Newer Glucose Lowering Medications: 
Agent-Specific Considerations

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Presenter Disclosure Information

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Joshua J. Neumiller, PharmD, CDE

Disclosed no conflict of interest.
If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:

- **If ASCVD Predominates:**
  - Add GLP-1 RA with proven CVD benefit, OR
  - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)

- **If HF or CKD Predominates:**
  - Add SGLT-2 inhibitor with evidence of benefit (if eGFR adequate)
  - If can’t take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit
## Currently Available SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>100 mg daily before breakfast; Increase to 300 mg daily if needed</td>
<td>5 mg daily in the AM; Increase to 10 mg daily if needed</td>
<td>10 mg daily in the AM; Increase to 25 mg if needed</td>
<td>5 mg daily in the AM; Increase to 15 mg if needed</td>
</tr>
</tbody>
</table>
| **Indication(s)** | • Adjunct to diet and exercise to improve glycemic control in T2D  
• To reduce the risk of major adverse CV events in adults with T2D and established CVD | • Adjunct to diet and exercise to improve glycemic control in T2D  
• To reduce the risk of CV death in adults with T2D and established CVD | • Adjunct to diet and exercise to improve glycemic control in T2D  
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• To reduce the risk of CV death in adults with T2D and established CVD |

*Low Risk of Hypoglycemia, Weight Loss, Renal Dose Adjustment*

* eGFR expressed as mL/min/1.73m²

**Canagliflozin Prescribing Information. Janssen Pharmaceuticals, Inc., 2018.**
**Dapagliflozin Prescribing Information. AstraZeneca Pharmaceuticals LP, 2018.**
**Empagliflozin Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc., 2018.**
**Ertugliflozin Prescribing Information. Merck & Co., Inc., 2018.**
### Currently Available GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Indication(s)</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
<th>Dulaglutide</th>
<th>Semaglutide</th>
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**GLP-1 RA “Type”**
- Short-Acting
- Long-Acting


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### Currently Available GLP-1 Receptor Agonists

<table>
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<tr>
<th>Dosing Frequency*</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
<th>Dulaglutide</th>
<th>Semaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice Daily</td>
<td>• ✔</td>
<td>• ✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Once Daily</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Once weekly</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Low Risk of Hypoglycemia

Weight Loss

*Also consider differences in devices for delivery.*

• If choosing a GLP-1 receptor agonist with good efficacy for weight loss:

Semaglutide > liraglutide > dulaglutide > exenatide

Insulin Glargine/Lixisenatide Fixed-Dose Combination (FDC)

**Fixed-dose combination product**
- Insulin glargine (U-100)
- Lixisenatide (short-acting GLP-1 RA) – 33 mcg/mL

**Initiation:**
- For patients on < 30 units basal insulin:
  - 15 units insulin glargine U-100 (5 mcg lixisenatide)
- For patients on 30 - 60 units basal insulin:
  - 30 units insulin glargine U-100 (10 mcg lixisenatide)

**Administration:** within 1 hour before the first meal of the day

**Titration:** 2 - 4 units (insulin glargine U-100 component) once weekly based on FPG or hypoglycemia
Insulin Degludec/Liraglutide
Fixed-Dose Combination (FDC)

• **Fixed-dose combination product**
  • Insulin degludec (U-100)
  • Liraglutide (once-daily GLP-1 RA) – 3.6 mg/mL

• **Initiation:**
  • 16 units insulin degludec (0.58 mg liraglutide) once daily

• **Administration:** same time once daily (with or without food)

• **Titration:**
  • Titrate by 2 units (insulin degludec) every 3 - 4 days based on FPG or hypoglycemia

Insulin degludec/liraglutide Prescribing Information. Available at: http://www.novo-pi.com/xultophy10036.pdf

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Basal + GLP-1 Receptor Agonist FDC Products: Device/Product Comparison

**Insulin Glargine/Lixisenatide**

• Unit dose markings from 0 to 2 for priming
• No markings from 3 to 14 units
• Dose unit markings from 15 to 60 units

**Insulin Degludec/Liraglutide**

• Dosing unit "line" at 2 units for priming
• No markings until 10 units
• Dose unit markings from 10 to 50 units

Insulin glargine/lixisenatide Prescribing Information. Available at: http://products.sanofi.us/Soliqua100-33/Soliqua100-33.pdf
Insulin degludec/liraglutide Prescribing Information. Available at: http://www.novo-pi.com/xultophy10036.pdf
Glucose-Lowering Agents in Late Stage Development

Oral Semaglutide

- Potentially the first orally available GLP-1 receptor agonist
- Co-formulated with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)aminocaprylate]—AKA “SNAC”
  - Facilitates transcellular absorption of semaglutide in the stomach
    - Increases local pH around the tablet
    - Increased drug solubility
    - Protection against proteolytic degradation
- PIONEER program

Davies M, et al. JAMA 2017;318:1460-1470
Bui V, Neumiller JJ. Clin Diabetes 2018;36(4):327-329
Sotagliflozin: A Dual SGLT1/SGLT2 Inhibitor

Potential Effects of Dual SGLT Inhibition

<table>
<thead>
<tr>
<th>SGLT2 Inhibition</th>
<th>SGLT1 Inhibition</th>
</tr>
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</table>
| • Decreased renal glucose reabsorption  
  • Glycemic efficacy diminishes with declining renal function | • Delay/reduce glucose absorption in proximal intestine  
  • Glycemic efficacy not affected with decline in renal function  
  • Increase in endogenous GLP-1 release |

• Glycemic effects of SGLT2/SGLT1 inhibition with sotagliflozin are insulin-independent  
  • Under investigation for both type 1 and type 2 diabetes


Wright EM, et al. Physiol Rev 2011;91:733-794
Sotagliflozin as Adjunct to Optimized Insulin Therapy in Type 1 Diabetes

Change in A1c from Baseline at Week 24


Net Benefit = Achieve A1C <7.0% without significant hypoglycemia or DKA

Sotagliflozin as Add-On to Insulin in T1D

• FDA’s Endocrinologic and Metabolic Drugs Advisory Committee voted 8 to 8 on use of sotagliflozin in people with T1D for whom optimal glycemic control was not achieved on insulin alone
  
  • Benefits:
    • A1C reduction (~0.3-0.4%)
    • Total insulin dose decrease (~4-9 units/day)
    • Body weight decrease (~2-3 kg)
  
  • Risks:
    • DKA: 3% (56 of 1,748 participants) vs. 0.4% (5 of 1,229 participants)

• Final FDA decision expected as early as March 2019

International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care 2019 Feb; dc182316.

Q&A Panel Discussion
Case Scenario: Joan

PMH:
- Type 2 diabetes mellitus (T2D)
- Hypertension
- Hypercholesterolemia (LDL > 130 mg/dL)
- Hx CABG (Dec 2017)
- Obesity

Current Medications:
- Metformin ER 1,000 mg BID
- Atorvastatin 40 mg PO QPM
- Lisinopril 10 mg PO QAM
- Atenolol 50 mg QAM
- ASA 81 mg QAM

Case Scenario: Joan

Weight: 232 lbs (BMI = 34)  
BP: 134/84 mmHg  
HR: 80
Cap BG: 233 mg/dL (2h PP)  
POC A1C: 8.2% (↑ from 7.5% in Nov)

Additional Laboratory Findings - Fasting (drawn November 2018):

SCr: 1.2 mg/dL  
eGFR: 48 mL/min/1.73m²
Na: 139 mEq/L  
K: 4.9 mEq/L

LDL-C: 88 mg/dL  
HDL-C: 40 mg/dL
Trig: 148 mg/dL