Dr. Joseph Pitone
Addressing Unmet Needs in Type 2 Diabetes Management with Injectable Medications

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Professor of Internal Medicine
Philadelphia College of Osteopathic Medicine
Challenge
Metformin although effective has become obsolete

• Does not address core needs as well as other agents (ominous octet)
• Does not address metabolic parameters (blood pressure, Hgb A1C) as well as other agents
• Micro and Macrovascular benefits not as robust as other agents
• Mortality data not as promising as other agents
Not the case with metformin – no mortality benefit

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Metformin Events</th>
<th>Metformin Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% Cl Year</th>
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<td>DeFronzo 1</td>
<td>0</td>
<td>143</td>
<td>0</td>
<td>146</td>
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<td>DeFronzo 2</td>
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<td>UKPDS 34a</td>
<td>50</td>
<td>342</td>
<td>89</td>
<td>411</td>
<td>25.7%</td>
<td>0.68 [0.49, 0.93] 1998</td>
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<tr>
<td>UKPDS 34b</td>
<td>47</td>
<td>268</td>
<td>31</td>
<td>269</td>
<td>20.4%</td>
<td>1.52 [1.00, 2.32] 1998</td>
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<td>Horton</td>
<td>1</td>
<td>178</td>
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<td>172</td>
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<td>Chiasson</td>
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<tr>
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<td>322</td>
<td>1</td>
<td>164</td>
<td>1.3%</td>
<td>1.02 [0.09, 11.15] 2002</td>
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<tr>
<td>Rachmani</td>
<td>62</td>
<td>195</td>
<td>64</td>
<td>198</td>
<td>27.2%</td>
<td>0.98 [0.74, 1.31] 2002</td>
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<tr>
<td>Garber</td>
<td>2</td>
<td>171</td>
<td>0</td>
<td>151</td>
<td>0.8%</td>
<td>4.42 [0.21, 91.32] 2003</td>
</tr>
<tr>
<td>COSMIC</td>
<td>79</td>
<td>7227</td>
<td>20</td>
<td>1505</td>
<td>17.6%</td>
<td>0.82 [0.51, 1.34] 2005</td>
</tr>
<tr>
<td>HOME</td>
<td>9</td>
<td>196</td>
<td>6</td>
<td>194</td>
<td>6.3%</td>
<td>1.48 [0.54, 4.09] 2009</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>9338</td>
<td>3502</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.99 [0.75, 1.31]</td>
</tr>
<tr>
<td>Total events</td>
<td>252</td>
<td></td>
<td>211</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.05; Chi² = 11.92, df = 7 (P = 0.10); I² = 41%
Test for overall effect: Z = 0.06 (P = 0.95)
Lots of other fish in the sea...

- Metformin

- Alpha-glucosidase inhibitor
- Amylin mimetics
- Bile acid sequestrants
- Dopamine-2 agonists
- DPP-4 inhibitors
- GLP-1 receptor agonists
- Insulin
- Insulin secretagogues
- SGLT2 inhibitors
- Thiazolidinediones
Key Knowledge Gaps

Fundamental questions about current therapies:

- Is metformin’s role as foundational therapy evidence-based or a quirk of history?
- Do SGLT2 inhibitors and GLP-1 receptor agonists have a role in primary prevention?
- Are they additive?

Better drugs:

- Glucose responsive insulin and hepatoselective insulin
- Safer/easier insulin sensitizers
Case Presentation

• 62 y/o female T2DM, hypertension, hyperlipidemia. Hx MI,
• T2DM 15 years Rxed metformin 1000 mg daily, linagliptin 5 mg daily, glargine insulin 46 units daily
• Other meds rosuvastatin 20 mg daily, lisinopril 10 mg daily

• Px 130/80 Ext DPN no ret. BMI 32

• Labs A1C 8.4% eGFR 64 cc/min
• Glycemic profile mean 160, lowest 122, highest 242 acb and acd smbg.
• Lipids TC 142 LDL-C 68, HDL-C 46, TG 124,
• Other labs negative
A1C and Mortality in Clinical Practice

Retrospective Cohort Study (N=27,965)

Con’t

• What therapeutic choices?
• 1. uptitrate metformin
• 2. add SU
• 3. substitute GLP-1 for linagliptin
• 4. add SGLT-2 inhibitor
• 5. Increase glargine insulin
• 6. split dose glargine insulin
• 7. begin mealtime insulin
• 8. start patch pump (VGO)
• 9. start insulin pump
• 10. revisit lifestyle modification    assess adherence
GLP-1 Receptor Agonists
# GLP1 Receptor Agonists

## FDA-Approved Agents
- Albiglutide*
- Dulaglutide
- Exenatide
- Exenatide ER
- Liraglutide
- Lixisenatide
- Semiglutide

## Key Features
- Subcutaneous administration
- Mimic action of native GLP1
- Increase glucose-dependent insulin secretion
- Suppress glucagon production
- Slow gastric emptying

---
*ER, extended release; GLP1, glucagon-like peptide 1.
Two classes of agents have been developed based on the therapeutic potential of enhancing GLP-1 activity:\(^1\)

- **GLP-1 receptor agonists**: agents that mimic the actions of GLP-1

- **Protease DPP-4 inhibitors**: agents that prolong the activity of endogenous GLP-1

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

Glucoregulatory Role of GLP-1 and GIP – Effects in Humans

On ingestion of food:
GLP-1 secreted by L-cells, GIP secreted by K-cells

β-cells: enhance glucose-dependent insulin secretion

Liver:
↑ Insulin/glucagon: reduces hepatic glucose output

Stomach:
slows gastric emptying

Promotes satiety and reduces appetite

β-cells:
β-cell workload

α-cells:
↓ Postprandial glucagon secretion

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide
GLP-1 Has a Broad Range of Biological Activity

1. Cardiovascular System
   - ↓ Cardiovascular risk factors
     - Weight
     - Blood pressure
     - Lipid profile

2. Liver
   - ↓ Glucose production

3. Muscle and Adipose Tissue
   - ↑ Glucose uptake

4. Intestine
   - Direct actions

5. Brain
   - ↓ Appetite
   - ↑ Satiety

6. Stomach
   - ↓ Gastric emptying

7. Pancreas
   - ↑ Insulin secretion
   - ↓ Glucagon secretion

Direct actions
Indirect actions

Glucose Reduction

DPP4 Inhibitors, GLP1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin
(Absolute Changes from Baseline; Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Baseline A1C (%)</th>
<th>DPP4 Inhibitors</th>
<th>GLP1 Receptor Agonists</th>
<th>SGLT2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alo¹ Lin² Sax³ Sit⁴</td>
<td>Alb⁶ Dul⁶ Exe⁷ Exe ER⁸ Lit⁹</td>
<td>Can¹⁰ Dap¹¹ Emp¹²</td>
</tr>
<tr>
<td>7.9</td>
<td>8.1</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>7.9</td>
<td>8.1</td>
<td>8.2</td>
<td>8.4</td>
</tr>
<tr>
<td>7.8</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Δ A1C (%)

-0.6  -0.5  -0.7  -0.7  -0.63  -0.8  -1.42  -1.5  -1.5  -0.93  -0.52  -0.77

6-Week Continuous GLP-1 Infusion Increases Satiety and Reduces Food Intake

Sensations of appetite in patients treated with GLP-1

GLP-1=glucagon-like peptide-1; AUC=area under curve
Mean±SE; N=10; Only data of patients treated with GLP-1 shown
Overall p values labeled for each sensation; *Only significant for week 0 vs week 1 after Bonferroni test
Weight Reduction

DPP4 Inhibitors, GLP1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin
(Separate Studies; Not Head-to-Head Trials)

NR, not reported.

# Safety Considerations with GLP1 Receptor Agonists

| GI adverse events | • Common  
|                  | • Usually dose dependent and transient  
|                  | • Usually reduced with dose titration |
| Pancreatitis     | • Pancreatitis has been reported with postmarketing use of some of incretin agents, although no causal relationship has been established  
|                  | • Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents  
|                  | • Labeling for all incretins states these agents should be immediately discontinued if pancreatitis is suspected  
|                  | • Labeling for GLP1 receptor agonists suggests consideration of other therapies for patients with a history of pancreatitis |
| Pancreatic cancer| • Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents  
|                  | • Further assessments required from long duration-controlled studies or epidemiological databases |
| Medullary thyroid cancer | • Animal data showed an increased incidence of C-cell tumors with liraglutide and exenatide ER treatment, but confirmatory population studies are lacking  
|                  | • Labeling for albiglutide, dulaglutide, exenatide ER, and liraglutide:  
|                  |   • Patients should be counseled regarding medullary thyroid carcinoma and the signs/symptoms of thyroid tumors  
|                  |   • Contraindicated in patients with personal/family history of MTC or multiple endocrine neoplasia syndrome type 2 |
| Renal impairment | • Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration. Use caution when initiating or escalating doses in patients with renal impairment. Exenatide should not be used in patients with severe renal insufficiency or ESRD. Liraglutide was found to be safe in patients with moderate renal impairment and may confer a beneficial effect. |

ER, extended release.

## Approved GLP-1 RAs – Structure and Half-life

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Structure and Action</th>
<th>Half-life and Filtration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exenatide BID</strong></td>
<td>HGEGTFTSDLKQMEEEA VRLFIEWLKNGPSSGAPPPS Resistant to DPP-4</td>
<td>$t_{1/2} = 3.3-4$ hours and renal filtration</td>
</tr>
<tr>
<td><strong>Liraglutide</strong></td>
<td>HAEGTFTSDVSSYLEGQA KEFIAWLVRGR Partial resistant to DPP-4</td>
<td>$t_{1/2} = 11-13$ hours and renal filtration</td>
</tr>
<tr>
<td><strong>Exenatide QW</strong></td>
<td>Poly (D,L lactic-co-glycolic acid) microspheres HGEGTFTSDLKQMEEEAVRLFIEWLKNGPSSGAPPPS Resistant to DPP-4</td>
<td>Steady state over 6-7 weeks and renal filtration</td>
</tr>
<tr>
<td><strong>Lixisenatide</strong></td>
<td>HGEGTFTSDLKQMEEEA VRLFIEWLKNGPSSGAPPPSKKKKKK Resistant to DPP-4</td>
<td>$t_{1/2} = ~3$ hours and renal filtration</td>
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<tr>
<td><strong>Albiglutide</strong></td>
<td>Recombinant fusion protein linked to human albumin HGEGTFTSDVSSYLEGQA KEFIAWLKGR</td>
<td>$t_{1/2} = ~5$ days and multiple organ filtration</td>
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<tr>
<td><strong>Semaglutide</strong></td>
<td>HGEGTFTSDVSSYLEGQA KEFIAWLVRGR Modified IgG4 Fc domain C-18 free fatty acid derivative via a glutamoyl-2xOEG spacer</td>
<td>$t_{1/2} = 165$ hours</td>
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<tr>
<td><strong>Dulaglutide</strong></td>
<td>HGEGTFTSDVSSYLEGQA KEFIAWLKG DPP-4 Resistant to DPP-4</td>
<td>$t_{1/2} = ~5$ days</td>
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### Currently Available GLP-1 RAs

#### Administration

<table>
<thead>
<tr>
<th>Daily</th>
<th>Weekly</th>
</tr>
</thead>
</table>
| **Reconstitution required** | Yes
| **Pre-injection waiting time after reconstitution** | None
| **Ready-to-use solution** | Yes
| **Dose volume** | 0.02 ml (5 µg) 0.04 ml (10 µg)
| **Titration required** | Yes*
| **Single-use/multi-use** | Multi-use
| **Hidden needle** | No
| **Needle attachment required** | Yes
| **Needle size (mm)/gauge** | 4 mm / 29 g
| **Auto needle retraction** | No
| **Dose confirmation** | Visual

| Exenatide BID<sup>1</sup> | Lixisenatide<sup>2</sup> | Liraglutide<sup>3</sup> | Albiglutide<sup>4</sup> | Dulaglutide<sup>5</sup> | EQW Pen<sup>6</sup> | EQW Bcise<sup>7</sup> | Semaglutide<sup>8</sup>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<td>No</td>
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<td>None</td>
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<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Reconstitution within device</td>
<td>Yes</td>
<td>Reconstitution within device</td>
<td>Mix within device</td>
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<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0.50 ml (30 mg)</td>
<td>0.50 ml (0.75 mg)</td>
<td>0.65 ml (2 mg)</td>
<td>0.85 ml (2 mg)</td>
<td>0.75 ml (1 mg)</td>
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<td>0.02 ml (5 µg)</td>
<td>0.20 ml (10 µg)</td>
<td>0.20 ml (1.2 mg)</td>
<td>0.50 ml (50 mg)</td>
<td>0.50 ml (1.5 mg)</td>
<td>0.65 ml (2 mg)</td>
<td>0.85 ml (2 mg)</td>
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<td>0.04 ml (10 µg)</td>
<td>0.20 ml (20 µg)</td>
<td>0.30 ml (1.8 mg)</td>
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<td>0.65 ml (2 mg)</td>
<td>0.85 ml (2 mg)</td>
<td>0.75 ml (1 mg)</td>
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<td>Yes*</td>
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<td>4 mm / 29 g</td>
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<td>5 mm / 29 g</td>
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<td>Unknown / 23 g</td>
<td>Unknown supply</td>
<td>Unknown</td>
<td>4-8 mm / 32 g</td>
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<td>4 mm</td>
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<td>4 mm</td>
<td>5 mm / 29 g</td>
<td>Pre-staked</td>
<td>Unknown</td>
<td>Unknown</td>
<td>4-8 mm / 32 g</td>
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<td>29-31 g Supplied separate</td>
<td>29-31 g Supplied separate</td>
<td>32 g Supplied separate</td>
<td>Unknown supply</td>
<td>Unknown / 23 g</td>
<td>Unknown</td>
<td>Unknown</td>
<td>4-8 mm / 32 g</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Titrate if necessary; †When administered in the prefilled pen, exenatide QW does not require reconstitution; however when administered in the single-dose kit, reconstitution is needed; ‡shake the autoinjector hard in up and down motion until the medicine is mixed evenly. If you do not see any white medicine along the sides, bottom or top then shake for at least 15 seconds; BD=Becton Dickinson; QW=once weekly.
Overview of Approved GLP-1 Receptor Agonists

GLP-1 receptor agonists subcutaneously administered peptides

Human GLP-1 backbone
- Weekly
  - Albīglutide
  - Dulaglutide
  - Semaglutide

Once daily
- Liraglutide

Exendin-4 backbone
- Weekly
  - Exenatide

Once daily or Twice daily
- Exenatide Twice daily
- Lixisenatide Once daily

Click here for more details on the backbone of GLP-1 analog

GLP-1=glucagon-like peptide-1
GLP-1 RAs: Key Efficacy and Safety

GLP-1 RAs

When to Start a GLP-1 RA Recommended as a Treatment Option by AACE and ADA After Metformin

2018 AACE/ACE Algorithm

- GLP-1 RA is a preferred option for:
  - Second-line monotherapy after MET
  - Use with MET in dual and triple therapy

2018 ADA Position

- If not at A1C goal with lifestyle intervention and MET after 3 months, add another agent
- If the A1C target is not achieved after approximately 3 months and patient does not have atherosclerotic cardiovascular disease:
  - Consider a combination of MET and any one of the preferred 6 treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin
  - The choice of which agent to add is based on drug-specific effects and patient factors
- If the A1C target is not achieved after approximately 3 months and patient does have atherosclerotic cardiovascular disease:
  - Add agent proven to reduce MACE and/or cardiovascular mortality

A1C=glycated hemoglobin; AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology; ADA=American Diabetes Association; DPP-4=dipeptidyl peptidase-4; GLP-1 RA=glucagon like peptide-1 receptor agonist; MET=metformin; RA=receptor agonist; SGLT2=sodium-glucose cotransporter-2 inhibitor; SU=sulfonylurea; TZD=thiazolidinedione.

BASAL INSULINS
Most Patients will Eventually Require Insulin Therapy

The UKPDS found that more than half of newly diagnosed people with type 2 diabetes (T2DM) will require insulin initiation within 6 years of starting other antidiabetic therapies.¹

Due to the progressive nature of T2DM, insulin secretion diminishes largely as a result of a deterioration of beta-cell function.²-⁴

AVAILABLE BASAL INSULINS

- NPH
- Glargine
- Toujeo (Glargine U300)
- Levemir
- Degludec (Tresiba U100 and U200)
Structural Forms of the Insulin Polypeptide

- **Insulin Monomers**
  - This is the active form of Insulin that circulates in blood and binds to the insulin receptor

- **Insulin Hexamers**
  - Composed of 6 monomers
  - These are the storage form of insulin both in the β-cell and in insulin vials

Insulin Detemir: Mechanism of Sustained Release and PK/PD

♦ Soluble, long-acting basal human insulin analog

♦ Delayed absorption due to self-association of the drug molecules upon injection; delayed distribution to peripheral target tissues because of binding to albumin

♦ Half-life: 5-7 hours

♦ Relatively constant, reduced peak concentration-time profile

♦ Median duration of action was 7.6 to >24 hours


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Clinical Outcomes with Insulin Degludec

DEVOTE Study Design

- N=7637 patients with T2D at high risk of CV events
  - Age ≥50 years with CVD or renal disease
  - Age ≥60 years with ≥1 CV risk factor
- Randomization
  - Degludec: n=3818
  - Glargine: n=3819
- Noninferiority study: prespecified margin <1.3 for upper bound of 95% CI of the HR for the primary endpoint; superiority tested if noninferiority criterion met
  - Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke
  - Key secondary endpoints
    - Adjudicated severe hypoglycemia
    - Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
    - All-cause death

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec With Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events; HR, hazard ratio; MI, myocardial infarction.

Clinical Outcomes with Insulin Degludec and Glargine

DEVOTE CV Outcomes (N=7637)

Median follow-up: 1.99 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.91 (0.78-1.06)</td>
<td>&lt;0.001 (NI)†</td>
</tr>
<tr>
<td>Expanded composite endpoint‡</td>
<td>0.92 (0.80-1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.91 (0.76-1.11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>0.84 (0.60-1.16)</td>
<td>0.28</td>
</tr>
<tr>
<td>CV death</td>
<td>0.96 (0.76-1.21)</td>
<td>0.71</td>
</tr>
<tr>
<td>CV death excluding undetermined cause of death</td>
<td>0.91 (0.69-1.20)</td>
<td>0.52</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.85 (0.68-1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.65-1.23)</td>
<td>0.50</td>
</tr>
<tr>
<td>Unstable angina hospitalization</td>
<td>0.95 (0.68-1.31)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI, or nonfatal stroke; †Confirmed noninferiority; superiori, P=0.21. ‡CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

Cl, confidence interval; CV, cardiovascular; MI, myocardial infarction; NI, noninferiority.

Clinical Outcomes with Insulin Degludec and Glargine

DEVOTE Safety Outcomes
(N=7637)

Median follow-up: 1.99 years

Hazard ratio (95% CI)  P value

Severe hypoglycemia*  0.60 (0.48-0.76)  <0.001†

Unconsciousness or coma  0.81 (0.55-1.19)  0.28

Seizure  1.02 (0.38-2.73)  0.97

Nocturnal severe hypoglycemia  0.47 (0.31-0.73)  <0.001

≥1 severe hypoglycemia event  0.73 (0.60-0.89)  <0.001

*Episode requiring assistance from another person to actively administer carbohydrate or glucagon or take other corrective actions.
CI, confidence interval.
More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial

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Figure 1

HbA$_{1c}$ levels (A), eight-point SMPG profiles (B), FPG levels (C), and fasting SMPG levels (D) over 24 weeks of treatment, ITT population. BL, baseline; FSMPG, fasting SMPG; W, week.
Insulin Therapy in T2DM

- The progressive nature of T2DM should be regularly and objectively explained to T2DM patients.
- Avoid using insulin as a threat, describing it as a failure or punishment.
- Give patients a self-titration algorithm.
Discharge Insulin Algorithm

Discharge Treatment

- A1C < 7%
  - Re-start outpatient treatment regimen (OAD and/or insulin)

- A1C 7%-9%
  - Re-start outpatient oral agents and D/C on glargine once daily at 50% of hospital dose

- A1C >9%
  - D/C on basal bolus at same hospital dose.
    - Alternative: re-start oral agents and D/C on glargine once daily at 80% of hospital dose

• Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed T2DM who are symptomatic and/or have A1C $\geq 10\%$ and/or blood glucose levels $\geq 300$ mg/dL. E

• Consider initiating dual therapy in patients with newly diagnosed T2DM who have A1C $\geq 9\%$. E
Combination Injectable Therapy in T2DM

**Initiate Basal Insulin**
Usually with metformin +/- other noninsulin agent

- **Start:** 10 U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 units once or twice weekly to reach FBG target
- **For hypo:** Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

If A1C not controlled, consider combination injectable therapy

**Add 1 rapid-acting insulin injection before largest meal**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↑ basal by same amount
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to basal-bolus

**Add GLP-1 RA**

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, consider changing to alternative insulin regimen

**Change to premixed insulin twice daily (before breakfast and supper)**

- **Start:** Divide current basal dose into ½ AM, ½ PM or ¼ AM, ¾ PM
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to 3rd injection

**Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)**

- **Start:** Add additional injection before lunch
- **Adjust:** ↑ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%
Xultophy® 100/3.6 Has Been Studied in Patients Converting From Lantus®

**Basal Insulin Conversion**

DUAL™ V¹
N=557

Xultophy®
100/3.6

VS
Lantus®

DUAL™ VII²
N=506

Xultophy®
100/3.6

VS
Lantus® + NovoLog®
(insulin aspart)

Lantus®=insulin glargine U-100.
¹The treatments used in all study arms were combined with MET.

Please see Important Safety Information for Xultophy® 100/3.6 throughout this presentation. Please see Novo Nordisk representative for Prescribing Information.
**Study Design**

**Inclusion criteria**
- IGlar U-100 (20–50 units) + MET
- A1C 7%–10%
- BMI ≤40 kg/m²

**Primary Endpoint**
- Change from baseline in A1C at EOT

**Secondary Endpoints**
- Change from baseline in weight at EOT
- Number of treatment-emergent severe or BG-confirmed hypoglycemic episodes during 26 weeks of treatment

**Xultophy® 100/3.6**
- **Starting dose**: 16 units (16 units Tresiba® [insulin degludec]/0.58 mg Victoza® [lixisenatide])
- **Maximum dose**: 50 units (50 units Tresiba®/1.8 mg Victoza®)

**IGlar U-100**
- **Starting dose**: Pretrial dose
- **Maximum dose**: None

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BG=blood glucose; BMI=body mass index; EOT=end of trial; FPG=fasting plasma glucose; IGlar U-100=insulin glargine U-100.

*Both products were titrated up or down 2 units twice weekly to achieve an FPG goal of 72–90 mg/dL. Lingvay I et al. JAMA. 2016;315(9):898-907.
**Combined Insulin and GLP-1 RA: LixiLan**

**Change in A1C (%)**
- iGlarLixi
- iGlar
- Lixi

**Change in BW (kg)**
- iGlarLixi
- iGlar
- Lixi

**Hypoglycemic Events (PPY)**
- +1.1 kg
- -0.3 kg
- -2.3 kg

*≤ 56 mg/dL
THANKYOU