To Insulin and Beyond: New Therapies for the Treatment of Type 2 Diabetes Mellitus

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The following presenters have nothing to disclose in relation to this presentation:
- Dr. Adenike Atanda
- Dr. Cheng Yuet
Learning Objectives - Pharmacists

1. Describe the clinical pharmacology of new glucagon-like peptide-1 (GLP-1) receptor agonists, rapid-acting human insulin analog and sodium-glucose cotransporter-2 (SGLT-2) inhibitors

2. Outline the benefits and risks of GLP-1 receptor agonists, rapid-acting human insulin analog and SGLT-2 inhibitors in the management of patients with type 2 diabetes mellitus

3. Summarize key findings from cardiovascular outcome trials (CVOTs) for GLP-1 receptor agonists and SGLT-2 inhibitors

4. Review novel drug formulations and delivery devices in the pipeline for the treatment of type 2 diabetes mellitus
Learning Objectives – Technicians

1. Identify insulin and non-insulin therapies used in the treatment of type 2 diabetes mellitus
2. Describe the clinical pharmacology of glucagon-like peptide-1 (GLP-1) receptor agonists, rapid-acting human insulin analog and sodium-glucose cotransporter-2 (SGLT-2) inhibitors
3. Identify key patient variables that warrant drug utilization review or patients counseling by the pharmacist
4. Review novel drug formulations and delivery devices in the pipeline for the treatment of type 2 diabetes mellitus
The Egregious Eleven

Updated from “The Ominous Octet”

Highlights pathways contributing to hyperglycemia

Disease targets for drug development

History of Non-Insulin Therapies

- 1955: Sulfonylureas
- 1995: Metformin
- 1995: Troglitazone
- 1999: Pioglitazone, Rosiglitazone
- 2006: Sitagliptin
- 2012: Linagliptin
- 2013: Canagliflozin
- 2016: Lixisenatide, Degludec/Liraglutide, Glargine/Lixisenatide
- 1983: 2nd Gen. Sulfonylureas
- 1996: Acarbose, Miglitol
- 1998: Repaglinide
- 2005: Exenatide
- 2010: Liraglutide
- 2013: Alogliptin
- 2014: Dulaglutide, Dapagliflozin, Empagliflozin
- 2017: Ertugliflozin, Semaglutide

Glucagon-Like Peptide-1 (GLP-1) Agonists

- **Incretin hormones:**
  - Glucose-dependent insulinotropic polypeptide
  - Glucagon-like peptide 1 (GLP-1)

- Native GLP-1 has a short half-life (1.5 - 5 minutes) and is subject to degradation by dipeptidyl peptidase-4 (DPP-4)

- Incretin effect is reduced in type 2 diabetes mellitus (T2DM)
  - Increased insulin stimulation elicited by oral administration of glucose vs. intravenous administration of glucose

GLP-1 Agonists: Effects and Agents

- Pharmacologic effects:
  - Glucose-dependent insulin secretion
  - Improved insulin sensitivity
  - Decreased glucagon concentrations
  - Slowed gastric emptying
  - Increased satiety
  - Decreased free fatty acid levels and body weight

- Agents in the United States:
  - Short-acting: exenatide IR (Byetta®), lixisenatide (Adlyxin®)
  - Intermediate-acting: liraglutide (Victoza®)
  - Long-acting: exenatide ER (Bydureon®), dulaglutide (Trulicity®), semaglutide (Ozempic®)

Novel GLP-1 Agonist Formulations

- Insulin Degludec / Liraglutide (Xultophy®)
- Insulin Glargine / Lixisenatide (Soliqua®)
- Semaglutide (Ozempic®)
Insulin Degludec / Liraglutide (Xultophy®)

• Approved November 2016

• Indicated for the management of T2DM inadequately controlled on < 50 units of basal insulin daily or ≤ 1.8mg daily of liraglutide

• Dosing considerations
  o Discontinue liraglutide therapy or basal insulin prior to initiation.
  o Fixed-ratio of 100 units of insulin degludec to 3.6mg of liraglutide. Recommended starting dose is 16 units (16 units of insulin degludec and 0.58mg of liraglutide) subcutaneously once daily. Maximum daily dose is 50 units.
  o Titrate by two units every 3 to 4 days (upwards or downwards). Can down-titrate to lower dose (10 to 15 units) temporarily. Discontinue if patient requires persistent dosage below 16 units or above 50 units daily.
  o Resume the daily dosing at the next scheduled dose if a dose is missed. If > 3 days since last dose, reinitiate at 16 units daily to minimize gastrointestinal symptoms.

• Storage
  o Package includes five 3ml pre-filled pen (300 units of insulin degludec and 10.8mg of liraglutide per pen).
  o Last 21 days at room temperature once in use.

• Retail Cost: approximately US $1,190 for five 3ml pens

Xultophy® Efficacy: DUAL II Trial

- 26 week, double blind, RCT among 413 patients with T2DM
- IDegLira + metformin or IDeg + metformin as add-on to pre-trial basal insulin and metformin ± sulfonylurea or meglitinides
- Select baseline characteristics
  - 58 years old, 79% white
  - DM duration of 11 years
  - BMI 34 kg/m²
  - A1C 8.8%, FPG 175 mg/dL
  - 52% on basal insulin, metformin and sulfonylureas/meglitinides
- Nausea and diarrhea: 6.5% (iDegLira) vs. 3.5% (iDeg)

Xultophy® Efficacy: DUAL IV Trial

- 26 week, double blind, RCT among 362 insulin-naïve patients with T2DM
- IDegLira or placebo as add-on to pre-trial sulfonylurea ± metformin
- Select baseline characteristics
  - 60 years old, 76% white
  - DM duration of 9 years
  - BMI 32 kg/m²
  - A1C 7.9%, FPG 165mg/dL
  - 90% on sulfonylurea + metformin
- Mean dose of IDegLira of 28 units

Rodbard HW, Bode BW, Harris SB. Diabet Med. 34, 189–196 (2017)
Xultophy® Safety

• **Post-marketing experience***
  - Dehydration from gastrointestinal adverse effects
  - Angioedema and anaphylactic reactions
  - Hepatobiliary disorders – elevated liver enzymes, hyperbilirubinemia, cholestasis and hepatitis

• **Warnings**
  - Risk of thyroid c-cell tumors
  - Pancreatitis (has not been studied in patients with a history of pancreatitis)
  - Acute kidney injury and hypokalemia
  - Fluid retention and heart failure with thiazolidinediones

• **Contraindications**
  - Hypersensitivity and hypoglycemia
  - Personal or family history of Medullary Thyroid Carcinoma (MTC)
  - Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

*Frequency and causal relationship to drug exposure has not been established
Insulin Glargine / Lixisenatide (Soliqua®)

• Approved November 2016

• Indicated for the management of T2DM inadequately controlled on < 60 units of basal insulin daily or lixisenatide.

• Dosing considerations
  o Discontinue lixisenatide therapy or basal insulin prior to initiation.
  o Fixed-ratio of 100 units of insulin glargine to 33mcg of lixisenatide. Recommended starting dose is 15 units (15 units of insulin glargine and 5mcg of lixisenatide) subcutaneously once daily for patients inadequately controlled on < 30 units of basal insulin or on lixisenatide. Recommended starting dose is 30 units (30 units of insulin glargine and 10mcg of lixisenatide) subcutaneously once daily for patients inadequately controlled on < 30 - 60 units of basal insulin. Maximum daily dose is 60 units.
  o Titrate by two to four units every week (upwards or downwards). Discontinue if patient requires persistent dosage below 15 units or above 60 units daily.
  o Resume the daily dosing at the next scheduled dose if a dose is missed.

• Storage
  o Package includes five 3ml pre-filled pen (300 units of insulin glargine and 99mcg of lixisenatide per pen).
  o Last 28 days at room temperature once in use.

• Retail Cost: approximately US $800 for five 3ml pens
Soliqua® Efficacy: LixiLan O Trial

- 34 week, open-label, randomized, parallel-group, multicenter trial among 1170 basal insulin-naïve patients with T2DM
- IGlarLixi or insulin glargine or lixisenatide as add-on to pre-trial metformin
- 4 week run in to discontinue other oral diabetes medications (sulfonylurea, meglitinides, SGLT-2 inhibitor or DPP-4 inhibitor)
- Select baseline characteristics
  - 58 years old, 92% white
  - DM duration of 8.8 years
  - BMI 32 kg/m²
  - A1C 8.1%, FPG 178mg/dL
- Mean dose of IGlarLixi and insulin glargine of 40 units
- Gastrointestinal adverse effects: 22% (iGlarLixi) vs. 13% (iGlar) vs. 37% (Lixi)

Soliqua® Efficacy: LixiLan L Trial

• 36 week, open-label, randomized, parallel-group, multicenter trial among 736 basal insulin treated patients with T2DM

• iGlarLixi or insulin glargine as add-on to pre-trial metformin
  ○ Other oral diabetes medications were stopped during the run in

• 6 week run in for glargine introduction and titration

• Select baseline characteristics
  ○ 60 years old, 92% white
  ○ DM duration of 12 years, insulin duration of 3 years
  ○ BMI 31 kg/m²
  ○ A1C 8.1%, FPG 132mg/dL

• Mean dose of iGlarLixi of 48 units

• Gastrointestinal adverse effects: 17% (iGlarLixi) vs. 8% (iGlar)

Soliqua® Safety

Common Adverse Reactions | Incidence (%) |
--------------------------|---------------|
Nausea                    | 10            |
Nasopharyngitis           | 7.0           |
Diarrhea                  | 7.0           |
Upper respiratory tract infection | 5.5   |
Headache                  | 5.4           |
Symptomatic hypoglycemia  | 25 - 40       |
Severe hypoglycemia       | 1.1           |

• **Warnings**
  o Pancreatitis
    ▪ Has not been studied in patients with a history of pancreatitis
  o Acute kidney injury and hypokalemia
  o Fluid retention and heart failure with thiazolidinediones

• **Contraindications**
  o Hypersensitivity
  o Hypoglycemia
Semaglutide (Ozempic®)

- Approved December 2017
- Indicated for the management of T2DM as adjunct to diet and exercise

**Dosing considerations**
- Recommended starting dose is 0.25 mg subcutaneously once weekly. Titrate to 0.5mg once weekly after 4 weeks. If additional control is needed, can increase to 1mg once weekly.
- Administer on the same day each week. Can change the day of administration as long as the time between doses is at least 2 days.
- Maximum dose is 1mg.
- If a dose is missed administer within 5 days of the missed dose.

**Storage**
- Package includes one or two 1.5ml pre-filled pen (2mg of semaglutide per pen)
- Last 56 days at room temperature once in use

**Retail Cost:** approximately US $800 for one 1.5 ml pen

Semaglutide Prescribing Information. Novo Nordisk. December 2017
Ozempic® Efficacy: Sustain 1 Trial

- 30 week, placebo controlled, double blind, randomized, parallel-group, multicenter trial among 388 treatment naïve patients with T2DM

- **Semaglutide** or placebo with no add-on glucose lowering medications (diet and exercise only)
  - 30 day run in

- Select baseline characteristics
  - 54 years old, 65% white
  - DM duration of 4 years
  - BMI 32 kg/m²
  - A1C 8.1%

- Gastrointestinal adverse effects: 38% (Semaglutide 0.5mg) vs. 38% (Semaglutide 1mg) vs. 15% (Placebo)

Semaglutide Prescribing Information. Novo Nordisk. December 2017
Ozempic® Comparative Efficacy

Figure 2. Proportion of subjects with baseline HbA1c >9% achieving HbA1c targets at week 40 in SUSTAIN 7

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of subjects (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide 0.5 mg vs dulaglutide 0.75 mg</td>
<td>44 (18; 95.6)</td>
<td>3.50 [1.40; 8.27]</td>
</tr>
<tr>
<td>Semaglutide 1.0 mg vs dulaglutide 1.5 mg</td>
<td>50 (80; 96.0)</td>
<td>2.15 [0.97; 4.75]</td>
</tr>
</tbody>
</table>

Overall mean at baseline: 95.8 kg

Pratley RE et al. Diabetes 2018 Jul; 67(Supplement 1); Ahmann AJ et al. Diabetes Care 2018 Feb; 41(2): 258-266
Ozempic® Safety

Common Adverse Reactions | Incidence (%) |
---|---|
Nausea | 15.8 - 20.3 |
Vomiting | 5 - 9.2 |
Diarrhea | 8.5 - 8.8 |
Abdominal pain | 5.7 - 7.3 |
Constipation | 3.1 – 5.0 |
Symptomatic hypoglycemia | 1.6 – 3.8 |
Severe hypoglycemia | 0 |

• **Warnings**
  - Risk of thyroid c-cell tumors
  - Diabetic retinopathy complications
    - Sustain 6: 3% (semaglutide) vs. 1.8% (placebo) (HR = 1.76; 95% CI, 1.11-2.78; P = 0.02)
  - Pancreatitis
    - Has not been studied in patients with a history of pancreatitis
  - Acute kidney injury

• **Contraindications**
  - Hypersensitivity
  - Personal or family history of medullary thyroid carcinoma (MTC)
  - Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
Which of the following challenges have been associated with combination GLP-1/insulin products in clinical trials?

A. Increase in hypoglycemia episodes in comparison to insulin products

B. Increased cost in comparison to treatment with individual GLP-1 and insulin agents

C. Multiple day dosing in comparison to insulin products

D. Increased gastrointestinal adverse effects in comparison to insulin products
Self-Assessment Question #2

Which of the following benefits have been associated with semaglutide therapy in clinical trials?

A. More patients achieved A1C goals in comparison to dulaglutide

B. Similar weight reduction in comparison to exenatide

C. Decreased gastrointestinal adverse effects when compared to other GLP-1 agonists

D. Decreased retinopathy when compared to other GLP-1 agonists
New GLP-1 Agonists: Take Home Points

• **Benefits**
  - Combination products
    - Possible reduction in hypoglycemia compared to insulin products
    - Weight loss compared to insulin products
    - Cost benefit for combination products
  - Semaglutide
    - A1C and weight reduction compared to other GLP-1 agonists
    - Once weekly administration

• **Challenges**
  - Combination products
    - Dosing schedule and flexibility
    - Increased GI adverse effects compared to insulin products
  - Semaglutide
    - Increased risk of retinal complications compared to other GLP-1 agonists and insulin products
    - Increased GI adverse effects compared to insulin products
GLP-1 Agonists: Cardiovascular Outcomes

- Major adverse cardiovascular event (MACE)
  - In 2008, the FDA mandated randomized controlled trials to assess potential MACE risk among new therapies to treat hyperglycemia in T2DM
  - Composite endpoint “3-point MACE” includes CV death, non-fatal myocardial infarction, and non-fatal stroke

- CV risk reduction found with select GLP-1 agonists but may not be a class-wide effect

- Completed trials: LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), and ELIXA (lixisenatide)

- Ongoing trials: HARMONY (albiglutide), REWIND (dulaglutide), Freedom-CVO (exenatide vs. osmotic pump), PIONEER 6 (oral semaglutide)
<table>
<thead>
<tr>
<th>Trial</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>EXSCEL</th>
<th>ELIXA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Drug</strong></td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Exenatide ER</td>
<td>Lixisenatide</td>
</tr>
<tr>
<td><strong>Trial details</strong></td>
<td>9,340 patients Duration 3.5 years Age – 64.3 Duration of DM – 12.7 years A1C – 8.7% CVD hx – 81%/stable</td>
<td>3,297 patients Duration 2.1 years Age – 64 Duration of DM – 13.9 years A1C – 8.7% CVD hx – 83%/stable</td>
<td>14,572 patients Duration 3.2 years Age – 62 Duration of DM – 12 years A1C – 8.0% CVD hx – 73%/stable</td>
<td>6,068 patients Duration 2.1 years Age – 60 Duration of DM – 9.3 years A1C – 7.7% CVD hx – 100%/ACS</td>
</tr>
<tr>
<td><strong>Composite primary CV endpoint</strong></td>
<td>Placebo 14.9% vs. liraglutide 13.0%</td>
<td>Placebo 8.9% vs. semaglutide 6.6%</td>
<td>Placebo 12.2% vs. exenatide 11.4%</td>
<td>Placebo 13.2% vs. lixisenatide 13.4%</td>
</tr>
<tr>
<td><strong>Primary endpoint outcome - MACE change (RRR, HR; p for non-inferiority; p for superiority)</strong></td>
<td>− 13%; HR 0.87 (0.78–0.97); p &lt; 0.001 for non-inferiority; p = 0.01 for superiority</td>
<td>− 26%; HR 0.74 (0.58–0.95) p &lt; 0.001 for non-inferiority; p = 0.02 for superiority</td>
<td>− 9%; HR 0.91 (0.83–1.00); p &lt; 0.001 for non-inferiority; p = 0.06 for superiority</td>
<td>+ 2%; HR 1.02 (0.89–1.17); p &lt; 0.001 for non-inferiority; p = 0.81 for inferiority</td>
</tr>
<tr>
<td><strong>Primary endpoint outcome - MACE change (ARR; NNT)</strong></td>
<td>1.9%; 53</td>
<td>2.3%; 43</td>
<td>0.8%; 125</td>
<td>0.2%; NNH 500</td>
</tr>
</tbody>
</table>

* Primary composite outcome (nonfatal stroke, nonfatal MI, or CV death)
Novel Insulin Formulation

- Insulin Aspart (Fiasp®)
  - Rapid acting human insulin analog
Insulin Aspart (Fiasp®)

• Approved September 2017

• Indicated for the management of diabetes mellitus (type 1 and 2) to improve glycemic control

• **Dosing considerations**
  - Subcutaneous injection at the **start of a meal or within 20 minutes** after starting a meal
  - Should be given with intermediate or long acting insulin regimen
  - Onset ~ 4 minutes, peak ~ 120 minutes and return to baseline ~ 6 hours

• **Storage**
  - Package includes five 3ml pre-filled pen (300 units per pen)
  - Vial includes 10ml (1000 units per vial)
  - Last 28 days at room temperature once in use

• **Retail Cost:** approximately US $ 580 for five 3 ml pens and US $300 for one 10 ml vial

Insulin Aspart Prescribing Information. Novo Nordisk. September 2017
Fiasp® Efficacy: Onset 1 Trial

- 26 week, active-controlled, randomized, parallel-group among 1143 patients with T1DM
- Insulin aspart (fiasp) or insulin aspart as add-on to insulin detemir
- 8 week run in for insulin detemir initiation and titration

Select baseline characteristics:
- 44 years old, 93% white
- DM duration of 12.3 years
- BMI 26.7 kg/m²
- A1C 7.6%, FPG 146mg/dL
- 100% on basal insulin
### Fiasp® Safety

**Warnings**
- Hypoglycemia
- Hypokalemia
- Fluid retention and heart failure with concomitant thiazolidinediones

**Contraindications**
- Hypersensitivity
- Hypoglycemia

<table>
<thead>
<tr>
<th>Common Adverse Reactions*</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>20.2–23.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.4 – 9.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.2 – 5.4</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.0 – 5.4</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>6.7 – 8.0</td>
</tr>
</tbody>
</table>

*with insulin detemir

Fiasp Prescribing Information. Novo Nordisk. September 2017
New Insulin Formulation: Take Home Points

• **Benefits**
  - Superior post prandial glucose control (meal time administration)
  - Faster onset
  - Convenience with administration time (taken before the meal)
  - Similar hypoglycemia profile with insulin aspart

• **Challenges**
  - Potential confusion with administration timing
Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

- Monotherapy or combination therapy adjunct to diet and exercise for T2DM
  - Canagliflozin and empagliflozin have additional indication for CV risk reduction
- SGLT-2 is expressed on the proximal renal tubules and modulates most of the reabsorption of filtered glucose from the tubular lumen
- SGLT-2 inhibition reduces the amount of glucose reabsorbed and increases its renal elimination
  - Results in unique adverse event profile


http://agscientific.com/blog/2016/01/diabetes-2016/
SGLT-2 Inhibitors: Effects and Agents

- Pharmacologic effects
  - Improves A1c and fasting plasma glucose (FPG)
  - Decreases blood pressure
  - Decreases body weight
  - Modest effects on lipid panel

- Agents available in the United States:
  - Canagliflozin (Invokana®)
  - Dapagliflozin (Farxiga®)
  - Empagliflozin (Jardiance®)
  - Ertugliflozin (Steglatro®)

Newly Approved SGLT2 Inhibitor Formulations

- Ertugliflozin (Steglatro®)
- Ertugliflozin / Sitagliptin (Steglujan®)
- Ertugliflozin / Metformin (Stegluromet®)
Ertugliflozin (Steglatro®)

• Approved December 2017

• Indicated for the management of T2DM as an adjunct to diet and exercise

• Dosing Considerations:
  o Recommended starting dose is 5 mg once daily in the morning with or without food
  o Increase dose to 15 mg once daily in those tolerating the medication and needing additional glycemic control
  o Do not use in eGFR < 30 mL/minute/1.73 m²
  o Initiation (or continued use) is not recommended in eGFR 30-60 mL/minute/1.73 m²

• Retail Cost: approximately US $300 for 30 tablets
Steglatro® Efficacy: Phase III Trial (Terra et al)

- 52 week, placebo controlled, double blind, randomized, parallel-group, multicenter trial among 461 patients with inadequately controlled T2DM despite diet and lifestyle
  - Results pertain to 26 week placebo controlled period

- Ertugliflozin or placebo with no add-on glucose lowering medications (diet and exercise only)

- Select baseline characteristics
  - 56 years old, 83% white
  - DM duration of 5 years
  - BMI 33 kg/m²
  - A1C 8.2%

- Statistically significant improvements in A1c and secondary endpoints (FPG, 2-hour PPG, body weight)

Steglatro® Efficacy: VERTIS MONO Extension Trial

- 52 week, placebo controlled, double blind, randomized, parallel-group, multicenter trial among 461 patients with inadequately controlled T2DM despite diet and lifestyle
  - Results pertain to 26 week active controlled period which followed the 26 week placebo controlled period described by Terra et al

- Ertugliflozin or placebo with metformin
  - A1c reductions from ertugliflozin arms observed at week 26 were maintained through week 52
  - Mean A1c reduction at week 52 was 1% for ertugliflozin 15 mg and placebo/metformin arms; 0.9% for ertugliflozin 5 mg arms

Steglatro® Safety

### Warnings
- Hypotension
- Ketoacidosis
  - This may occur in patients who are euglycemic
  - Acute kidney injury and renal impairment
  - Urosepsis and pyelonephritis
  - Lower limb amputation
    - Seen in canagliflozin trials
    - No causal association established with ertugliflozin
  - Hypoglycemia with concomitant insulin and insulin secretagogues
  - Genital mycotic infections
  - Increased low-density lipoprotein cholesterol
  - Macrovascular outcomes
    - No evidence of CV risk reduction at this time

### Contraindications
- Hypersensitivity
- Severe renal impairment, end-stage renal disease, or dialysis

### Common Adverse Reactions

<table>
<thead>
<tr>
<th>Common Adverse Reactions</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital mycotic infections</td>
<td>9.1 – 12.2</td>
</tr>
<tr>
<td>Male genital mycotic infections</td>
<td>3.7 – 4.2</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>4.0 – 4.1</td>
</tr>
<tr>
<td>Headache</td>
<td>2.9 – 3.5</td>
</tr>
<tr>
<td>Vaginal pruritus</td>
<td>2.4 – 2.8</td>
</tr>
<tr>
<td>Increased urination</td>
<td>2.4 – 2.7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.0 - 2.5</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.7 - 2.5</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>1.2 – 2.4</td>
</tr>
<tr>
<td>Thirst</td>
<td>1.4 -2.7</td>
</tr>
</tbody>
</table>
Self-Assessment Question #3

Which of the following effects has been demonstrated with ertugliflozin use?

A. Decreased albuminuria
B. Decreased blood pressure
C. Decreased cardiovascular risk
D. Increased amputation risk
New SGLT-2 Inhibitor: Take Home Points

• **Benefits**
  - Ertugliflozin
    - Decreased body weight
    - Improved blood pressure
    - Clinical trials in progress to determine impact on cardiovascular and renal outcomes

• **Challenges**
  - Ertugliflozin
    - Increased risk of genital mycotic infections compared to placebo and metformin monotherapy
    - Other adverse effects (e.g., thirst) may be similar to symptoms of uncontrolled T2DM
    - Yet to determine if ertugliflozin causes amputation risk as seen with canagliflozin
SGLT-2 Inhibitors: Cardiovascular Outcomes

• The composite “3-point MACE” is the primary outcome.

• Two agents are FDA-approved for CV risk reduction in patients with T2DM.

• CV risk reduction found with select SGLT-2 inhibitors but may not be a class-wide effect.

• Completed trials: EMPA-REG OUTCOME (empagliflozin), CANVAS (canagliflozin).

• Ongoing trials: DECLARE-TIMI58 (dapagliflozin), VERTIS CV (ertugliflozin), CREDANCE (canagliflozin).

# SGLT-2 Inhibitor: CVOT Results

## Composite primary CV endpoint*

<table>
<thead>
<tr>
<th>Trial</th>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drug</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
</tr>
<tr>
<td><strong>Trial details</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7,020 patients</td>
<td>10,142 patients</td>
<td></td>
</tr>
<tr>
<td>Duration 3.1 years</td>
<td>Duration 5.7 years</td>
<td></td>
</tr>
<tr>
<td>Age – 63</td>
<td>Age – 63.3</td>
<td></td>
</tr>
<tr>
<td>Duration of DM – 10</td>
<td>Duration of DM – 13.5</td>
<td></td>
</tr>
<tr>
<td>A1C – 8.0%</td>
<td>A1C – 8.2%</td>
<td></td>
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<tr>
<td>CVD hx - 99%/stable</td>
<td>CVD hx – 65.6%/stable</td>
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<tr>
<td><strong>Composite primary CV endpoint</strong>*</td>
<td>Placebo 12.1% vs. empagliflozin 10.5%</td>
<td>Placebo 31.5 vs. canagliflozin 26.9 per 1000 patient years</td>
</tr>
<tr>
<td><strong>Primary endpoint outcome - MACE change (RRR, HR; p for non-inferiority; p for superiority)</strong></td>
<td>− 14%; HR 0.86 (0.74–0.99); p &lt; 0.001 for non-inferiority; p = 0.04 for superiority</td>
<td>− 14%; HR 0.86 (0.75–0.97) p &lt; 0.001 for non-inferiority; p = 0.02 for superiority</td>
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<tr>
<td><strong>Primary endpoint outcome - MACE change (ARR; NNT)</strong></td>
<td>1.6%; 63</td>
<td>0.45%; 224</td>
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</tbody>
</table>

Product Updates

2017 to Present

Discontinued Product
- Albiglutide (Tanzeum®)

Delivery Device Change
- Exenatide (Bydureon BCise®)

New Combination
- Dapagliflozin / Saxagliptin (Qtern®)

In Development
- Oral Semaglutide
Oral Semaglutide: Pioneer 1 Trial

**Study Design**
- 26 week, randomized, double blind, placebo controlled phase 3a trial for 703 patients with uncontrolled T2DM on diet and exercise (no drug therapy)
- Oral semaglutide (3, 7, or 14 mg once daily) or placebo
- Select baseline characteristics
  - 55 years old, 89% female
  - DM duration of 3.5 years
  - A1c 8.0%
  - Body weight 89 kg

**Outcomes**
- Study endpoints (see next slide)
  - Primary endpoint is change from baseline in A1c
  - Secondary endpoint is change from baseline in body weight
- Rate of adverse events was similar across all groups
- Most common adverse event for oral semaglutide was mild-to-moderate nausea
  - 5-16% of patients on oral semaglutide vs. 6% on placebo

Aroda V et al. *Diabetes* 2018;67(Supplement 1): https://doi.org/10.2337/db18-2-LB
# Pioneer 1 Trial: Study Endpoints

ENDPOINTS AT WEEK 26 BY ESTIMAND

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<tbody>
<tr>
<td><strong>Change from baseline in HbA1c</strong></td>
<td>-0.9 ± 0.1</td>
<td>-0.8 ± 0.1</td>
<td>-1.2 ± 0.1</td>
<td>-1.3 ± 0.1</td>
<td>-1.4 ± 0.1</td>
<td>-1.5 ± 0.1</td>
<td>-0.3 ± 0.1</td>
<td>-0.1 ± 0.1</td>
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<tr>
<td><strong>HbA1c (−points) treatment difference vs placebo [95%CI]</strong></td>
<td>-0.6^t</td>
<td>-0.7^t</td>
<td>-0.9^t</td>
<td>-1.2^t</td>
<td>-1.1^t</td>
<td>-1.4^t</td>
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<td></td>
<td>[-0.8; -0.4]</td>
<td>[-0.9; -0.5]</td>
<td>[-1.1; -0.6]</td>
<td>[-1.5; -1.0]</td>
<td>[-1.3; -0.9]</td>
<td>[-1.7; -1.2]</td>
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<tr>
<td><strong>Change from baseline in body weight, kg ± SE (secondary confirmatory endpoint)</strong></td>
<td>-1.5 ± 0.3</td>
<td>-1.7 ± 0.3</td>
<td>-2.3 ± 0.4</td>
<td>-2.5 ± 0.3</td>
<td>-3.7 ± 0.3</td>
<td>-4.1 ± 0.3</td>
<td>-1.4 ± 0.3</td>
<td>-1.5 ± 0.3</td>
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<tr>
<td><strong>Weight (kg) treatment difference vs placebo [95%CI]</strong></td>
<td>-0.1</td>
<td>-0.2</td>
<td>-0.9</td>
<td>-1.0^</td>
<td>-2.3^</td>
<td>-2.6^</td>
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<tr>
<td></td>
<td>[-0.9; 0.8]</td>
<td>[-1.0; 0.6]</td>
<td>[-1.9; 0.1]</td>
<td>[-1.8; -0.2]</td>
<td>[-3.1; -1.5]</td>
<td>[-3.4; -1.8]</td>
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<tr>
<td><strong>Proportion of subjects with HbA1c &lt;7%, %</strong></td>
<td>55.1^</td>
<td>59.1^</td>
<td>68.8^</td>
<td>71.9^</td>
<td>76.9^</td>
<td>80.3^</td>
<td>31.0</td>
<td>33.8</td>
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<tr>
<td><strong>Proportion of subjects with weight loss ≥5%, %</strong></td>
<td>19.6</td>
<td>21.3</td>
<td>26.9^</td>
<td>28.7^</td>
<td>41.3^</td>
<td>44.3^</td>
<td>14.9</td>
<td>15.7</td>
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</table>

n, number of randomized subjects in the full analysis set; SE, standard error; ^p<0.05; ^^p<0.001 vs placebo. Baseline data are means unless specified otherwise. Changes and treatment differences are LSMeans; proportions are observed. The primary and confirmatory secondary endpoints were controlled for multiplicity for the primary estimand. The primary estimand (treatment policy) was evaluated by a pattern-mixture model using multiple imputation to handle missing data. The secondary estimand (hypothetical) was evaluated by a MMRM.

Aroda V et al. Diabetes 2018;67(Supplement 1): https://doi.org/10.2337/db18-2-LB
Which of the following is a TRUE statement associated with the impact of SGLT-2 inhibitors on cardiovascular outcomes?

A. Only canagliflozin is indicated for CV risk reduction in patients with T2DM

B. Improved CV outcomes should be weighed against the risk of amputations for patients taking empagliflozin

C. The number needed to treat (NNT) is lower for empagliflozin compared to canagliflozin

D. CV risk reduction appears to be a class-wide effect for SGLT-2 inhibitors
Summary of New Agents and Role in Therapy

• New agents in the GLP-1 agonist and SGLT-2 inhibitor drug classes have been approved by the FDA since 2017

• Agents from these two classes are recommended more prominently in the 2019 American Diabetes Association (ADA) *Standards of Medical Care in Diabetes*

• It is unclear whether CV risk reduction is a class-wide effect

• Oral semaglutide is a novel agent currently studied in phase 3 trials
To Insulin and Beyond:
New Therapies for the Treatment of Type 2 Diabetes Mellitus

Adenike Atanda, PharmD, BCACP, CDE
Cheng Yuet, PharmD, BCACP