or more serious once insulin is initiated
- Fear that insulin causes complications and/or that insulin will impose constant demands on patient

1. Peragallo V. *Diabetes Educ.* 2007;33:60S–65S.
Strategies to Overcome Patient Barriers to Insulin Use

- **Starting insulin** – get help from Certified Diabetes Educators, dietitians, pharmacists; consider group instruction

- **Needle phobia** – show fine needles, pens, demonstrate technique

- **Convenience** – use pens or other devices

- Begin therapy with **simple regimen** – detemir or glargine pen at bedtime

Injectable Therapies for T2DM

Thank You!