2020 Vision: Implementing the New ADA 2020 Guidelines for GLP-1 RAs in Clinical Practice
Learning Objectives

• Describe the pathophysiology of T2DM and the clinical utility of incretin therapy in patients with T2DM
• Apply the 2020 ADA recommendations for GLP-1 RAs to the care of patients with T2DM who require better glucose control, weight mitigation, and/or CVD risk reduction
• Partner with patients to use shared decision-making to select and improve adherence to therapies

ADA = American Diabetes Association; CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.
GLP-1 in T2DM: The Incretin Effect

- In a glucose-dependent manner, GLP-1 works to maintain normal glucose levels by:
  - Stimulating release of insulin from pancreatic β cells when glucose levels are elevated, particularly in response to food
  - Suppressing glucagon secretion from pancreatic α cells

- This “incretin effect” is diminished in patients with T2DM, contributing to hyperglycemia
- GLP-1 RAs restore this effect by potentiating the action of endogenous GLP-1

The “Ominous Octet”: Multiple, Complex Pathophysiologic Abnormalities in T2DM


- Impaired insulin secretion
- Increased glucagon secretion
- Increased hepatic glucose production
- Neurotransmitter dysfunction
- Increased lipolysis
- Increased glucose reabsorption
- Decreased incretin effect
- Decreased glucose uptake

HYPERGLYCEMIA
The “Ominous Octet”: Multiple, Complex Pathophysiologic Abnormalities in T2DM

- Impaired insulin secretion
- Increased glucagon secretion
- Increased hepatic glucose production
- Decreased incretin effect
- Decreased glucose uptake
- Increased glucose reabsorption
- Increased lipolysis
- Neurotransmitter dysfunction

DPP-4i = dipeptidyl peptidase-4 inhibitor; SGLT2 = Sodium glucose co-transporter 2; SGLT2i = SGLT2 inhibitor; SU = sulfonylurea; TZD = thiazolidinediones.

Case Study: Don, a 69-Year-Old With a 4-Year History of T2DM

• Don has not pursued regular medical care since his T2DM diagnosis. He was recently diagnosed with peripheral arterial disease (PAD). At his wife Betty’s urging, he agrees to a telehealth appointment to assess his overall health

• Don is a retired machinist whose father died of an MI at 62. He enjoys woodworking and is a former smoker who quit 15 years ago

• **Physical exam findings**
  – Height: 5 ft 11 in
  – Weight: 213 lb
  – BMI: 29.8 kg/m²
  – BP: 148/96 mm Hg on an ACE inhibitor
  – No history of MI, DVT/PE
  – Last ECG was normal

ACE = angiotensin-converting enzyme; DVT/PE = deep vein thrombosis/pulmonary embolism; MI = myocardial infarction.
Case Study (cont’d): Don’s Medications and Lab Values

- **Lab results**
  - FPG: 190 mg/dL
  - PPG: 205 mg/dL
  - A1C: 8.3%
  - LDL-C: 110 mg/dL on statin
  - CBC, CMP/LFT: within normal ranges
  - Mild renal impairment (eGFR: 55 mL/min/1.73²)
  - No albuminuria

- **Current medications**
  - Metformin 1500 mg/day
  - Ramipril 10 mg/day
  - Atorvastatin 40 mg/day
  - Aspirin 81 mg/day
  - Clopidogrel 75 mg/day
  - Cilostazol 100 mg twice/day

CBC = complete blood count; CMP = comprehensive metabolic panel; FPG = fasting plasma glucose; LDL-C = low density lipoprotein cholesterol; LFT = liver function tests; PPG = post-prandial glucose.
## Approach to Individualization of A1C Targets for Treatment

### Patient/Disease Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>More Stringent</th>
<th>A1C 7.0%</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of hypoglycemia/drug adverse effects</td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
<td></td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>High motivation/adherence</td>
<td>Low motivation/adherence</td>
<td></td>
</tr>
<tr>
<td>Resources and support system</td>
<td>Readily available</td>
<td>Limited</td>
<td></td>
</tr>
</tbody>
</table>

### Important Aspects

- **Risk of hypoglycemia/drug adverse effects**: Usually not modifiable
- **Disease duration**
- **Life expectancy**
- **Important comorbidities**
- **Established vascular complications**
- **Patient attitude and expected treatment efforts**
- **Resources and support system**

**American Diabetes Association. Diabetes Care. 2020;43:S1-S212.**
**ADA 2020: Comprehensive Medical Evaluation for Patients With T2DM**

- Evaluate for complications and comorbidities
- Review previous treatment and risk factor control in patients with established diabetes
- Assess 10-year ASCVD risk using a validated pooled cohort equations tool
- Engage patient in creating and adhering to management plan
- Repeat at follow-up visits, plus:
  - Assess diabetes self-management
  - Conduct foot exam
  - Discuss nutrition
  - Explore psychosocial health (eg, depression, anxiety, eating disorders)
  - Evaluate need for referrals, immunizations, routine health screening
- Assess patient’s familiarity with diabetes technology (eg, continuous glucose monitoring, health apps)

Lifestyle Modifications Are a Cornerstone of Treatment for T2DM

- Assess eating patterns and weight history, physical activity, sleep behaviors
- Assess tobacco/alcohol/other substance use
- Consider referral for:
  - Medical nutrition therapy education and support
  - Diabetes self-management education and support
  - Anxiety and stress reduction
Among patients with T2DM who have established ASCVD or indicators of high-risk, established kidney disease or heart failure (HF):

- An SGLT2i or GLP-1 RA with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors.
ADA 2020: Use Agents That Address Patient-Specific Comorbidities

For all patients: lifestyle modification
For most patients: metformin

Indicators of high-risk or established ASCVD, HF, or CKD

ASCVD predominates

PREFERABLY: GLP-1 RA with proven CVD benefit

SGLT2i with proven CVD benefit if eGFR is adequate

If A1C above target

If further intensification required or patient unable to tolerate GLP-1 RA and/or SGLT2i, choose agents with CV safety

HF or CKD predominates

PREFERABLY: SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR is adequate

OR

If SGLT2i not tolerated or contraindicated or inadequate eGFR, add GLP-1 RA with proven CVD benefit

If A1C above target

Choose agent with CV safety; Avoid TZD in setting of HF

CKD = chronic kidney disease; CVOT = cardiovascular outcome trial.
ADA 2020: Use Agents That Address Patient-Specific Comorbidities

**For all patients:** lifestyle modification
**For most patients:** metformin

**Indicators of high-risk or established ASCVD, HF, or CKD**

**ASCVD predominates**
- **PREFERABLY:** GLP-1 RA with proven CVD benefit
- **EITHER/OR**
  - If A1C above target
  - SGLT2i with proven CVD benefit if eGFR is adequate

**HF or CKD predominates**
- **PREFERABLY:** SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR is adequate
  - **OR**
    - If SGLT2i not tolerated or contraindicated or inadequate eGFR, add GLP-1 RA with proven CVD benefit
- **If A1C above target**
- **Choose agent with CV safety; Avoid TZD in setting of HF**

**If further intensification required or patient unable to tolerate GLP-1 RA and/or SGLT2i, choose agents with CV safety**

CKD = chronic kidney disease; CVOT = cardiovascular outcome trial;
ADA 2020: Pathways for Patients Without Indicators of High-Risk or Established ASCVD, CKD, or HF

First-line is metformin + lifestyle modification; if above A1C target, proceed as below

If NO established ASCVD or CKD

Compelling need to minimize hypoglycemia
- DPP-4
- GLP-1 RA
- SGLT2i
- TZD

If A1C above target
- SGLT2i or TZD

If A1C above target, continue with addition of other agents outlined above

Compelling need to minimize weight gain/promote weight loss
- GLP1-RA with good efficacy for weight loss
- EITHER/ OR
- SGLT2i

If A1C above target
- SGLT2i

If A1C above target
- GLP1-RA with good efficacy for weight loss

If triple therapy required or GLP-1 RA/SGLT2i not tolerable, use agent with lowest risk of weight gain

GLP-1 RAs Are Recommended for Patients With Established ASCVD or at High Risk for ASCVD

- GLP-1 RAs address multiple aspects of T2DM pathophysiology
- All are safe for patients with CVD, and several have proven benefit in CV risk reduction for patients with ASCVD or CV risk factors
- ADA 2020: For patients in whom ASCVD predominates or who have indicators of high risk for ASCVD, use a GLP-1 RA with proven CVD benefit*

GLP-1 RA Decision-Making Tool

• PCE discussion guide/checklist developed to help clinicians step through options in a patient-friendly manner, including
  – Mode of administration – injectable vs oral
  – Frequency of administration – twice daily, daily, weekly
  – CV benefit
  – A1C-lowering potential
  – Weight mitigation potential
  – Side-effect profile

• Tool is available for download at PCE.is/GLPdecisiontool
## GLP-1 RA Decision-Making: Frequency of Administration, Glycemic Control, Weight Reduction

<table>
<thead>
<tr>
<th>Effect</th>
<th>Exenatide</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Exenatide LAR</th>
<th>Dulaglutide</th>
<th>Semaglutide SC</th>
<th>Semaglutide Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration frequency</td>
<td>Twice daily</td>
<td>Daily</td>
<td>Daily</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
<tr>
<td>Typical A1C reduction, *%</td>
<td>0.5-0.9</td>
<td>0.7</td>
<td>1.0</td>
<td>1.6</td>
<td>1.0-1.4</td>
<td>1.5-1.8</td>
<td>1.0-1.3</td>
</tr>
<tr>
<td>FPG reduction, mg/dL</td>
<td>5.4-28.8</td>
<td>0-20.9</td>
<td>15.12-44.0</td>
<td>31.1-47.0</td>
<td>26.0-43.0</td>
<td>35.0-43.0</td>
<td>36</td>
</tr>
<tr>
<td>PPG reduction, mg/dL</td>
<td>30.0-52.2</td>
<td>55.8-143.3</td>
<td>29.0-49.0</td>
<td>NR</td>
<td>41.4-46.1</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Weight reduction, kg</td>
<td>1.0-2.6</td>
<td>2.7</td>
<td>2.6-2.8</td>
<td>2.3</td>
<td>2.4-2.9</td>
<td>4.6-6.5</td>
<td>3.8</td>
</tr>
</tbody>
</table>

NR = not reported.

*In trials with GLP-1 RA added to metformin.

# GLP-1 RA Decision-Making: Dosage and Administration

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Initial Dose*</th>
<th>Maintenance Dose</th>
<th>Relation to Meals</th>
<th>Missed Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>5 mcg twice daily x ≥1 month</td>
<td>5 or 10 mcg twice daily, depending on clinical response</td>
<td>&lt;60 min before 2 main meals</td>
<td>Continue with next scheduled dose</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>10 mcg daily x 14 day</td>
<td>20 mcg daily</td>
<td>&lt;60 min before 1st daily meal</td>
<td>Take dose within 1 hour before next meal</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6 mg daily ≥1 week</td>
<td>1.2 to 1.8 mg daily</td>
<td>None</td>
<td>Continue with next scheduled dose</td>
</tr>
<tr>
<td>Exenatide LAR</td>
<td>N/A</td>
<td>2 mg weekly</td>
<td>None</td>
<td>≥3 days until next scheduled dose: ASAP; &lt;3 days: skip dose, take next planned dose</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75 mg weekly</td>
<td>0.75 or 1.5 mg weekly depending on clinical response</td>
<td>None</td>
<td>≥3 days until next scheduled dose: ASAP; &lt;3 days: skip dose, take next planned dose</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>0.25 mg weekly x 4 weeks</td>
<td>0.5 or 1.0 weekly depending on clinical response</td>
<td>None</td>
<td>≥5 days until next scheduled dose: ASAP; &lt;5 days: skip dose, take next planned dose</td>
</tr>
<tr>
<td>Semaglutide (oral)</td>
<td>3 mg daily x 30 days</td>
<td>7 or 14 mg daily depending on clinical response</td>
<td>&lt;30 minutes before 1st food/other intake of day</td>
<td>Continue with next dose the following day</td>
</tr>
</tbody>
</table>

*Initial lower doses are used to minimize GI side effects for liraglutide and semaglutide subcutaneous/oral. These initial doses are not effective for glycemic reduction, and the dose must be increased as recommended for glycemic effect.

# GLP-1 RAs in Context With Other T2DM Medications

<table>
<thead>
<tr>
<th>Effect</th>
<th>MET</th>
<th>SGLT2i</th>
<th>GLP-1 RA</th>
<th>DPP-4i</th>
<th>TZD</th>
<th>SU</th>
<th>Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical A1C reduction, %</td>
<td>1.0 to 2.0</td>
<td>≤1.0</td>
<td>0.6 to 1.8</td>
<td>0.5 to 0.8</td>
<td>0.5 to 1.0</td>
<td>1.0 to 2.0</td>
<td>1.5 to 2.5</td>
</tr>
<tr>
<td>Efficacy</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight Δ</td>
<td>Neutral*</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td>Bone</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate fracture risk</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Neutral</td>
<td>Potential**</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

**MET** = metformin.

*Potential for moderate weight loss; **Can occur in various stress settings.

ADA 2020: Decision Cycle for Patient-Centered Glycemic Management in T2DM

Assess Key Patient Characteristics

Consider Specific Factors That Impact Choice of Treatment

Review and Agree on Management Plan (at least once or twice a year)

Shared Decision-making to Create a Management Plan

Ongoing Monitoring and Support

Implement Management Plan

Agree on Management Plan
Baseline Characteristics of GLP-1 RA CVOTs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ELIXA Lixisenatide</th>
<th>LEADER Liraglutide</th>
<th>SUSTAIN-6 Semaglutide</th>
<th>PIONEER-6 Oral semaglutide</th>
<th>EXSCEL Exenatide LAR</th>
<th>REWIND Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6068</td>
<td>9340</td>
<td>3297</td>
<td>3183</td>
<td>14,752</td>
<td>9901</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>60.3</td>
<td>64.3</td>
<td>64.6</td>
<td>66 \pm 7</td>
<td>62.0</td>
<td>66.2</td>
</tr>
<tr>
<td>Male, %</td>
<td>69.3</td>
<td>64.3</td>
<td>60.7</td>
<td>68.4</td>
<td>62.0</td>
<td>53.7</td>
</tr>
<tr>
<td>Established ASCVD, %</td>
<td>100</td>
<td>72.5</td>
<td>83.0</td>
<td>84.7</td>
<td>73.1</td>
<td>31.4</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>23.2</td>
<td>23.1</td>
<td>28.5</td>
<td>26.9</td>
<td>21.6</td>
<td>22.2</td>
</tr>
<tr>
<td>History of HF, %</td>
<td>20.3</td>
<td>17.8</td>
<td>23.6</td>
<td>12.2</td>
<td>16.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Median follow-up time, years</td>
<td>2.1</td>
<td>3.8</td>
<td>2.1</td>
<td>1.3</td>
<td>3.2</td>
<td>6.0</td>
</tr>
</tbody>
</table>

### Outcomes in CVOTs: GLP-1 RA vs Placebo

<table>
<thead>
<tr>
<th>Outcome&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ELIXA Lixisenatide</th>
<th>LEADER Liraglutide</th>
<th>SUSTAIN-6 Semaglutide</th>
<th>PIONEER-6 Oral semaglutide</th>
<th>EXSCEL Exenatide LAR</th>
<th>REWIND Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>3 pt MACE</td>
<td>3 pt MACE</td>
<td>3 pt MACE</td>
<td>3 pt MACE</td>
<td>3 pt MACE</td>
<td>3 pt MACE</td>
</tr>
<tr>
<td>Est. ASCVD, %</td>
<td>100</td>
<td>72.5</td>
<td>83.0</td>
<td>84.7</td>
<td>73.1</td>
<td>31.4</td>
</tr>
<tr>
<td>MACE</td>
<td>1.02 (0.89-1.17)</td>
<td><strong>0.88 (0.79-0.97)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.74 (0.58-0.95)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.79 (0.57-1.11)</td>
<td>0.91 (0.83-1.00)</td>
<td><strong>0.896 (0.81-0.99)</strong></td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.98 (0.78-1.22)</td>
<td><strong>0.78 (0.66-0.93)</strong></td>
<td>0.98 (0.65-1.48)</td>
<td><strong>0.49 (0.27-0.92)</strong></td>
<td>0.88 (0.76-1.02)</td>
<td>0.92 (0.79-1.06)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.03 (0.87-1.22)</td>
<td>0.88 (0.75-1.03)</td>
<td>0.74 (0.51-1.08)</td>
<td>1.18 (0.73-1.90)</td>
<td>0.97 (0.85-1.10)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.12 (0.79-1.58)</td>
<td>0.89 (0.72-1.11)</td>
<td><strong>0.61 (0.38-0.99)</strong></td>
<td>0.74 (0.35-1.57)</td>
<td>0.85 (0.70-1.03)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>HHF</td>
<td>0.96 (0.75-1.22)</td>
<td>0.88 (0.74-1.05)</td>
<td>1.09 (0.76-1.56)</td>
<td>0.88 (0.49-1.57)</td>
<td>0.94 (0.78-1.13)</td>
<td>0.94 (0.78-1.13)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data expressed as hazard ratio (95% confidence interval).<sup>b</sup>Est. ASCVD denotes estimated 10-year risk of ASCVD. MACE denotes major adverse CV event (death related to CV causes, nonfatal MI, or nonfatal stroke; EXSCEL included fatal or nonfatal MI, fatal or nonfatal stroke).<sup>c</sup>Fatal or nonfatal MI or stroke.

## Current Indications for GLP-1 RAs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year Approved</th>
<th>FDA Indication in T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>2005</td>
<td>• Adjunct to diet and exercise to improve glycemic control in adults</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>2016</td>
<td>• Adjunct to diet and exercise to improve glycemic control in adults</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>2010</td>
<td>• Adjunct to diet and exercise to improve glycemic control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduce risk of MACE in adults with T2DM and established CVD</td>
</tr>
<tr>
<td>Exenatide LAR</td>
<td>2005</td>
<td>• Adjunct to diet and exercise to improve glycemic control in adults</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>2014</td>
<td>• Adjunct to diet and exercise to improve glycemic control in adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduce risk of MACE in adults with T2DM and established CVD or multiple CV risk factors</td>
</tr>
<tr>
<td>Semaglutide SC</td>
<td>2017</td>
<td>• Adjunct to diet and exercise to improve glycemic control in adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduce risk of MACE in adults with T2DM and established CVD</td>
</tr>
<tr>
<td>Semaglutide oral</td>
<td>2017</td>
<td>• Adjunct to diet and exercise to improve glycemic control in adults</td>
</tr>
</tbody>
</table>

Oral Semaglutide: An Alternative to Injectable Therapy

- Taken once daily in morning, 30 min before first food, beverage, or other oral medications of the day (take with no more than 4 ounces of water)
- Starting dose: 3 mg once daily for 30 days
- After 30 days on 3 mg, increase to 7 mg once daily
- After 30 days on 7 mg, increase to 14 mg once daily if more glycemic control needed
  - Taking two 7 mg tablets to achieve a 14 mg dose is contraindicated
- Studied as monotherapy and as add on to metformin, OADs, and basal insulin
- Shares characteristics with other GLP-1 RAs
  - A1C reduction, weight loss, low hypoglycemia risk
  - Noninferior to placebo in CVOT (PIONEER 6)

OAD = oral antidiabetic drug.
Factor Clinical Characteristics of GLP-1 RAs Into Shared Decision-Making

• Highly effective glucose-lowering agents, with some variability between agents
• Depending on the agent, treatment may have a greater or lesser effect in terms of reductions in A1C, FPG, and PPG
• Associated with low risk of hypoglycemia, unless administered in combination with insulin or a sulfonylurea
• May support patients’ efforts to maintain or reduce weight
• Administration frequency and expected glycemic and nonglycemic benefits should be part of patient-clinician discussion and shared decision-making
Important Educational Points to Help Patients Understand, Avoid, and Manage Adverse GI Effects

Discuss expectations

- Nausea is usually transient
- Unfamiliar sense of fullness may be interpreted as “nausea”

Severe abdominal pain is not normal or typical

- Persistent severe abdominal pain may indicate presence of pancreatitis
- No increased risk of pancreatitis was noted in CVOTs
- Discontinue GLP-1 RA and promptly report pain to healthcare provider

GI symptoms can be minimized

- Titrate GLP-1 RA slowly
- Stop eating when fullness is first sensed

Suggest behavioral changes

- Decrease portion sizes and fat content
- Keep a log of foods that cause nausea

Other Considerations and Precautions

- Injection site reactions may occur
- Adding to SU or insulin may increase hypoglycemia risk
- Do not use in patients with a history of pancreatitis
- Boxed warning for all long-acting GLP-1 RAs
  - Contraindicated in patients with a history of medullary thyroid cancer or multiple endocrine neoplasia syndrome (MENS)
- Monitor patients with history of diabetic retinopathy for treatment-related changes
  - Diabetic retinopathy complications reported in patients with semaglutide injection in SUSTAIN-6
- Not recommended for use during pregnancy
GLP-1 RAs in Patients with Renal Impairment

<table>
<thead>
<tr>
<th>CKD Stages</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
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<tbody>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>&lt;15</td>
<td>15-29</td>
<td>30-59</td>
<td>60-89</td>
<td>≥90</td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
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</table>

- **Liraglutide**: Use with caution
- **Dulaglutide**: Use with caution
- **Semaglutide**: Use with caution
- **Lixisenatide**: Not recommended
- **Exenatide BID**: Not recommended
- **Exenatide QW**: Not recommended

<table>
<thead>
<tr>
<th>Drug</th>
<th>CKD Stage 5</th>
<th>CKD Stage 4</th>
<th>CKD Stage 3</th>
<th>CKD Stage 2</th>
<th>CKD Stage 1</th>
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<td>Exenatide QW</td>
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</table>

Ongoing Management of T2DM

- Assess glycemic control: if not at goal, evaluate adherence or need for therapy change
- Reinforce lifestyle modification recommendations
- Refer, if necessary, for additional support with self-management, nutrition, psychosocial health, technology
- Refer for annual eye exams, regular dental care, and family planning as needed

PCE Action Plan

✓ Consider a GLP-1 RA with proven benefit in CV risk reduction for patients with existing ASCVD or multiple CV risk factors
✓ Match the GLP-1 RA to the patient’s needs, abilities, preferences, and support
✓ Educate patients on the GI side effects associated with GLP-1 RAs and how to minimize them
✓ To maintain progress, set date and goals for follow-up visit and reassess patient engagement, adherence, and need for referral, if not met

PCE Promotes Practice Change