Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs
Learning Objectives

- Identify features that differentiate DPP-4 inhibitors from GLP-1 RAs
- Integrate GLP-1 RAs into the management of patients with T2DM based on current treatment guidelines and a personalized treatment approach
- Evaluate clinical trial data on current and emerging GLP-1 RAs in terms of their glycemic and nonglycemic features

DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.
Current State of T2DM Management

- T2DM accounts 90%-95% of cases of diabetes; it is a progressive disease characterized by increasing insulin resistance and relative insulin deficiency and is associated with increased risk of CV complications\(^1\)
- Often undiagnosed for years (~28% in US not diagnosed)\(^2\)
- Progress in meeting cardiometabolic goals is mixed\(^3\)

BP = blood pressure; LDL = low-density lipoprotein cholesterol.

The “Ominous Octet”: Multiple Defects in T2DM Present Multiple Targets for Intervention

- 5 major classes of oral agents
- 2 types of injected agents
- Multiple options within classes
- Multiple ways to combine classes

SGLT2 = sodium-glucose cotransporter-2; TZD = thiazolidinedione.
What Are Incretins? Why Are They Beneficial?

• Produced by GI tract in response to incoming nutrients: GLP-1, GIP
• Difference in insulin response between oral and intravenous glucose challenge = “incretin effect”
• ≤65% of postprandial insulin release is due to the incretin effect
• Incretins regulate glucose homeostasis in multiple ways:

<table>
<thead>
<tr>
<th>α cells</th>
<th>Liver</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ postprandial glucagon secretion</td>
<td>↓ glucagon, reduces hepatic glucose output</td>
<td>↑ insulin secretion, overcome insulin resistance</td>
</tr>
<tr>
<td>↑ glucose-dependent insulin secretion</td>
<td>↑ peripheral glucose disposal</td>
<td></td>
</tr>
<tr>
<td>↑ β-cell growth, regeneration</td>
<td></td>
<td>↓ β-cell apoptosis</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; GIP = gastric inhibitory polypeptide.

Patients With T2DM Have Reduced Incretin Effect

Role of GLP-1

• Low plasma levels in fasting state increase rapidly in response to meals, which:
  – Enhances glucose-dependent insulin secretion
  – Inhibits gastric acid secretion and glucagon secretion
  – Slows gastric emptying and glucose absorption
  – Induces satiety (may induce weight loss)
  – Expands β-cell mass (inhibits apoptosis and stimulates new growth)

• However, endogenous GLP-1 is rapidly inactivated by the enzyme DPP-4, limiting its activity

Differing Mechanisms of Action to Enhance GLP-1 Action: DPP-4 Inhibitors

GLP-1 release after meal

- Protease inhibitors
  - Inhibit DPP-4 enzyme activity to prolong time that endogenous GLP-1 and GIP levels are elevated

DPP-4 inhibitors
- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin

Physiologic effects + lower blood glucose

Incretin-Based Therapy to Enhance GLP-1 Action: GLP-1 RAs

GLP-1 RAs with greater postprandial glucose control
- Exenatide twice daily
- Lixisenatide once daily

GLP-1 RAs with greater fasting glucose control
- Albiglutide once weekly
- Dulaglutide once weekly
- Exenatide once weekly
- Liraglutide once daily

GLP-1 release after meal

• Degradation-resistant GLP-1 RA
• Pharmacologic stimulation of GLP-1 receptors
• Enhances and prolongs actions of GLP-1

Physiologic effects + lower blood glucose

# Overview: GLP-1 RAs and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GLP-1 RA</th>
<th>DPP-4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice daily, once daily, once weekly</td>
<td>Once daily</td>
</tr>
<tr>
<td>A1C absolute reduction</td>
<td>0.6% to 1.9%</td>
<td>0.5% to 0.8%</td>
</tr>
<tr>
<td>Body weight</td>
<td>Reduction</td>
<td>Neutral</td>
</tr>
<tr>
<td>Appetite</td>
<td>Suppressed</td>
<td>No effect</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

# CV Safety: Randomized Trials of DPP-4 Inhibitors With Primary CV End Point

## Risk of Hospitalization for HF

<table>
<thead>
<tr>
<th>Study</th>
<th>DPP-4 Inhibitor</th>
<th>Population</th>
<th>Follow-up</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (N = 16,492)</td>
<td>Saxagliptin</td>
<td>CV disease or CV risk factors</td>
<td>2.1 y</td>
<td>1.27 (1.07-1.51)</td>
</tr>
<tr>
<td>EXAMINE (N = 5389)(^a)</td>
<td>Alogliptin</td>
<td>Post-ACS: With HF Without HF</td>
<td>1.5 y</td>
<td>1.19 (0.90-1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00 (0.71-1.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.76 (1.07-2.90)</td>
</tr>
<tr>
<td>TECOS (N = 14,671)</td>
<td>Sitagliptin</td>
<td>CV disease</td>
<td>3.0 y</td>
<td>1.00 (0.83-1.20)</td>
</tr>
</tbody>
</table>

\(^a\)Total; n = 1533 with HF history, n = 3847 without HF history.

ACS = acute coronary syndrome; HF = heart failure; HR = hazard ratio.

### CV Safety: Randomized Trials of GLP-1 RAs With Primary CV End Point

<table>
<thead>
<tr>
<th>Study</th>
<th>GLP-1 RA</th>
<th>Design</th>
<th>Population</th>
<th>Primary End Point</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA&lt;sup&gt;1,a&lt;/sup&gt; (N = 6068)</td>
<td>Lixisenatide vs placebo</td>
<td>Non-inferiority</td>
<td>MI or unstable angina</td>
<td>Composite 1</td>
<td>1.02 (0.89-1.17)</td>
</tr>
<tr>
<td>LEADER&lt;sup&gt;2,a&lt;/sup&gt; (N = 9340)</td>
<td>Liraglutide vs placebo</td>
<td>Non-inferiority</td>
<td>High CV risk</td>
<td>Composite 2</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>EXSCEL&lt;sup&gt;3,b&lt;/sup&gt; (N ~14,000)</td>
<td>Exenatide LAR vs usual care</td>
<td>Superiority</td>
<td>CV disease or CV risk factors</td>
<td>Composite 2</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Composite 1 = CV death, MI, stroke, or hospitalization for unstable angina.
Composite 2 = CV death, nonfatal MI, or nonfatal stroke.
<sup>a</sup>Designed to demonstrate noninferiority vs placebo.
<sup>b</sup>Designed to demonstrate superiority vs usual care.
LAR = long-acting release; MI = myocardial infarction.

Case Study: Meet Josef, 59

- Diagnosed with T2DM 4 years ago; works as UPS dispatcher
- Physical findings:
  - BP = 140/85 mm Hg on ACE inhibitor
  - 5 ft 10 in, 185 lb (BMI = 26.5 kg/m²)
- Taking venlafaxine 150 mg/d for depression
- Lab results:
  - A1C = 7.9%
  - LDL-C = 85 mg/dL treated with atorvastatin
  - Mild renal impairment (eGFR = 68 mL/min/1.73 m²)
- Current T2DM medications:
  - Metformin XR 1500 mg/d
  - Recently discontinued NPH insulin due to 2 episodes of symptomatic hypoglycemia

ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; XR = extended release.
# Glycemic Targets in Context of Individual Patient Factors

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Most Intensive: A1C ≤6.5%</th>
<th>For Many Patients: A1C ≤7.0%</th>
<th>Least Intensive: A1C &gt;7.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Established</td>
<td>Long-standing disease</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Moderate</td>
<td>Short</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>None</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>None</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Attitude, resources, support system</td>
<td>Highly motivated; readily available</td>
<td>Motivated; some resources available</td>
<td>Less motivated; limited</td>
</tr>
</tbody>
</table>
ADA and AACE: Individualized Goal-Setting and Treatment in Context of Team-Based Care

• Set patient-specific glycemic goals:
  – Generally <6.5% to <7.5%
  – Implement lifestyle modifications, including weight-loss medication if necessary
• Address CV and other risk factors: hypertension, lipids, renal impairment, psychological well-being
• Manage patients across their life-span: T2DM diagnosed at younger ages and patients living to old age
• Use collaborative, multidisciplinary teams and a chronic care model to coordinate all aspects of care

AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association.
2016 ADA Standards: Rational Approach to T2DM Medication Choice

Choice based on:
- Healthy eating, weight control, increased physical activity
- Efficacy (Δ A1C)
- Avoiding hypoglycemia and weight gain
- Side effects
- Costs

Consider initial dual therapy if A1C >9.0% at presentation
Proceed to a dual therapy if A1C is not reached in ~3 months
Proceed to triple therapy if A1C is not reached in ~3 months

Metformin

- Metformin + Sulfonylurea
- Metformin + TZD
- Metformin + DPP-4 inhibitor
- Metformin + SGLT2 inhibitor
- Metformin + GLP-1 RA
- Metformin + Insulin (basal)

Insulin (multiple daily doses)

Oral drug classes are listed oldest to newest from left to right; injectable agents are at far right. American Diabetes Association. *Diabetes Care*. 2016;39(Suppl 1):S1-S112.
AACE Algorithm for Glycemic Control, 2015

**Lifestyle Modification**

- **Entry A1C <7.5%**
  - **Monotherapy**
    - Metformin
    - GLP-1 RA
    - SGLT2 inhibitor
    - DPP-4 inhibitor
    - AG inhibitor
    - TZD
    - SU/GLN
    - If not at goal in 3 months, proceed to dual therapy

- **Entry A1C ≥7.5%**
  - **Dual therapy**
    - GLP-1 RA
    - SGLT2 inhibitor
    - DPP-4 inhibitor
    - TZD
    - Basal insulin
    - Colesevelam
    - Bromocriptine QR
    - AG inhibitor
    - SU/GLN
    - If not at goal in 3 months, proceed to triple therapy

- **Entry A1C >9.0%**
  - **Symptoms**
    - **NO**
      - Dual therapy
      - OR triple therapy
    - **YES**
      - Insulin ± other agents
        - Add or intensify insulin
        - Possible benefits or few adverse events
        - Use with caution

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Further Recommendations for Common Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>ADA recommended treatments by goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoiding hypoglycemia</td>
</tr>
<tr>
<td>DPP-4 inhibitor, GLP-1 RA, metformin, TZD</td>
</tr>
<tr>
<td>Avoiding weight gain</td>
</tr>
<tr>
<td>DPP-4 inhibitor, GLP-1 RA, metformin</td>
</tr>
<tr>
<td>Minimizing cost</td>
</tr>
<tr>
<td>Metformin, sulfonylureas, basal insulin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AACE recommended treatments by properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential nonglycemic benefits or few AEs</td>
</tr>
<tr>
<td>DPP-4 inhibitor, GLP-1 RA, metformin</td>
</tr>
<tr>
<td>Use with caution</td>
</tr>
<tr>
<td>Basal insulin, sulfonylurea, TZD</td>
</tr>
</tbody>
</table>

AE = adverse event.

Self-Monitoring of Blood Glucose (SMBG)

- An educational and motivational tool that should be used in conjunction with a diabetes management action plan, including:
  - Patient education in treatment and targets
  - Specific recommendations on treatment and timing
  - Identifying hypoglycemic and hyperglycemic patterns
  - Healthcare follow-up based on results, with additional education as appropriate

SMBG: General Principles

• SMBG is a valuable adjunct to the use of A1C targets in achieving glycemic control
  – Provides “real-time” feedback
  – Detects abnormal glycemic profiles
  – Facilitates appropriate medication management
  – Acts as both education and motivational tool
• Should be performed at various times of day
• If FPG and preprandial blood glucose are controlled but A1C is above target, PPG should be emphasized

### Cardiometabolic Factors: Goals for Patients With T2DM

<table>
<thead>
<tr>
<th>Blood Pressure Targets (mm Hg)(^1,2)</th>
<th>Lipid Goals (mm Hg)(^3)</th>
<th>Weight(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 yrs: &lt;140/90</td>
<td>LDL-C: &lt;100</td>
<td>Normal BMI: (&lt;25 kg/m(^2))</td>
</tr>
<tr>
<td>Age 60+ yrs: &lt;150/90</td>
<td>HDL-C: ≥40 (men),</td>
<td>Weight loss education, nutrition counseling</td>
</tr>
<tr>
<td>Any age with T2DM or CKD: &lt;140/90</td>
<td>≥50 (women)</td>
<td>Increase physical activity (if possible): 30 min 3X/week</td>
</tr>
<tr>
<td>&lt;130/80 appropriate for certain patients if achieved without excess treatment burden</td>
<td>Triglycerides: &lt;150</td>
<td>Bariatric surgery if extreme weight loss required</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol.

Individualize Treatment in Patients With T2DM

- Consider individual patient factors when determining A1C target goals
- For patients with A1C <8.0%, obtain SMBG information to clarify which glycemic component predominates
- Manage all cardiometabolic factors and review at each visit
Fasting and Postprandial Glycemic Effects of GLP-1 RAs

• GLP-1 RAs with greater effect on FPG than on PPG:
  – Albiglutide once weekly
  – Dulaglutide once weekly
  – Exenatide LAR once weekly
  – Liraglutide once daily

• GLP-1 RAs with greater effect on PPG than on FPG:
  – Exenatide twice daily
  – Lixisenatide once daily
GLP-1 RAs With Greater Fasting Glucose Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liraglutide</th>
<th>Exenatide LAR</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>11-15 h</td>
<td>2 wks</td>
<td>6-7 d</td>
<td>~4 d</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once-daily</td>
<td>Once-weekly</td>
<td>Once-weekly, Q2W, monthly</td>
<td>Once-weekly</td>
</tr>
<tr>
<td>Δ A1C, %</td>
<td>–0.84 to –1.50</td>
<td>–1.0 to –2.0</td>
<td>–0.24 to –0.83</td>
<td>–0.71 to –1.64</td>
</tr>
<tr>
<td>Δ FPG, mg/dL</td>
<td>–15.1 to –44.0</td>
<td>–31.1 to –47.0</td>
<td>–12.4 to –43</td>
<td>–26 to –43</td>
</tr>
<tr>
<td>Δ PPG, mg/dL</td>
<td>–29 to –49</td>
<td>ND</td>
<td>ND</td>
<td>–41.4 to –46.1</td>
</tr>
<tr>
<td>Safety</td>
<td>GI, ↑ HR</td>
<td>GI, gastroenteritis, ↑ HR, ISP, hypoglycemia</td>
<td>Headache, GI</td>
<td>GI, headache, anorexia, ↑ HR</td>
</tr>
</tbody>
</table>

HR = heart rate; ISP = injection-site pruritus; ND = not determined; Q2W = every 2 weeks.
## GLP-1 RAs With Greater Postprandial Glucose Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exenatide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>2.4 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td>Dosing</td>
<td>Twice-daily</td>
<td>Once-daily</td>
</tr>
<tr>
<td>$\Delta$ A1C</td>
<td>$-0.4%$ to $-1.5%$</td>
<td>$-0.7%$ to $-0.9%$</td>
</tr>
<tr>
<td>$\Delta$ FPG, mg/dL</td>
<td>$-5.4$ to $-28.8$</td>
<td>$+5.4$ to $-20.9$</td>
</tr>
<tr>
<td>$\Delta$ PPG, mg/dL</td>
<td>$-30$ to $-52.2$</td>
<td>$-55.8$ to $-143.3$</td>
</tr>
<tr>
<td>Safety</td>
<td>Nausea, vomiting, diarrhea, URTI</td>
<td>GI, including nausea and vomiting</td>
</tr>
</tbody>
</table>

URTI = upper respiratory tract infection.

## Efficacy and Weight Change in Key Comparative Trials

<table>
<thead>
<tr>
<th>Comparators</th>
<th>Δ A1C, %</th>
<th>Δ FPG, mg/dL</th>
<th>Δ Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide vs exenatide BID¹</td>
<td>–0.79 vs –0.96</td>
<td>–22.0 vs –26.1</td>
<td>–2.8 vs –3.8</td>
</tr>
<tr>
<td>Liraglutide vs exenatide BID²</td>
<td>–1.12 vs 0.79</td>
<td>–28.8 vs –10.8</td>
<td>–3.24 vs –2.87</td>
</tr>
<tr>
<td>Lixisenatide vs liraglutide³</td>
<td>–0.06 vs –0.07</td>
<td>1.8 vs 1.8</td>
<td>–1.6 vs –2.4</td>
</tr>
<tr>
<td>Albiglutide vs liraglutide⁴</td>
<td>–0.78 vs –0.99</td>
<td>–22 vs –30.2</td>
<td>–0.65 vs –2.19</td>
</tr>
<tr>
<td>Dulaglutide vs liraglutide⁵</td>
<td>–1.42 vs –1.36</td>
<td>–34.7 vs –34.2</td>
<td>–2.9 vs –3.61</td>
</tr>
<tr>
<td>Exenatide LAR vs liraglutide⁶, %</td>
<td>–1.28 vs –1.48</td>
<td>–31.7 vs –38.2</td>
<td>–2.68 vs –3.57</td>
</tr>
</tbody>
</table>

BID = twice daily.

Effects on PPG Versus FPG: Clear Differences Among GLP-1 RAs

Δ A1C: Lixisenatide –0.32% vs Liraglutide –0.51%

Added to background metformin in patients with inadequately controlled T2DM.
Longer-acting Versus Twice-Daily GLP-1 RAs: Patients Achieving Glycemic Goals

Patients achieving goals after 24 weeks of treatment.
Candidates for GLP-1 RAs

• Consider GLP-1 RAs for patients who require additional glycemic control:
  – Without hypoglycemia
  – With weight loss
• Determine whether patient requires additional PPG control or additional FPG control and choose GLP-1 RA accordingly
GLP-1 RAs: Safety

- Generally well tolerated; GI AEs most common, can be minimized with slow titration at initiation
- Beneficial effects on CV risk factors, including blood pressure and LDL-C reductions
- May be used for patients with mild renal impairment; avoid exenatide twice daily for patients with ESRD
- Contraindicated in patients with personal or family history of medullary thyroid carcinoma or MEN2
  - Albiglutide, dulaglutide, exenatide LAR, liraglutide

MEN2 = multiple endocrine neoplasia syndrome type 2.
GI AEs in Comparative Clinical Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID vs lixisenatide,1 %</td>
<td>35.1 vs 24.5</td>
<td>13.3 vs 10.1</td>
<td>13.3 vs 10.4</td>
</tr>
<tr>
<td>Lixisenatide vs liraglutide,2 %</td>
<td>22.1 vs 22.5</td>
<td>10.4 vs 7.0</td>
<td>2.6 vs 15.5</td>
</tr>
<tr>
<td>Albiglutide vs liraglutide,3 %</td>
<td>9.9 vs 29.2</td>
<td>5.0 vs 9.3</td>
<td>14.9 vs 13.5</td>
</tr>
<tr>
<td>Dulaglutide vs liraglutide,4 %</td>
<td>20.0 vs 18.0</td>
<td>7.0 vs 8.0</td>
<td>12.0 vs 12.0</td>
</tr>
<tr>
<td>Exenatide LAR vs liraglutide,5 %</td>
<td>9.0 vs 21.0</td>
<td>4.0 vs 11.0</td>
<td>6.0 vs 13.0</td>
</tr>
</tbody>
</table>

All, added to metformin ± other oral antidiabetics.

FDA/EMA Statement Regarding Potential Pancreatitis Risk With GLP-1 RAs

• Comprehensive evaluation using multiple data sources, prompted by postmarketing safety signal
• Agencies agree that “…assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer…are inconsistent with the current data…”
• Conclusion: “…current knowledge is adequately reflected in the product information and labeling…”
• Investigation, including data from long-term safety trials, will continue

EMA = European Medicines Agency; FDA = US Food and Drug Administration.
Recommendations for GLP-1 RA Use: Potential Pancreatitis Risk

• Educate patients
  – Monitor for signs, symptoms
  – Ask about pancreatitis history and other risk factors (eg, gallstones, history of alcoholism, high blood triglycerides)

• Discontinue promptly if pancreatitis symptoms occur

• Consider other agents if patient has a history of pancreatitis

• If acute pancreatitis confirmed, do not restart GLP-1 RA

• Report cases of pancreatitis to www.fda.gov/medwatch

Minimizing GI Events With GLP-1 RAs

- Titrate GLP-1 RA dose slowly when starting treatment to reduce risk of nausea and other GI effects
- Explain to patients that GI effects are transient and usually diminish after a few weeks
- Reduce dose if nausea persists and retitrate slowly

Case Study: Conclusion

• Josef is doing well with a GLP-1 RA that addresses FPG
• Experienced some nausea, but it abated after 1 month; had only 1 episode of vomiting and rare diarrhea
• At his 3-month checkup:
  – A1C = 7.0%
  – BP = 135/85 mm Hg
  – Weight: 175 lbs (BMI = 25.1 kg/m²)
Emerging Options With GLP-1 RAs

- Fixed-ratio combinations of GLP-1 RA + basal insulin
  - Lixisenatide + insulin glargine
  - Liraglutide + insulin degludec
  - Associated with greater A1C reductions, less weight gain, fewer GI effects than individual components as monotherapy\(^1,2\)

- In advanced development: semaglutide
  - Once-weekly administration
  - Greater reductions in A1C vs exenatide LAR (\(-1.5% \text{ vs } -0.9\%)\(^3\)
  - SUSTAIN 6: semaglutide reduces CV risk by 26%\(^3\)

Summary: Choosing GLP-1 RAs

- Associated with significant reductions in A1C and weight loss; low risk of hypoglycemia
- Improve cardiometabolic risk profile in patients with hypertension, dyslipidemia, obesity
  - Use individual agent profiles to choose appropriate GLP-1 RA
- If A1C ≥7.0% and FPG at target:
  - Consider exenatide twice daily, lixisenatide
  - Recommended as alternative to prandial insulin in patients inadequately controlled on basal1-3
- If A1C ≥7.0% and FPG uncontrolled:
  - Consider albiglutide, dulaglutide, exenatide LAR, liraglutide
  - Recommended as a preferred add-on to metformin or an alternative to basal insulin1-3

PCE Action Plan

- Use collaborative multidisciplinary care to coordinate all aspects of treatment
- Set goals and make treatment decisions based on individual patient factors and glycemic patterns
- Consider a GLP-1 RA for patients who require additional glycemic control without hypoglycemia or weight gain
- Titrate GLP-1 RAs slowly at initiation to reduce risk of nausea and GI AEs