Type 2 Diabetes: An Evidence Based Pharmacotherapy Update

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Faculty Disclosure

• I do not have anything to declare as I do not speak for or consult for any pharmaceutical manufacturer.
Learning Objectives

- Apply the pharmacological treatment of diabetes to case studies.
- Describe the current 2018 ADA Standards of Medical Care for the diagnosis and management of diabetes mellitus
- Review the data on the newer FDA approved medications for the management of Type 2 diabetes
- Discuss the appropriate use of evidence-based and cost effective therapies in the management of patients with Type 2 DM.

Prevention or Delay of Type 2 Diabetes 2018

- Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate intensity physical activity (such as brisk walking) to at least 150 min/week. A
- Pharmacologic Intervention: **Metformin therapy for prevention of type 2 diabetes should be considered** in those with prediabetes, especially for those with BMI >35 kg/m2, those aged < 60 years, and women with prior gestational diabetes mellitus. A
  - Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitaminB12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B
  - Diabetes Care Volume 41, Supplement 1, January 2018 S53
2018 ADA Standards of Medical Care in Diabetes

Highlights related to drug therapy:

- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C >10% and/or blood glucose levels>300mg/dL. E

- Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C>9%. E

- In patients without atherosclerotic cardiovascular disease, if monotherapy or dual therapy does not achieve or maintain the A1C goal over 3 months, add an additional antihyperglycemic agent based on drug-specific and patient factors. A
  - Diabetes Care 2018;41(Suppl. 1):S73–S85

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2018 ADA Standards of Medical Care in Diabetes

- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, renal effects, delivery method (oral versus subcutaneous), cost, and patient preferences. E

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. A*
  - Canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific and patient factors. C* (Black Box Warning Risk of amputations, also warning about increase risk of fractures with canagliflozin)

  - Diabetes Care 2018;41(Suppl. 1):S73–S85
2018 ADA Standards of Medical Care in Diabetes

• Continuous reevaluation of the medication regimen and adjustment as needed to incorporate patient factors and regimen complexity is recommended. E

• For patients with type 2 diabetes who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed. B

• Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated. A
  • Diabetes Care 2018;41(Suppl. 1):S73–S85

ADA and ACE Glycemic Goals

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Normal</th>
<th>ADA 2018</th>
<th>AACE/ACE Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting/preprandial plasma glucose (mg/dL)</td>
<td>&lt;100</td>
<td>80–130</td>
<td>≤110</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mg/dL)</td>
<td>&lt;140</td>
<td>&lt;180</td>
<td>≤140</td>
</tr>
<tr>
<td>Hemoglobin A&lt;sub&gt;1c&lt;/sub&gt; (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>≤6.5</td>
</tr>
</tbody>
</table>

*Goals should be individualized based on: duration of diabetes; age/life expectancy; comorbid conditions; known CVD or advanced microvascular complications; hypoglycemia unawareness; and individual patient considerations. Providers might reasonably suggest more stringent A1C goals (such as <6.5%) if it can be achieved without significant hypoglycemia including patients with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions. B
## Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- A1C is less than 9%, consider Maximal Therapy.
- A1C is greater than or equal to 9%, consider Maximal Therapy.

### Maximal Therapy

Initiate maximal therapy if no contraindications (See Table 6.2)

<table>
<thead>
<tr>
<th>A1C at target after 6 months of maximal therapy?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor A1C every 3-4 months</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoid medication-naïve behavior</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Consider Dual Therapy</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Dual Therapy

Lifestyle Management + Metformin

<table>
<thead>
<tr>
<th>A1C at target after 6 months of dual therapy?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add agent to reduce major adverse cardiovascular events and/or cardiovascular mortality (low recommendations w/ Hgb A1C 7.5%)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoid medication-naïve behavior</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Consider Triple Therapy</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Triple Therapy

Lifestyle Management + Metformin + Additional Agent

<table>
<thead>
<tr>
<th>A1C at target after 3 months of triple therapy?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add third agent based on drug-specific effects and patient factors (See Table 6.2)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoid medication-naïve behavior</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Consider Combination therapies (See Figure 6.3)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Efficacy, Hypoglycemia, Weight Change, CV Effects, Cost, QALY, Prevision of DRI, Avoiding hyperglycemia, Additional Considerations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV Effects</th>
<th>Cost</th>
<th>QALY</th>
<th>Prevention of DRI</th>
<th>Avoiding hyperglycemia</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral, modest loss</td>
<td>Neutral</td>
<td>Low</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Gastrointestinal side effects common (nausea, vomiting)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral, modest weight loss</td>
<td>Neutral</td>
<td>High</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Risk factors for cardiovascular disease, weight loss, glycemic control</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td>Neutral</td>
<td>High</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Gastrointestinal side effects common (diabetes, weight loss)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td>Neutral</td>
<td>High</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Potential risk of acute pancreatitis</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>Gain potential for/against weight gain</td>
<td>Potential for/against weight gain</td>
<td>Increased</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Risk of edema, weight gain, bone fractures</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Benefits in weight loss, renal function, glycemic control</td>
</tr>
<tr>
<td>Sodium-glucose Cotransporter 2 Inhibitors</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>QALY</td>
<td>Prevention of DRI</td>
<td>Avoiding hyperglycemia</td>
<td>Benefits in heart failure, glycemic control</td>
</tr>
</tbody>
</table>

**Diabetes Care Volume 41, Supplement 1, January 2018 576**

**Diabetes Care Volume 41, Supplement 1, January 2018 577**
Combination injectable therapy for type 2 diabetes.

**Initiate Basal Insulin**
- Usually with metformin and/or other noninsulin agent
- Start: 10 U/day or 0.1-0.2 U/kg/day
- Adjust: 10-15% or 2-4 U/day once or twice weekly to reach HbA1c target
- For hyperglycemia: Determine and address causes; if no clear reason for hyperglycemia, consider dose by 4 U or 10-20%

**Change to Premixed Insulin Twice Daily (Before Breakfast and Supper)**
- Start: Divide current basal dose into 1/2 ANH, 1/2 PM or 1/3 ANH, 2/3 PM
- Adjust: 1/2 U or 10-20% once or twice weekly until HbA1c target reached
- For hyperglycemia: Determine and address causes; if no clear reason for hyperglycemia, consider dose by 2-4 U or 10-20%

**Add 1 Rapid-Acting Insulin Injection Before Last Meal**
- Start: 4 U or 1 U/kg (0.5 U/kg or 40 U/m²)
- Adjust: 1 U/kg or 40 U/m² once or twice weekly to achieve HbA1c target
- For hyperglycemia: Consider dose by 2-4 U or 10-20%

**Change to Premixed Insulin Twice Daily (Before Breakfast and Supper)**
- Start: Divide current basal dose into 1/2 ANH, 1/2 PM or 1/3 ANH, 2/3 PM
- Adjust: 1/2 U or 10-20% once or twice weekly until HbA1c target reached
- For hyperglycemia: Determine and address causes; if no clear reason for hyperglycemia, consider dose by 2-4 U or 10-20%

**Add 2 Rapid-Acting Insulin Injections Before Last Meal**
- Start: 4 U or 1 U/kg (0.5 U/kg or 40 U/m²)
- Adjust: 1 U/kg or 40 U/m² once or twice weekly to achieve HbA1c target
- For hyperglycemia: Consider dose by 2-4 U or 10-20%

**Change to Premixed Insulin Twice Daily (Before Breakfast and Supper)**
- Start: Divide current basal dose into 1/2 ANH, 1/2 PM or 1/3 ANH, 2/3 PM
- Adjust: 1/2 U or 10-20% once or twice weekly until HbA1c target reached
- For hyperglycemia: Determine and address causes; if no clear reason for hyperglycemia, consider dose by 2-4 U or 10-20%
**Algorithm for Adding/Intensifying Insulin**

**Start Basal (Long-Acting Insulin)**

- **A1C < 8%**
  - **TDD** 0.1–0.2 U/kg
- **A1C > 8%**
  - **TDD** 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjusting regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 5% of TDD
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10%–20%
    - BG 70–100 mg/dL: 5%–10%
    - BG > 100 mg/dL: 2.5%–5%

Consider discontinuing or reducing sulfonylureas after starting basal insulin (basal analogs preferred to NPH).

*Glycemic Goal:
- <7% for most patients with T2D, fasting and premeal BS < 150 mg/dL absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of complications, diabetic complications, and hypoglycemia risk

**Intensify (Prandial Control)**

- **Add GLP-1 RA**
  - Basal Plus 1, Plus 2, Plus 3
- **Add Prandial Insulin**
  - Basal Bolus

- **Begin prandial insulin before each meal**
  - Basal 0.3–0.5 U/kg
  - Start 10% of basal dose or 5 units

**Profiles of Antidiabetic Medications**

<table>
<thead>
<tr>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGL</th>
<th>TZD (double dose)</th>
<th>SU</th>
<th>COLSFR</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRaml</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutal</td>
<td>Moderate</td>
<td>Gln</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Gain</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td>RENAL / GU</td>
<td>Insulin Dose Required eGFR &lt; 30 mL/min</td>
<td>Not Indicated for eGFR &lt; 45 mL/min, 1.73 m²</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>More Hypo Risk</td>
<td>Neutal</td>
<td>Neutal</td>
<td>More Hypo Risk</td>
<td>Neutal</td>
</tr>
<tr>
<td>GI Side</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Moderate</td>
<td>Neutal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutal</td>
<td>Moderate</td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Possible Benefit of Empagliflozin</td>
<td>Possible Risk for Sodium-Potassium-Adrenaline</td>
<td>Neutal</td>
<td>Moderate</td>
<td>More CHF Risk</td>
<td>Neutal</td>
<td>Neutal</td>
<td>More CHF Risk</td>
<td>Neutal</td>
</tr>
<tr>
<td>ASCVD</td>
<td>Neutral</td>
<td>Possible CV Benefit</td>
<td>Possible Risk for Sodium-Potassium-Adrenaline</td>
<td>Neutal</td>
<td>Moderate</td>
<td>More CHF Risk</td>
<td>Neutal</td>
<td>Neutal</td>
<td>More CHF Risk</td>
<td>Neutal</td>
</tr>
<tr>
<td>BONE</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
<td>Neutal</td>
</tr>
</tbody>
</table>

- Few adverse events or possible benefits
- Use with caution
- Unknown or adverse effects
- Uncertain effect
- **FDA indication to prevent CHF death in diabetes plus prior CHF events**

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UK Prospective Diabetes Study
Glucose Interventional Trial

<table>
<thead>
<tr>
<th>Outcome at 10 years</th>
<th>Diet/Met</th>
<th>Diet/Sulf/Insulin</th>
<th>Diet</th>
<th>RRR/ARR/NNT (Diet/Met vs. Diet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM related endpoint</td>
<td>28.7%</td>
<td>36.8%</td>
<td>38.9%</td>
<td>26.2%/10.2%/10</td>
</tr>
<tr>
<td>Diabetes related death</td>
<td>8.2%</td>
<td>10.8%</td>
<td>13.4%</td>
<td>38.8%/5.2%/19</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>14.6%</td>
<td>20%</td>
<td>21.7%</td>
<td>32.7%/7.1%/14</td>
</tr>
<tr>
<td>MI</td>
<td>11.4%</td>
<td>14.6%</td>
<td>17.8%</td>
<td>36%/6.4%/16</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.5%</td>
<td>6.3%</td>
<td>5.6%</td>
<td>44.4%/2.8%/36</td>
</tr>
<tr>
<td>Micro-vascular events</td>
<td>7.0%</td>
<td>7.8%</td>
<td>9.2%</td>
<td>N/S</td>
</tr>
</tbody>
</table>

Lancet, 1998;352: 854 - 865

Long-term Effects of Metformin on Metabolism
and Microvascular and Macrovascular Disease
in Patients With Type 2 Diabetes Mellitus Treated with Insulin
Arch Intern Med. 2009;169(6):616-625

• 390 patients treated with insulin in the outpatient clinics of 3 hospitals in a randomized, placebo-controlled trial with a follow-up period of 4.3 years. Either metformin hydrochloride, 850 mg, or placebo (1-3 times daily) was added to insulin therapy.

• The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality. The secondary end points were microvascular and macrovascular morbidity and mortality independently.
  • “Hyperinsulinemia the Outcome of its Metabolic Effects (HOME))”
Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus Treated with Insulin

Arch Intern Med. 2009;169(6):616-625

Results:

• Metformin treatment prevented weight gain (mean weight gain, −3.07 kg [range, −3.85 to −2.28 kg]; P < .001),
• Improved glycemic control (mean reduction in HbA1c level, 0.4% percentage point [95% CI, 0.55-0.25]; P < .001), despite the aim of similar glycemic control in both groups,
• Reduced insulin requirements (mean reduction, 19.63 IU/d [95% CI, 24.91-14.36 IU/d]; P < .001).
• Metformin was not associated with an improvement in the primary end point.
• It was, however, associated with an improvement in the secondary, macrovascular end point (hazard ratio, 0.61 [95% CI, 0.40-0.94; P = .02), which was partly explained by the difference in weight.
• The number needed to treat to prevent 1 macrovascular end point was 16.1 (95% CI, 9.2-66.6).
• These sustained beneficial effects support the policy to continue metformin treatment after the introduction of insulin in any patient with DM2, unless contraindicated.

FDA Updates Metformin Dosing Information 4-8-2016

• The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information: Before starting metformin, obtain the patient’s eGFR.
• Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m2.
• Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m2 is not recommended.
• Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
• In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient’s eGFR later falls below 30 mL/minute/1.73 m2.
• Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Metformin Pricing?

- Glucophage AB1 500 mg/60: $68.00; 850 mg $115.00; 1000 mg $136.00
- Generic Glucophage AB1 500 mg/60 $0.00-12.00; 850 mg and 1000 mg $0.00-12.00
- Glucophage XR 500 mg/60 $70.00; 750 mg $100.00
- Generic Glucophage XR 500 mg/60 $4-12.00; 750 mg $10-20.00
- Glumetza AB3 500 mg/60 $3,250.00; 1000 mg/60 $6,800-7,200.00 (Santarus)
- Generic Glumetza AB3 500 mg/60 $1,000-2,500.00; 1000 mg/60 $1,500.00-5,512.00 (Lupin, Sun and Activis)
- Fortamet AB2 500 and 1000 mg/60 $2,100.00 (Andrx)
- Generic Fortamet AB2 1000 mg/60 $400.00-$775.00 (Lupin and Mylan)

— GoodRx.com 1-4-2018

FDA Removes Restrictions on Rosiglitazone - Avandia

- Potential risks listed in the current FDA approved label for pioglitazone and rosiglitazone;
  - Significant weight gain and edema
  - Heart failure (NNH=34 at 3 yrs) in PROactive
  - Upper and lower extremity fractures ~ twice the risk as comparators including PROactive after only 1 year of use
  - Diabetes related macular edema ~ twice the risk in multiple retrospective data sets and increased more when used in combination with insulin
  - Potential for bladder cancer in males with pioglitazone (~40% increase?)
Insulin Glargine – Basaglar by Lilly and BI

- Dec 16, 2015 FDA approved Basaglar (insulin glargine) but not launched until after Dec 2016 based upon court action. The first insulin product approved through an abbreviated approval pathway under the FDA 505(b)(2) application which did rely partly on the safety and effectiveness of Lantus (insulin glargine by Sanofi).
- Cost: ~$343.00 / 5 pens
- Lantus SoloStar ~$403.00 / 5 pens ~15% lower than Lantus

The FDA determined that Basaglar was sufficiently similar to Lantus and in addition Basaglar was studied in two large trials (543 Type 1 and 744 Type 2 patients with diabetes). Like Lantus FDA approved for patients age 6 and up.

Basaglar is considered a “follow-on” NOT FDA approved as a “Biosimilar” product. (There is no reference listed drug for Lantus under the Public Health Services Act)

CVS/Caremark is now excluding Lantus as of 2017
Insulin Degludec- Tresiba by Novo Nordisk

- U-100 FlexTouch - 3 mL 100 units/mL - 300 Units/pen – max dose 80 Units in 1 Unit increments – available 5 pens/pack ~$450.00
- U-200 FlexTouch - 3 mL 200 units/mL - 600 Units/pen – max dose 160 Units in 2 Unit increments - available 3 pens/pack ~$550.00
- T1/2 ~25 hrs, duration ~ 42 hrs
- Keep under refrigeration (NOT frozen) but stable for 56 days (8 weeks) at room temperature.
- The Institute for Clinical and Economic Review (ICER) insulin degludec provides moderate certainty of equivalent glycemic control with a 25-35% reduction in nocturnal hypoglycemia in comparison to other long-acting insulins.

DEVOTE Trial

- DEVOTE (Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events)
- Patients were randomized in a double-blind fashion to receive either insulin degludec (n=3818) or glargine (n=3819).
- Primary composite outcome was first occurrence of 3-point MACE (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke).
- Secondary endpoints included severe hypoglycemia (defined as an episode requiring assistance from another person or an episode temporally associated with an accident, convulsion, or death) and change from baseline in HbA1c, fasting plasma glucose, and total insulin dose by trial end.

– NEJM June 12, 2017 published on-line
DEVOTE Trial

• The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% CI 0.78 to 1.06; P<0.001 for noninferiority).

• At 24 months, the mean glycated hemoglobin level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter, P<0.001).

• Prespecified adjudicated severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, ARR = 1.7% (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). NNT = 59

• Rates of adverse events did not differ between the two groups.
  – NEJM June 12, 2017 published on-line

American Diabetes Association Issues Resolution and Launches Petition Calling for Access to Affordable Insulin

• November 17, 2016 he American Diabetes Association issued a resolution and the launch of a petition calling on all entities in the insulin supply chain to increase transparency and to ensure that no person with diabetes is denied affordable access to insulin. The Association is also calling on Congress to hold hearings with all entities in the insulin supply chain to identify the reasons for the dramatic increases in insulin prices (3 fold ion 10 years) and to take action to ensure affordable access to insulin for all who need it.

Lowest Priced Insulins

• WalMart contracts with Novo Nordisk for Reli-On Regular, NPH and 70/30 NPH/Reg Insulins in 10 cc vials only for ~$25.00/vial
• CVS/Caremark is partnering with Novo Nordisk on a new program called Reduced Rx to provide Regular, NPH and 70/30 NPH/Reg insulins available for $25.00 a 10cc vial
• BD Insulin Syringes Ultra-Fine 6mm Needle with Half-Unit Scale - 31G 3/10cc 15/64" - BX 100 ~$36.00
• BD Ultra-Fine II Short Needle Insulin Syringe - 31G 1cc 5/16" - BX 90 ~$25.00
• BD Ultra Fine Pen Needles Mini 5mm X 31G (100 Needles) ~$40.00

Human Insulin for Type 2 Diabetes
An Effective, Less-Expensive Option
JAMA July 4, 2017 Volume 318, Number 1

How Treatment With Human Insulins Differs - Some differing properties of human N insulin and human R insulin, compared with those of insulin analogues, require modest but important differences in therapeutic approaches.

• Duration of Action. The action of human N insulin does not reliably cover 24 hours so more than 1 daily injection is often required.
• Hypoglycemia Risk. Among patients with type 2 diabetes, long-acting insulin analogues modestly reduce the rate of nocturnal hypoglycemia compared with human N insulin. (A1c goal, education and bedtime snacks).
• Timing With Meals. Human R insulin begins to act no sooner than 30 minutes after injection, while rapid acting insulin analogues (lispro, aspart, and glulisine) have a shorter onset of action of 5 to 15 minutes.
Human Insulin for Type 2 Diabetes
An Effective, Less-Expensive Option

JAMA July 4, 2017 Volume 318, Number 1

• Vial vs Pen. NPH, Regular and 70/30 are only available in a vial
• Injection Techniques. Human N insulin is a cloudy particulate suspension. To avoid inconsistent effects, it must be gently agitated before drawing into a syringe for injection. Absorption of human R insulin is fastest when injected in abdominal sites, followed by the upper arm and thigh; whereas absorption kinetics of rapid-acting insulin analogues seem less site dependent.
• Premixed 70/30human insulin (70% N insulin with 30% R insulin) can be used as a 2-injection regimen, taken before breakfast and dinner. Although this regimen is simple, it is limited by higher risk of hypoglycemia in midday and near midnight, the times of its peaks of action.

Human Insulin for Type 2 Diabetes
An Effective, Less-Expensive Option

Switching to Human Insulin

• Patients can safely switch from insulin analogues to human insulins. Total daily insulin dose can be initially reduced by 20%, because of the different profiles of action and because some patients may have been taking less analogue insulin than had been prescribed.
• For patients already treated with multiple insulin analogue injections, the number of injections and distribution of dosage can remain the same but with a 20% reduction of dosage for safety. Early contact between the physician and the patient by phone or in person is desirable to ensure that an unexpectedly large reduction of glucose has not occurred due to improved adherence.
• In summary, many patients with type 2 diabetes can be treated with human insulin. Due to high costs of analogue insulins, use of human insulin may be the only practical option for some patients, and clinicians should be familiar with its use.
New Ultra-Rapid Insulin Aspart – Fiasp by Novo-Nordisk

- Sept. 29, 2017 the U.S. Food and Drug Administration (FDA) approved Fiasp® (insulin aspart injection) 100 Units/mL, a fast-acting mealtime insulin indicated to improve glycemic control in adults with type 1 and type 2 diabetes.
- Fiasp® can be dosed at the beginning of a meal or within 20 minutes after starting a meal. Fiasp® is a new formulation of NovoLog®, in which the addition of niacinamide (vitamin B3) helps to increase the speed of the initial insulin absorption, resulting in an onset of appearance in the blood in approximately 2.5 minutes.
- Fiasp® will be available in a pre-filled delivery device FlexTouch® pen and a 10 mL vial at the same price as Novolog

New Ultra-Rapid Insulin Aspart – Fiasp

- The approval of Fiasp® is based on results from the onset phase 3a clinical development program. The clinical trials enrolled more than 2,000 adults with type 1 and type 2 diabetes to evaluate the efficacy and safety of Fiasp® administered both at mealtime and after starting a meal. Data from the trials showed that Fiasp® demonstrated a reduction in A1C in adults with type 1 and type 2 diabetes. Common adverse reactions, excluding hypoglycemia, occurring in ≥5% of subjects included nasopharyngitis, upper respiratory tract infection, nausea, diarrhea and back pain.
New Ultra-Rapid Insulin Aspart – Fiasp

- Pharmacokinetic results from a euglycemic clamp study in adult patients with type 1 diabetes (N=51) showed that insulin aspart appeared in the circulation ~2.5 minutes and maximum insulin concentrations was achieved ~63 minutes after administration of FIASP. T1/2 elimination is ~1.1 hrs.
- If converting from another mealtime insulin to FIASP, the change can be done on a unit-to-unit basis.
- DO NOT dilute or mix FIASP with any other insulin products or solutions, except infusion fluids.
- May be stored at room temperature for up to 28 days.

Insulin Lispro follow on – Admelog by Sanofi

- Dec. 11, 2017: The FDA approved Sanofi's Admelog®, the first follow-on insulin lispro.
- 100 Units/mL will be available in U.S. in vial and SoloStar pen. It was approved in Europe as a Biosimilar earlier this summer under the proprietary name, Insulin lispro Sanofi®.
- Indicated in adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus.
- Approved for use as an injection, via pump, or intravenously.
GLP-1 Agonist Comparison

GLP-1 Agonist Medications Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Dosing Schedule</th>
<th>Mixing Required</th>
<th>Pre-injection waiting time</th>
<th>Dosing</th>
<th>Smallest Needle Size</th>
<th>Needles included</th>
<th>Use with basal insulin</th>
<th>Auto Injector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>QID</td>
<td>No</td>
<td>None</td>
<td>5mcg, 10mcg</td>
<td>32 gauge, 4mm needle</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bydureon Kit</td>
<td>Exenatide extended release</td>
<td>QW</td>
<td>Yes</td>
<td>None</td>
<td>2mg</td>
<td>23-gauge, 8mm needle</td>
<td>Yes</td>
<td>No</td>
<td>Currently studies are evaluating</td>
</tr>
<tr>
<td>Bydureon Pen</td>
<td>Exenatide extended release</td>
<td>QW</td>
<td>Yes</td>
<td>None</td>
<td>2mg</td>
<td>23-gauge, 8mm needle</td>
<td>Yes</td>
<td>No</td>
<td>Currently studies are evaluating</td>
</tr>
<tr>
<td>Tanzeum Discontinued</td>
<td>Abiligitide</td>
<td>QW</td>
<td>Yes</td>
<td>None</td>
<td>30mg, 50mg</td>
<td>5mm 29-gauge thin-walled needle</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Trulicity</td>
<td>Dulaglitide</td>
<td>QW</td>
<td>No</td>
<td>None</td>
<td>0.75mg, 1.5mg</td>
<td>Built in to device 29g</td>
<td>Yes part of device 29g</td>
<td>No</td>
<td>Currently studies are evaluating</td>
</tr>
<tr>
<td>Victoza</td>
<td>Liraglutide</td>
<td>QD</td>
<td>No</td>
<td>None</td>
<td>0, 1.2, 1.6mg</td>
<td>32 gauge, 4mm needle</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Adyxin Lixisenatide QD No None 10 mcg, 20 mcg 32 gauge, 4-8 mm No Yes No

Liraglutide – Victoza by Novo-Nordisk

• A human analog of the glucagon-like peptide-1 (GLP-1) with 97% amino acid sequence homology to endogenous human GLP-1.
  – T1/2 ~11-15 hrs
  – 1.2 mg dose (2 pens/mo)*
    – $536.00 GoodRx.com
  – 1.8 mg dose (3 pens/mo)
    – $800.00 GoodRx.com
  – Adjunct to diet and exercise for Type 2 DM but not first line and no data in combo with prandial insulin
  – *preferred dose based upon the A1c reductions
Liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies

Diabetes, Obesity and Metabolism, 11 (Suppl. 3), 2009, 26–34

![Graph showing change in HbA1c (%) for different treatments]

LEADER CV Safety Trial with Liraglutide

- **9340 patients with type 2 diabetes and high cardiovascular risk** to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
  - The median follow-up was 3.8 years.

- **The primary outcome** occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P = 0.01 for superiority) ARR 1.9%, NNT=53
LEADER CV Safety Trial with Liraglutide

• **Death from cardio-vascular causes** in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P = 0.007). **ARR 1.3%, NNT 77**

• The rate of **death from any cause** was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02). **ARR 1.4%, NNT=72**
  • N Engl J Med 2016; 375:311-322

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LEADER CV Safety Trial with Liraglutide

• The rates of **nonfatal myocardial infarction** (HR 0.88), **nonfatal stroke** (HR 0.89), and hospitalization for heart failure (HR 0.87) were all nonsignificantly lower in the liraglutide group than in the placebo group.
  • N Engl J Med 2016; 375:311-322
Liraglutide – Victoza (New Indication)

• August 25, 2017- The US Food and Drug Administration (FDA) has approved a new indication for liraglutide (Victoza, Novo Nordisk), for reducing the risk for myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes who have established cardiovascular disease based upon the data from the Leader Trial.

LEADER CV Safety Trial with Liraglutide

• Microvascular Outcomes: The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI, 0.73 to 0.97; P = 0.02)
  • The difference that was driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; HR 0.78; 95% CI, 0.67 to 0.92; P = 0.003)
  • The incidence of retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR 1.15; 95% CI, 0.87 to 1.52; P = 0.33).

• N Engl J Med 2016; 375:311-322
LEADER CV Safety Trial with Liraglutide

- The **most common adverse events** leading to the **discontinuation of liraglutide** were gastrointestinal **events**. The incidence of **pancreatitis** was non-significantly lower in the **liraglutide group** (18 vs. 23) than in the placebo group.
  - Pancreatic carcinoma 13 (0.3) with liraglutide vs. 5 (0.1) with placebo p=0.06
  - Medullary thyroid carcinoma 0 with liraglutide vs. 1 (<0.1) with placebo p=0.32

Dulaglutide – Trulicity by Lilly

- Available in 0.75-mg and 1.5-mg single-dose pens which do not require mixing, measuring or needle attachment and can be administered any time of day.
  - Insert states that for added comfort patients may want to take the pen out of the refrigerator for ~30 min prior to administration (DO NOT microwave or run under hot water)
- Box of 4 pens (either dose) ~$672.00 retail (GoodRx.com)
Dulaglutide – Trulicy

• The AWARD-6 study, once-weekly dulaglutide 1.5 mg achieved the primary endpoint of non-inferiority to once-daily liraglutide 1.8 mg, as measured by the reduction of hemoglobin A1c (HbA1c) from baseline at 26 weeks in 599 patients. (to date the only GLP-1 agonist to demonstrate non-inferiority to liraglutide to date)
  – The Lancet, Early Online Publication, 11 July 2014
doi:10.1016/S0140-6736(14)60976-4

Dulaglutide – Trulicy

• At the primary endpoint of 26 weeks, once-weekly dulaglutide 1.5 mg and once-daily liraglutide 1.8 mg significantly reduced HbA1c levels from baseline (-1.42 percent and -1.36 percent, respectively), with dulaglutide demonstrating non-inferiority compared to liraglutide. A similar majority of patients in both treatment groups (68 percent) reached the American Diabetes Association's recommended HbA1c target of less than 7 percent. Patients treated with once-weekly dulaglutide and once-daily liraglutide showed significant weight reductions from baseline (-2.9 kg, -3.6 kg, respectively). This weight reduction was statistically greater in the liraglutide treatment arm.
Dulaglutide – Trulicity

• FDA required Rewind CV safety trial ~9600 patients 50 and older with Type 2 diabetes with CV disease or older patients with 2 or more CV risk factors treated for up to 6.5 years. The Rewind Trial is expected to be completed July 2018.

GLP-1 Analogue

• FDA Box Warning: (Same as for all members of the GLP-1 class of medications)
  – “Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.”
  – symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).
• Additional Warnings and Precautions;
  – In clinical trials, acute pancreatitis has been reported in association with dulaglutide.
    • Consider other antidiabetic therapies inpatients with a history of pancreatitis.
Lixisenatide – Adlyxin by Sanofi

- FDA approved 7-27-2016 a once a day GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose)
  - Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose)
  - Cost: ~$600.00/ 2 pens (28 day supply)
  - Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily
    - Administer once daily within one hour before the first meal of the day

Lixisenatide – Adlyxin

Replace the cap to protect from light

Number of doses remaining

You must activate the pen one time before the first use and not again or you will loose doses, the orange window should only appear prior to the first dose which is discarded and thereafter remain white

Pull the injection button out firmly until it stops and the arrow will now be pointing towards the needle

An insulin needle must be attached to deliver any dose including the discarded initial dose
ELIXA: No Cardiovascular Risks or Benefits With Lixisenatide Vs Placebo

Primary composite endpoint: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA

<table>
<thead>
<tr>
<th></th>
<th>Lixisenatide (n=3,034)</th>
<th>Placebo (n=3,034)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Subjects who experienced primary endpoint</td>
<td>13.4%</td>
<td>13.2%</td>
</tr>
</tbody>
</table>

HR=1.02
95% CI, 0.89-1.17

About ELIXA
- First events-driven CV outcomes study to provide data for a GLP-1 receptor agonist
- Randomized, double-blind, placebo-controlled trial
- N=6,068 subjects with type 2 diabetes and recent ACS event

Randomization:
- Lixisenatide 10 mcg/d*
- Placebo

*Up- or down-titrated to maximum 20 mcg/d
ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide
HR=hazard ratio; UA=unstable angina
Lixisenatide is an investigational agent; not yet FDA approved in the United States

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ELIXA: Cardiovascular Outcomes for Lixisenatide Vs Placebo

No increased risk for lixisenatide vs placebo for:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Lixisenatide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome: CV death,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonfatal MI, nonfatal stroke,</td>
<td>13.4%</td>
<td>13.2%</td>
</tr>
<tr>
<td>hospitalization for UA</td>
<td></td>
<td></td>
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<tr>
<td>HR=1.02</td>
<td></td>
<td></td>
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<tr>
<td>(95% CI: 0.89-1.17)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome plus hospitalization for heart failure</td>
<td>0.97 (95% CI: 0.85-1.10)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.96 (95% CI: 0.75-1.23)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.94 (95% CI: 0.78-1.13)</td>
<td></td>
</tr>
</tbody>
</table>

ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes
AHA=Acute Coronary Syndrome During Treatment With Lixisenatide
HR=hazard ratio

Bydureon Pen – Extended Release Exenatide

- 2 mg pens: remove from refrigerator 15 min prior to reconstituting.
- Attach needle to the pen
- Hold the pen straight up and turn the knob until the green part of the pen disappears and it clicks, then tap the pen in the palm of your hand to mix the medication, turning the pen every 10 taps (up to 80 times or more) and check for even mixing
- Still holding the pen upright, you must now expel any air in the pen by pushing the knob until the orange part of the pen disappears and the injection button is released.
- Pull off the needle cover and inject.
  - Cost $670.00 for 4 pens

New Bydureon Bcise Autoinjector

- Store flat in the refrigerator at 36°F to 46°F (2°C to 8°C), or Store flat at room temperature (up to 86°F) for up to 4 weeks, Do Not FREEZE,
- Remove from refrigerator for 15 minutes prior to mixing.
- Mix the injection by shaking hard for at least 15 seconds, do not unlock prior to mixing and may need to continue to shake if not in suspension. Once mixed,
- Hold the autoinjector up straight with the orange cap toward the ceiling. Turn the knob from the Lock to the Unlock position until you hear a click.
- While still holding the autoinjector straight up, firmly unscrew the orange cap.
- A green shield will pop up after the cap is removed. The green shield hides the needle. It is normal to see a few drops of liquid inside the cap.
- Push the autoinjector against your skin. You will hear a “click” when the injection begins. Keep holding the autoinjector against the skin for 15 seconds. This is to make sure you get the full dose.
- After you receive your injection, you will see an orange rod in the window, and then dispose of the device in a sharps container.
EXSCEL Trial: Bydureon CV Safety Trial

- EXSCEL is a Phase IIIb/IV, double-blind, placebo-controlled, global CV outcomes trial conducted in 35 countries and enrolled more than 14,000 patients with type-2 diabetes with or without additional CV risk factors or prior CV events. Participants were randomized to receive exenatide once-weekly 2mg or matching placebo by subcutaneous injections. **Primary composite CV endpoint** risk of MACE, a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke.
  - EXSCEL was run jointly by two academic research organizations - the Duke Clinical Research Institute (Durham, NC, US) and the University of Oxford Diabetes Trials Unit (Oxford, UK)
  - Astra/Zeneca Press Release May 23, 2017

EXSCEL Trial: Bydureon CV Safety Trial

- The EXSCEL trial met its primary safety objective of non-inferiority for MACE. These results address the US Food and Drug Administration (FDA) requirement that medicines to treat T2D are not associated with an increase in CV risk. **Fewer CV events were observed in the Bydureon arm of the trial, however, the efficacy objective of a superior reduction in MACE did not reach statistical significance.**
  - A full evaluation of the EXSCEL data is ongoing. The results will be presented at the European Association for the Study of Diabetes (EASD) annual meeting on Thursday, 14 September 2017 in Lisbon, Portugal.
Semaglutide - Ozempic a once a week GLP-1 analog
by Novo Nordisk

- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Available as a carton of 1 Pen (NDC 0169-4132-12) Pen delivers doses of 0.25 mg or 0.5 mg per injection 6 NovoFine® Plus needles Intended for treatment initiation at the 0.25 mg dose and maintenance treatment at the 0.5 mg dose
- Carton of 2 Pens (NDC 0169-4136-02) Pen delivers doses of 1 mg per injection 4 NovoFine® Plus needles Intended for maintenance treatment at the 1 mg dose only
- SC solution single-patient-use pen 1.34mg/mL; delivers doses of 0.25mg, 0.5mg, or 1mg. The company has announced that the drug will cost $676 per prescription, which it described as “at parity” with drugs in the same class.

Semaglutide – Ozempic

- Dosage: Start with a 0.25 mg subcutaneous injection once weekly for 4 weeks. The 0.25 mg dose is intended for treatment initiation and is not effective for glycemic control. After 4 weeks on the 0.25 mg dose, increase the dosage to 0.5 mg once weekly. If additional glycemic control is needed after at least 4 weeks on the 0.5 mg dose, the dosage may be increased to 1 mg once weekly. The maximum recommended dosage is 1 mg once weekly.
  - Administer semaglutide once weekly, on the same day each week, at any time of the day, with or without meals.
  - Prior to first use, Ozempic should be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Ozempic and do not use if it has been frozen.
  - After first use of the Ozempic pen, the pen can be stored for 56 days at controlled room temperature (59ºF to 86ºF; 15ºC to 30ºC) or in a refrigerator (36ºF to 46ºF; 2ºC to 8ºC).
Semaglutide CV Data – SUSTAIN 6 Trial

- Sustain 6 randomly assigned **3297 patients with type 2 diabetes** who were on a standard-care regimen to receive once-weekly (GLP-1 agonist) semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks.
- The **primary composite outcome** was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
  - At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both.
  - Mean duration of diabetes was 13.9 years and mean HbA1c was 8.7%. 93.5% were taking antihypertensive medication, 76.5% were receiving lipid-lowering drugs, and 76.3% were receiving antithrombotic medications.
  - Drug is investigational and was recommended for FDA approval by the FDA Advisory Committee 10/18/2017
  - NEJM on-line 9-16-2016

Semaglutide CV Data – SUSTAIN 6 Trial

- The **primary outcome** occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, **0.74**; 95% confidence interval [CI], 0.58 to 0.95; **P<0.001 for noninferiority**). NNT 45
- **Nonfatal myocardial infarction** occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, **0.74**; 95% CI, 0.51 to 1.08; **P=0.12**); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, **0.61**; 95% CI, 0.38 to 0.99; **P=0.04**).
- **Rates of death from cardiovascular causes** were similar in the two groups.
  - NEJM on-line 9-16-2016
Semaglutide CV Data – SUSTAIN 6 Trial

- From an overall baseline of 8.7%, semaglutide significantly reduced HbA1c by 1.4% and 1.1% (for the two doses) vs 0.4% for placebo.
  - Body weight "decreased by almost 5 kg with the 1.0-mg dose of semaglutide, from a mean of 92.1 kg," compared with weight loss of 3.6 kg, on average, in the 0.5-mg group and 0.5 to 0.7 kg in the placebo recipients.
  - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher 3.2% vs. 1.7%(hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02). NEJM on-line 9-16-2016
  - This trend was also seen in the LEADER Trial with liraglutide and in the DCCT with rapid lowering of BG with insulin)

Semaglutide CV Data – SUSTAIN 6 Trial

- The FDA's consulting ophthalmologist expressed several concerns about the way the retinopathy data were collected, including:
  - No standardized approach to fundus evaluations -- dilation was not required, and the evaluation could be performed by the investigator or by a local ophthalmologist or optometrist
  - No formal grading of retinopathy findings
  - No uniform agreement on what retinopathy characteristics dictated a need for treatment; the independent committee evaluating the data required that treatment be administered, not just "needed," in order to count as a complication
Semaglutide – Ozempic

• Given that the Sustain-6 outcomes trial was relatively brief (~2 years), with fewer patients (~3300) than a trial designed to prove CV benefits, Novo did not ask the FDA for a CV risk-reduction claim for semaglutide and the FDA did not approve a CV label claim.

• The company does plan a more extensive follow-up study beginning next year to assess those benefits, just as it did with Victoza, which now has an FDA approval as a CV risk-reduction tool.

Semaglutide - SUSTAIN 7 Trial

• August 16, 2017 - SUSTAIN 7 a phase 3b, 40-week, efficacy and safety trial of 0.5 mg semaglutide vs 0.75 mg dulaglutide and 1.0 mg semaglutide vs 1.5 mg dulaglutide, both once-weekly, as add-on to metformin in 1,201 people with type 2 diabetes. The primary outcome measure was change in HbA1c from baseline after 40 weeks of treatment with semaglutide compared to dulaglutide.

• From a mean baseline HbA1c of 8.2%, 0.5 mg semaglutide achieved a statistically significant and superior reduction of 1.5% compared with a reduction of 1.1% with 0.75 mg dulaglutide. People treated with 1.0 mg semaglutide experienced a statistically significant and superior reduction of 1.8% compared with a reduction of 1.4% with 1.5 mg dulaglutide.
Semaglutide - SUSTAIN 7 Trial

• 68% of people treated with 0.5 mg semaglutide compared with 52% of people treated with 0.75 mg dulaglutide reached the ADA treatment goal A1c of <7.0%, and 79% of people treated with 1.0 mg semaglutide compared to 67% with 1.5 mg dulaglutide reached the treatment goal.

• From a mean baseline body weight of 95 kg and a BMI of 33.5 kg/m², people treated with 0.5 mg semaglutide experienced a statistically significant and superior weight loss of 4.6 kg compared to 2.3 kg with 0.75 mg dulaglutide. People treated with 1.0 mg semaglutide experienced a statistically significant and superior weight loss of 6.5 kg compared to 3.0 kg with 1.5 mg dulaglutide.

• Adverse effects mainly GI (nausea) were similar.

Xultophy (IDegLira) (combination of insulin degludec/Tresiba plus liraglutide/Victoza) by Novo/Nordisk

• Liraglutide - Victoza: 1.2 mg dose (2 pens/mo) $497.00 GoodRx.com
• 1.8 mg dose (3 pens/mo) $743.00 GoodRx.com
• Insulin Degludec- Tresiba U-100 FlexTouch - 3 mL 100 units/mL - 300 Units/pen – max dose 80 Units in 1 Unit increments – available 5 pens/pack ~$450.00
• The combo price will be about 20% less than the two separately ~ $1,000.00/mo
Insulin degludec plus liraglutide - Xultophy

• Dose Titration:

  - The label recommends that the patient titrate the dose up or down by 2 units every 3 to 4 days based on self-monitored FPG until the desired FPG is achieved (IE. 80-130 mg/dl?)
  - The maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide)
  - If persistent dosages below 16 units or above 50 units are required, discontinue and use alternative therapy (including the two components separately IE max dose of liraglutide (1.2 vs. 1.8 mg?) plus whatever dose of basal insulin required).
  - Cost: 5 x 3 ml U100/3.6 mg pens $1,020.00

Soliqua™ 100/33 (insulin glargine & lixisenatide injection) 100 Units/mL & 33 mcg/mL by Sanofi

• Soliqua 100/33 will be delivered in a single pre-filled pen for once-daily dosing covering 15 to 60 Units of insulin glargine 100 Units/mL and 5 to 20 mcg of lixisenatide using SoloStar technology, Soliqua 100/33 will be available in U.S. retail pharmacies in January 2017.

  Price ~$680.00/5 pens GoodRx.com 1-25-2017
Soliqua™ 100/33 (insulin glargine & lixisenatide injection)
100 Units/mL & 33 mcg/mL

Dosage and Administration:
• Discontinue therapy with lixisenatide or basal insulin prior to initiation of Soliqua 100/33.
• In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily.
• In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily.
• Inject once a day within the hour prior to the first meal of the day.
• Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide).
• Soliqua 100/33 Pen delivers doses from 15 to 60 units with each injection.

DPP-4 Inhibitors
• Sitagliptin – Januvia 25, 50 and 100 mg tabs $429.00/30 tabs
• Sitagliptin + metformin IR – Janumet 50/500 & 50/1000 mg tabs $429.00/60 tabs
• Sitagliptin + metformin XR – Janumet XR 100/1000 mg tabs $429.00/30
• Saxagliptin – Onglyza 2.5 and 5 mg tabs $416.00/30 tabs
• Saxagliptin + metformin – Kombiglize XR 2.5/1000, 5/500 & 5/1000 mg tabs ~ $416.00/month supply at 5 mg dose
• Linagliptin – Trajenta 5 mg tabs $412.00/30 tabs
• Linagliptin + metformin IR – Jentadueto (BID) 2.5/500, 2.5/850 & 2.5/1000 mg tabs $412.00/60 tabs
• Linagliptin + metformin XR – Jentadueto XR 2.5/1000 $206.00/30 tabs & 5/1000 mg tabs $412.00/30 tabs
### DPP-4 Inhibitors

- **Sitagliptin** – Januvia 25, 50 and 100 mg tabs, Sitagliptin + metformin IR – Janumet 50/500 & 50/1000 mg tabs and Sitagliptin + metformin XR – Janumet XR 100/1000 mg tabs ~ $429.00/month
- **Saxagliptin** – Onglyza 2.5 and 5 mg tabs and Saxagliptin + metformin – Kombiglize XR 2.5/1000, 5/500 & 5/1000 mg tabs ~ $416.00/month
- **Linagliptin** – Trajenta 5 mg tabs, Linagliptin + metformin IR – Jentaduento (BID) 2.5/500, 2.5/850 & 2.5/1000 mg tabs and Linagliptin + metformin XR – Jentaduento XR 2.5/1000 $206.00/30 tabs & 5/1000 mg tabs ~$412.00/month
- **Alogliptin** – Nesina 6.25, 12.5 and 25 mg tabs (Generic available), Alogliptin + metformin IR – Kanzeo 12.5/500 & 12.5/1000 mg tabs (Generic available) and Alogliptin + pioglitazone – Oseni 12.5 and 25 mg alogliptin with 15, 30 and 45 mg pioglitazone/tab (Generic available) ~$404.00/month brand and ~$182.00/month generic

### DPP-4 Inhibitors

- **Alogliptin** – Nesina 6.25, 12.5 and 25 mg tabs $404.00/30 tabs (Generic available $204.00/30 tabs)
- **Alogliptin** + metformin IR – Kanzeo 12.5/500 & 12.5/1000 mg tabs $404.00/60 tabs (Generic available $204.00/60 tabs)
- **Alogliptin** + pioglitazone – Oseni 12.5 and 25 mg alogliptin with 15, 30 and 45 mg pioglitazone/tab $404.00/30 tabs (Generic available $182.00/30 tabs)
SAVOR-TIMI 53 Summary

- 16,492 patients with T2D with CVD or high CVD risk
- Randomized to saxagliptin vs placebo
- 1<sup>o</sup> outcome: CV Death/MI/CVA
  - Median follow-up = 2.1 years
- Met the 1<sup>o</sup> safety objective of noninferiority (HR, 1.0; 95% CI, 0.89-1.12)
  - Superiority P value = .99
- Hospitalization for heart failure: saxagliptin group (3.5%); placebo group (2.8%); HR: 1.27; 95% CI: 1.07, 1.51; p-value = 0.007 NNH 142

SAVOR – TIMI 53 CV Trial with Saxagliptin

- April 14, 2015: 14 of 15 panelists from the FDA Endocrinologic and Metabolic Drugs Advisory Committee voted to update the label for saxagliptin, primarily on the increased risk for heart failure. They also wanted to see information on the trend toward higher all-cause mortality.
  - Death from any cause 420 (4.9%) Saxagliptin vs 378 (4.2%) Placebo HR: 1.11 (0.96–1.27) P = 0.15
  - Warnings and Precautions: Heart Failure: In the SAVOR cardiovascular outcomes trial, more patients treated with ONGLYZA were hospitalized for heart failure compared to placebo. Patients with a prior history of heart failure or renal impairment had a higher risk for hospitalization for heart failure. Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart failure. Monitor for signs and symptoms. If heart failure develops, consider discontinuation of ONGLYZA.
In the alogliptin trial, 3.9% of alogliptin-treated patients were hospitalized for heart failure versus 3.3% in the placebo group. This is the same as 39 out of every 1,000 patients compared to 33 out of every 1,000 patients.

In the alogliptin trial, 3.9% of alogliptin-treated patients were hospitalized for heart failure versus 3.3% in the placebo group. This is the same as 39 out of every 1,000 patients compared to 33 out of every 1,000 patients.


- An FDA safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. As a result, FDA is adding new warnings to the drug labels about this safety issue.

- **RECOMMENDATION:** Health care professionals should consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control. If a patient’s blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.

- Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:
  - Unusual shortness of breath during daily activities
  - Trouble breathing when lying down
  - Tiredness, weakness, or fatigue
  - Weight gain with swelling in the ankles, feet, legs, or stomach
### TECOS Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sitagliptin (n=7382)</th>
<th>Placebo (n=7339)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>11.4%</td>
<td>11.6%</td>
<td>0.98 (0.89-1.08)</td>
</tr>
<tr>
<td>CV Death, non-fatal MI, non-fatal CVA</td>
<td>10.2%</td>
<td>10.2%</td>
<td>0.99 (0.89-1.10)</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.2%</td>
<td>5.0%</td>
<td>1.03 (0.89-1.19)</td>
</tr>
<tr>
<td>Hospitalization unstable angina</td>
<td>1.6%</td>
<td>1.8%</td>
<td>0.90 (0.70-1.16)</td>
</tr>
<tr>
<td>Fatal or non-fatal MI</td>
<td>4.1%</td>
<td>4.3%</td>
<td>0.95 (0.81-1.11)</td>
</tr>
<tr>
<td>Fatal or non-fatal CVA</td>
<td>2.4%</td>
<td>2.5%</td>
<td>0.97 (0.79-1.19)</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>3.1%</td>
<td>3.1%</td>
<td>1.00 (0.83-1.20)</td>
</tr>
<tr>
<td>Hospitalization for HF or CV Death</td>
<td>7.3%</td>
<td>7.2%</td>
<td>1.02 (0.90-1.15)</td>
</tr>
</tbody>
</table>

NEJM: on-line June 8, 2015

### CAROLINA Trial with Linagliptin

- **CAROLINA study** is to investigate the long-term impact on cardiovascular morbidity and mortality, relevant efficacy parameters (e.g., glycaemic parameters) and safety (e.g., weight and hypoglycaemia) of treatment with linagliptin in patients with type 2 diabetes at elevated cardiovascular risk receiving usual care, and compare outcome against glimepiride.
  - 6072 patients randomized
  - Expected completion early 2019
FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

• 8-28-15 FDA is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling.

• The FDA found 33 patients and all experienced arthralgia that resulted in a substantial reduction in their prior level of activity, including 10 patients who were hospitalized due to disabling joint pain.

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

• In 22 cases, symptoms appeared within 1 month of initiation of treatment with a DPP-4 inhibitor. In 20 of the 33 cases, the DPP-4 inhibitor was suspected as a possible cause of arthralgia and was discontinued within a month following the onset of symptoms. However, 8 of the remaining 13 cases reported a period of 44 days to 1 year between the onset of symptoms and discontinuation of the DPP-4 inhibitor. In 23 of the 33 cases, symptoms resolved less than 1 month after discontinuation of the drug.
  - eight of the 33 cases documented a positive rechallenge with the same or other drug in the class
SGLT-2 Inhibitors

Characteristics of Approved SGLT2Is

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2 selectivity</td>
<td>1:414</td>
<td>1:1200</td>
<td>&gt;1:2500</td>
</tr>
<tr>
<td>(vs SGLT-1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosages (tablets)</td>
<td>100 mg, 300 mg</td>
<td>5 mg, 10 mg</td>
<td>10 mg, 25 mg</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>12-15 h</td>
<td>17 h</td>
<td>10-19 h</td>
</tr>
<tr>
<td>Peak Levels (h)</td>
<td>2.8-4.0 h</td>
<td>1.5 h</td>
<td>1.5 h</td>
</tr>
<tr>
<td>(#h after dosing)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr UGE</td>
<td>300 mg: 51.4 g±a</td>
<td>10 mg: 40.8 g±a</td>
<td>25 mg: 56.5 g±a</td>
</tr>
</tbody>
</table>

*In healthy participants
Renal Dosing AVOID with eGFR
<45 <60 <45

Cost: All cost ~ $465.00/month supply

Plasma Glucose
(180 L/day) (900 mg/L) = 162 g/day

Normally we filter ~ 180 L of plasma per day with ~90 mg/dl of plasma glucose or ~ 162 Gms of glucose per day is filtered and reabsorbed by SGLT-2 (90%) and SGLT-1 (10%).

With an SGLT-2 inhibitor we reset the renal threshold for glucose reabsorption from ~ 180 mg/dl down to 70-90 mg/dl.

From: Role of Sodium-Glucose Cotransporter 2 (SGLT 2) Inhibitors in the Treatment of Type 2 Diabetes
Endocr Rev | Copyright © 2011 by The Endocrine Society
Empagliflozin – Jardiance New Indication
December 2, 2016

• The U.S. Food and Drug Administration today approved a new indication for Jardiance (empagliflozin) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

• Based on a post market Empa Reg Outcome trial of more than 7,000 patients with type 2 diabetes and cardiovascular disease. In the trial, Jardiance was shown to reduce the risk of cardiovascular death compared to a placebo when added to standard of care therapies for diabetes and atherosclerotic cardiovascular disease.

EMPA-REG OUTCOME Trial

• The primary outcome (CV mortality, non-fatal MI and non-fatal stroke) occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority).
  – ARR = 1.6%, NNT 63
  – No significant differences in rates of MI or CVA
  – No significant difference with 10 vs. 25 mg doses.
  – Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46
• NEJM on-line 9-17-2015
EMPA-REG OUTCOME Trial

- Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction) NNT = 72
- Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) NNT = 39
- Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events.  
  – NEJM on-line 9-17-2015

EMPA-REG OUTCOME Trial: Renal Data

Microvascular Outcome

- The prespecified composite microvascular outcome in the overall trial population occurred in 577 of 4132 patients (14.0%) in the empagliflozin group and in 424 of 2068 patients (20.5%) in the placebo group, a significant RRR 38%  ARR 6.5%, NNT=16
  – the overall result for this composite microvascular outcome was driven entirely by the renal component  
  NEJM on-line June 14, 2016
CANVAS and CANVAS R Trials

• Integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk (65.6% had a history of ASCVD). Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks (3.62 years).

• The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
  – Initially tested for non-inferiority (p<0.001) and then if appropriate for superiority (p=0.02)
  – NEJM June 12, 2017 published on-line

CANVAS and CANVAS R Trials

• Primary end-point (CV death, non-fatal MI and non-fatal stroke) 26.9 events/1000 pt years canagliflozin vs. 31.5 placebo; HR = 0.86 (95% CI 0.75-0.97); NNT = ~200

• Secondary end-points (events/1000 patient years)
  – CV death 11.6 vs 12.8; HR = 0.87 (95% CI 0.72-1.06) NS
  – Non-fatal MI 9.7 vs. 11.6; HR = 0.85 (95% CI 0.69-1.05) NS
  – Non-fatal stroke 7.3 vs. 8.4; HR = 0.90 (95% CI 0.71-1.15) NS
  – Hospitalization for heart failure 0.5 vs. 0.9; HR = 0.67 (95% CI 0.52-0.87); NNT = ~250
  – Death any cause 17.3 vs. 19.5; HR = 0.87 (95% CI 0.74- 1.01) NS
    • NEJM June 12, 2017 published on-line
CANVAS and CANVAS R Trials

- 40% reduction in eGFR, renal replacement therapy or renal death: 5.5/1000 pt. yrs. Vs. 9.0; HR = 0.60 (95% CI 0.47-0.77); NNT = ~250
  - NEJM June 12, 2017 published on-line

- Diabetic ketoacidosis: 0.6/1000 pt. yrs. vs. 0.3 (p=0.14 NS)
- Amputations: 6.3/1000 pt. yrs. vs. 3.4 (p<0.001) NNH = ~300
- Fractures (all): 15.4/1000 pt. yrs. vs. 11.9 (p=0.02) NNH = ~286
- Volume depletion: 26/1000 pt. yrs. vs. 18.5 (p=0.009) NNH = ~140
- Infection of male genitalia : 34.9/1000 pt. yrs. vs. 10.8 (p<0.001) NNH = ~42
- Female mycotic genital infection: 68.8/1000 pt. yrs. vs. 17.5 (p<0.001) NNH = ~19
  - NEJM June 12, 2017 published on-line
### CANVAS Trial Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1,441</th>
<th>Canagliflozin 100 mg N=1,445</th>
<th>Canagliflozin 300 mg N=1,441</th>
<th>Canagliflozin (pooled) N=2,886</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>22 (1.5)</td>
<td>50 (3.5)</td>
<td>45 (3.1)</td>
<td>95 (3.3)</td>
</tr>
<tr>
<td>Total amputations*</td>
<td>33</td>
<td>83</td>
<td>79</td>
<td>162</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1,000 patient-years)</td>
<td>2.8</td>
<td>6.2</td>
<td>5.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>—</td>
<td>2.24 (1.36, 3.69)</td>
<td>2.01 (1.20, 3.34)</td>
<td>2.12 (1.34, 3.38)</td>
</tr>
</tbody>
</table>

* Some patients had more than one amputation.

Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs.

Canagliflozin combined data 3.3% vs 1.5% placebo; HR 2.12, ARI 1.8%, NNH 56


### CANVAS R Trial Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=2,903</th>
<th>Canagliflozin 100 mg - to 300 mg) N=2,904</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>25 (0.9)</td>
<td>45 (1.5)</td>
</tr>
<tr>
<td>Total amputations*</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1,000 patient-years)</td>
<td>4.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>—</td>
<td>1.80 (1.10, 2.93)</td>
</tr>
</tbody>
</table>

* Some patients had more than one amputation.

Canagliflozin combined data 1.5% vs. 0.9% with placebo; HR 1.80; ARI 0.6%, NNH 167

(This renal safety study was only a mean duration of 2.1 years)

CVD-REAL Data
American College of Cardiology 66th Annual Scientific Session 19 March 2017

• CV data from a large retrospective international data set including more than 364,000 patients with type-2 diabetes, (87% of whom did not have a history of cardiovascular disease).
  – mean age 57, 44% females
• Treatment with SGLT-2 inhibitors reduced all-cause mortality by 51% and risk of hospitalization for heart failure by 39%.
  – 41.8% of patients were on dapagliflozin, 52.7% on canagliflozin and 5.5% on empagliflozin. (A/Z sponsored the trial)
  – Results are consistent with the Empa-Reg Outcome Trial

On-Going CV/Outcome Trials with Dapagliflozin

• DECLARE is a robust randomized, double-blind, multicenter, placebo-controlled cardiovascular outcomes trial enrolling more than 17,000 patients around the world, designed to evaluate the cardiovascular outcomes of dapagliflozin compared with placebo in addition to standard of care, in adults with T2D and high risk of cardiovascular disease (either established cardiovascular disease or multiple cardiovascular risk factors).
• DAPA-HF and DAPA-CKD trials, to help to define the potential role of dapagliflozin in the management of chronic heart failure and chronic kidney disease respectively, in people with and without type-2 diabetes
On-Going CV/Outcome Trials with Dapagliflozin

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• DAPA-HF and DAPA-CKD trials, to help to define the potential role of dapagliflozin in the management of chronic heart failure and chronic kidney disease respectively, in people with and without type-2 diabetes

FDA Drug Safety Alert 5-18-2016

• Canagliflozin (Invokana, Invokamet): Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations
  – FDA is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes.
  – Patients taking canagliflozin should notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.
New FDA Safety Alert

• [5-16-2017]: “Based on new data from two large clinical trials, the FDA has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. We are requiring new warnings, including our most prominent Boxed Warning, to be added to the canagliflozin drug labels to describe this risk.”

• Before initiating canagliflozin, consider factors in the patient’s history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.

Concerns with SGLT-2 Inhibitors?

• I would not routinely recommend an SGLT-2 inhibitor in the following patients:
  – Patients with impaired renal function (eGFR of < 45 ml/min maybe less than 60?).
  – Patients with diabetic neuropathy, previous foot ulcers, previous amputations and/or peripheral vascular disease.
  – Patients at risk for falls or with orthostatic hypotension.
  – Patients with a history of osteoporosis, osteopenia, decreased BMD or history of fractures.
**FDA Safety Announcement**

- [5-15-2015] The FDA is warning that the SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.

- Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness.

**SGLT-2 Inhibitors and DKA**

- A new analysis from Wake Forest, UNC and Duke) found 39 cases of DKA among 11,197 people with prescriptions for SGLT2 inhibitors (74% in patients with Type 2 DM/ 82% C; 15% D and 3% E). Of these, 26 patients had glucose ≤300 mg/dL, with a mean glucose of 266 mg/dL. Symptoms reported included nausea and vomiting (49%), although researchers said “it is unclear if that was a cause, contributor, or consequence of the DKA.” Also, 67% of the patients had some other obvious event such as surgery, an insulin dose reduction, or weight loss.

- The authors recommend “a high index of suspicion for DKA in patients taking SGLT2 inhibitors with unexplained malaise or gastrointestinal symptoms and recommend measuring urine or plasma ketones in that setting,”

Ertugliflozin – Steglatro by Merck and Pfizer

- Dec. 20, 2017 the FDA approved ertugliflozin – Steglatro a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- **Dosage: Recommended starting dose is 5 mg once daily, taken in the morning, with or without food. Increase dose to 15 mg once daily in those tolerating ertugliflozin and needing additional glycemic control.**
  - Elimination T1/2 is ~ 16.5 hours
  - Initiation or continued use is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m2.

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### Table 4: Results at Week 26 from a Placebo-Controlled Monotherapy Study of STEGLATRO in Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>STEGLATRO 5 mg</th>
<th>STEGLATRO 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%) Baseline (mean)</td>
<td>N = 153</td>
<td>N = 155</td>
<td>N = 151</td>
</tr>
<tr>
<td></td>
<td>8.1</td>
<td>8.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Change from baseline (LS mean^1)</td>
<td>-0.2</td>
<td>-0.7</td>
<td>-0.9</td>
</tr>
<tr>
<td>Difference from placebo (LS mean, 95% CI)</td>
<td>-0.6^6 (-0.8, -0.4)</td>
<td>-0.7^6 (-0.9, -0.4)</td>
<td></td>
</tr>
<tr>
<td>Patients [N (%)] with HbA1c &lt;7%</td>
<td>26 (16.9)</td>
<td>47 (30.1)</td>
<td>59 (38.8)</td>
</tr>
<tr>
<td>FPG (mg/dL) Baseline (mean)</td>
<td>N = 150</td>
<td>N = 151</td>
<td>N = 149</td>
</tr>
<tr>
<td></td>
<td>180.2</td>
<td>180.9</td>
<td>179.1</td>
</tr>
<tr>
<td>Change from baseline (LS mean^1)</td>
<td>-11.6</td>
<td>-31.0</td>
<td>-36.4</td>
</tr>
<tr>
<td>Difference from placebo (LS mean, 95% CI)</td>
<td>-19.4^7 (-27.6, -11.2)</td>
<td>-24.8^7 (-33.2, -16.4)</td>
<td></td>
</tr>
</tbody>
</table>

Ertugliflozin – Steglatro

Table 5: Results at Week 26 from a Placebo-Controlled Study for STEGLATRO Used in Combination with Metformin in Patients with Type 2 Diabetes Mellitus*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>STEGLATRO 5 mg</th>
<th>STEGLATRO 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>N = 207</td>
<td>N = 205</td>
<td>N = 201</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.2</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Change from baseline (LS mean)</td>
<td>-0.2</td>
<td>-0.7</td>
<td>-0.9</td>
</tr>
<tr>
<td>Difference from placebo (LS mean, 95% CI)</td>
<td>-0.5 (-0.7, -0.4)</td>
<td>-0.7 (-0.9, -0.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Patients [N (%)] with HbA1c &lt;7%</strong></td>
<td>38 (18.4)</td>
<td>74 (38.3)</td>
<td>87 (43.3)</td>
</tr>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td>N = 202</td>
<td>N = 199</td>
<td>N = 201</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>169.1</td>
<td>168.1</td>
<td>167.9</td>
</tr>
<tr>
<td>Change from baseline (LS mean)</td>
<td>-8.7</td>
<td>-30.3</td>
<td>-40.9</td>
</tr>
<tr>
<td>Difference from placebo (LS mean, 95% CI)</td>
<td>-21.6 (-27.8, -15.5)</td>
<td>-32.3 (-38.5, -26.0)</td>
<td></td>
</tr>
</tbody>
</table>


Ertugliflozin – Steglatro

Table 7: Results at Week 26 from an Add-on Study of STEGLATRO in Combination with Metformin and Sitagliptin in Patients with Type 2 Diabetes Mellitus*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>STEGLATRO 5 mg</th>
<th>STEGLATRO 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>N = 152</td>
<td>N = 155</td>
<td>N = 152</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>8.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Change from baseline (LS mean)</td>
<td>-0.2</td>
<td>-0.7</td>
<td>-0.8</td>
</tr>
<tr>
<td>Difference from placebo (LS mean, 95% CI)</td>
<td>-0.5 (-0.7, -0.3)</td>
<td>-0.6 (-0.8, -0.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Patients [N (%)] with HbA1c &lt;7%</strong></td>
<td>31 (20.2)</td>
<td>54 (34.6)</td>
<td>64 (42.3)</td>
</tr>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td>N = 152</td>
<td>N = 156</td>
<td>N = 152</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>169.6</td>
<td>167.7</td>
<td>171.7</td>
</tr>
<tr>
<td>Change from baseline (LS mean)</td>
<td>-6.5</td>
<td>-25.7</td>
<td>-32.1</td>
</tr>
<tr>
<td>Difference from placebo (LS mean, 95% CI)</td>
<td>-19.2 (-26.8, -11.6)</td>
<td>-25.6 (-33.2, -18.0)</td>
<td></td>
</tr>
</tbody>
</table>

VERTIS SITA2 Trial
Diabetes Obes Metab. 2017 Sep 17. doi: 10.1111/dom.13116. [Epub ahead of print]
Ertugliflozin – Steglatro

Table 1: Adverse Reactions Reported in ≥2% of Patients with Type 2 Diabetes Mellitus Treated with STEGLATRO® and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of STEGLATRO Monotherapy or Combination Therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo N = 515</th>
<th>STEGLATRO 5 mg N = 519</th>
<th>STEGLATRO 15 mg N = 510</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital mycotic infections¹</td>
<td>3.0%</td>
<td>9.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Male genital mycotic infections²</td>
<td>0.4%</td>
<td>3.7%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Urinary tract infections³</td>
<td>3.0%</td>
<td>4.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.3%</td>
<td>3.5%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Vaginal pruritus⁴</td>
<td>0.4%</td>
<td>2.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Increased urination⁵</td>
<td>1.0%</td>
<td>2.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.3%</td>
<td>2.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.3%</td>
<td>1.7%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>1.0%</td>
<td>1.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Thirst⁶</td>
<td>0.6%</td>
<td>2.1%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Lower Limb Amputation: Across seven Phase 3 clinical trials in which ertugliflozin was studied as monotherapy and in combination with other antihyperglycemic agents, non-traumatic lower limb amputations occurred in 1 of 1,450 (0.1%) in the non-ertugliflozin group, 3 of 1,716 (0.2%) in the ertugliflozin 5 mg group, and 8 of 1,693 (0.5%) in the ertugliflozin 15 mg group.

– consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers.
Ertugliflozin – Steglatro

• Cost:
• Place in therapy? Probably not first line SGLT-2 inhibitor, does not appear to be any more effective or safer.
• The CVOT Trial VERTIS CV Study (MK-8835-004) has enrolled 8,000 patients with evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems. Randomized to 5 mg or 15 mg of ertugliflozin or placebo and followed for up to 6 plus years, anticipated completion fall of 2019.
• Primary Outcome: Time to First Occurrence of MACE (Composite Endpoint of Major Adverse Cardiovascular Events [Cardiovascular Death, Non-fatal Myocardial Infarction or Non-fatal Stroke])

Ertugliflozin Combinations

• Steglumet (ertugliflozin plus metformin) BID
  – 2.5 mg plus 500 mg
  – 2.5 mg plus 1000 mg
  – 7.5 mg plus 500 mg
  – 7.5 mg plus 1000 mg

• Steglujan (ertugliflozin plus sitagliptin) QD
  – 5 mg plus 100 mg
  – 15 mg plus 100 mg
STENO 2 Trial

• The original intervention (mean treatment duration 7.8 years) involved **160 patients with type 2 diabetes and microalbuminuria** who were randomly assigned (using sealed envelopes) to receive either conventional therapy or intensified, multifactorial treatment including both behavioral and pharmacological approaches.

• After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group.
  
  — Diabetologia 2016 DOI 10.1007/s00125-016-4065-6

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STENO Type 2 DM Trial


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intensive</th>
<th>Standard</th>
<th>RRR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy</td>
<td>11%</td>
<td>25%</td>
<td>56%</td>
<td>7</td>
</tr>
<tr>
<td>Retinopathy progression</td>
<td>26%</td>
<td>43%</td>
<td>49%</td>
<td>6</td>
</tr>
<tr>
<td>Blindness in 1 eye</td>
<td>1%</td>
<td>9%</td>
<td>85%</td>
<td>13</td>
</tr>
<tr>
<td>Progression of autonomic neuropathy</td>
<td>11%</td>
<td>29%</td>
<td>62%</td>
<td>6</td>
</tr>
<tr>
<td>Combined death and macrovascular events</td>
<td>34%</td>
<td>54%</td>
<td>37%</td>
<td>5</td>
</tr>
</tbody>
</table>
STENO 2 Trial after 21 Years

• The primary endpoint of this follow-up 21.2 years after intervention start was difference in median survival time between the original treatment groups with and without incident cardiovascular disease.

• The patients in the intensive therapy group survived for a median of 7.9 years longer than the conventional-therapy group patients. Median time before first cardiovascular event after randomization was 8.1 years longer in the intensive-therapy group (p = 0.001).

• The hazard for all microvascular complications was decreased in the intensive-therapy group in the range 0.52 to 0.67, except for peripheral neuropathy (HR 1.12).

  — Diabetologia 2016 DOI 10.1007/s00125-016-4065-6

Self-Assessment Questions

1. Which statement concerning metformin is false?

• A. Do not start metformin if the eGFR is between 30 and 45mL/minute/1.73 m2.

• B. Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated.

• C. Metformin should be stopped when the serum creatinine is 1.4 mg/dl or greater in females.

• D. Metformin has been demonstrated to reduce CV events in patients with Type 2 diabetes in the UKPDS Trial.
Self-Assessment Questions

2. “In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality, after considering drug-specific and patient factors.”

• Which medication(s) are recommended by the ADA to reduce ASCVD risk based upon outcome data? (you can use more than 1 answer if appropriate)
  • A. Pioglitazone
  • B. Liraglutide
  • C. Empagliflozin
  • D. Dulagultide
  • E. Dapagliflozin

Self-Assessment Questions

3. Match the insulins with the correct statement:
  • A. Tresiba _____ 1. Fastest onset
  • B. Fiasp _____ 2. Longest duration
  • C. Basaglar _____ 3. Similar to Humalog
  • D. Admelog _____ 4. Similar to Lantus
Self-Assessment Questions

4. Based on new data from two large clinical trials, the FDA has concluded that the type 2 diabetes medicine __________ causes an increased risk of leg and foot amputations. The FDA has added a new Box Warning to describe this risk.

• Before initiating __________, consider factors in the patient’s history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.

• What medication(s) goes in the blank?
  • A. Empagliflozin
  • B. Canagliflozin
  • C. Dapagliflozin
  • D. Ertagliflozin
  • E. All of the above