Jeopardy: Update on Diabetes Pharmacotherapy

Susan Cornell, BS, PharmD, CDE, FAPhA, FAADE
Associate Professor
Midwestern University - Chicago College of Pharmacy

Objectives

• Describe the mechanism of action and unique features of the 6 classes of medications that are recommended by the ADA as second-line therapies for type 2 diabetes.
• Discuss contraindications and side effect considerations when recommending second-line therapies for type 2 diabetes.
• Given a patient case where the patient has reached the maximal dosage of metformin, select among second line treatment options for individualize care.

Why is Glucose Control Important?

• 60% of people with type 2 diabetes have at least 1 complication because of diabetes
  – Complications are often present at time of diagnosis

β-cell Decline in Prediabetes and T2DM


Change in insulin / change glucose / IR

Normal glucose tolerance

Impaired glucose tolerance

Type 2 diabetes

IR = insulin resistance

The Ominous Octet: Circa 2008


Fat cells (adipose tissue)

Hyperglycemia

Treatment Approach to T2DM

• Dietary changes
  • Reduce consumption of calories
  • Reduce consumption of simple carbohydrates

• Increase physical activity

• Medications
  • Improve or replace insulin secretion
  • Reduce insulin resistance
  • Reduce glucagon secretion
  • Reduce hepatic glucose production
  • Increase urinary glucose excretion

12 Pharmacotherapy Options

Insulin (1)
- Bolus insulin
  - insulin lispro
    - U100
    - U200
  - insulin aspart
  - insulin glulisine
  - regular human insulin

- Basal insulin
  - insulin NPH
  - insulin detemir
  - insulin degludec
    - U100
    - U200
  - insulin glargine
    - U100
    - U300

Oral Medications (9)
- α-glucosidase inhibitors (AGI)
- biguanides
- bile acid sequestrants (BAS)
- DPP-4 inhibitors (gliptins)
- dopamine agonists
- glinides
- sodium-glucose co-transporter-2 (SGLT-2)
- thiazolidinediones (TZDs or glitazones)

Non-insulin injectable agents (2)
- exenatide, exenatide-2 (GLP-1) agonists
- amylinomimetic

ADA Standards of Medical Care in Diabetes (2015)
Oral Agents

- Affordable
- Possible weight loss benefit
- Low risk of hypoglycemia
- GI side effects can be managed
- Risk of lactic acidosis far less than feared
- Effectively lowers BG and A1c
  - Though not sustainable as monotherapy

Metformin:
Current Cornerstone of Therapy

- Affordable
- Possible weight loss benefit
- Low risk of hypoglycemia
- GI side effects can be managed
- Risk of lactic acidosis far less than feared
- Effectively lowers BG and A1c
  - Though not sustainable as monotherapy

Rational Choices for second-line add-on to Metformin

- Drugs that target different metabolic defects
  - Combine medications that work at different tissue sites for synergy
- Drugs that target fasting and postprandial glucose control
- Select therapies that support patient goals
  - Low hypo risk
  - Weight neutral, loss
**Sulfonylureas**

- **Glimepiride**
  - *Amaryl®*
  - 1mg, 2mg, 4mg
  - Once daily

- **Glipizide**
  - *Glucotrol®*
  - 1mg, 5mg
  - Once to twice daily
  - *Glucotrol XL®*
  - 2.5mg, 5mg, 10mg
  - Once daily

- **Glyburide**
  - *Micronase®*
  - 1.25mg, 2.5mg, 5mg
  - Once to twice daily
  - *Diabeta®*
  - 1.25mg, 2.5mg, 5mg
  - Once to twice daily
  - *Glynase®*
  - 1.5mg, 3mg, 6mg
  - Once to twice daily

**Sulfonylureas: 1st Generation**

### First Generation Sulfonylureas

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Daily Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetohexamide (DIYMELOR®)</td>
<td>1-2 daily</td>
<td>250-1500mg</td>
</tr>
<tr>
<td>Chlorpropamide (DIABINSEB®)</td>
<td>Daily</td>
<td>100-500mg</td>
</tr>
<tr>
<td>Tolbutamide (ORINASE®)</td>
<td>3 times daily</td>
<td>500-3000mg</td>
</tr>
<tr>
<td>Tolazamide (TOLINASE®)</td>
<td>1-2 daily</td>
<td>100-1000mg</td>
</tr>
</tbody>
</table>

Titrated every 2-4 weeks based on FPG

**Sulfonylureas**

- Stimulates insulin release from the pancreas
  - Long acting stimulation (>6 hours)
  - Requires endogenous insulin to be affective; therefore better used early in the disease, if necessary
  - Short durability

- Lowers fasting and postprandial glucose
  - Decreases A1c by 1.5-2% (~45-60 mg/dl)

- Most common side effects
  - Hypoglycemia
  - Weight gain
  - May inhibit ischemic pre-conditioning

Meglitinides

- Repaglinide
  - Prandin®
  - 0.5mg, 1mg, 2mg
  - Up to three times daily before meals

- Nateglinide
  - Starlix®
  - 60mg, 120mg
  - Up to three times daily before meals

Glinides

- Stimulates insulin release from the pancreatic beta cells
- Short acting stimulation (30 minutes to 4 hours)
- Requires endogenous insulin to be effective; therefore better used early in the disease; if necessary
- Short durability

- Lowers postprandial glucose
- Decreases A1c by 0.5-1% (~15-30 mg/dl; more postprandial)

- Most common side effects
  - Hypoglycemia
  - Weight gain

TZD’s (Glitazones)

- Pioglitazone
  - Actos®
  - 15mg, 30mg, 45mg
  - Once daily

- Rosiglitazone
  - Avandia®
  - 2mg, 4mg, 8mg
  - Once to twice daily

TZD’s (Glitazones)

- Stimulates PPARγ to increase GLUT-4 transporter production, thereby moving glucose from the blood into the peripheral tissue.
- Also reduces adipose fat
  - Can be used thru duration provided insulin is present
  - Good durability

- Lowers fasting and postprandial glucose
- Decreases A1c by 1.0-1.5% (~30-45 mg/dl)

- Most common side effects:
  - Edema (swelling) usually in the legs
  - Weight gain
  - Possible ↑ risk of fractures.

- Takes 4-6 weeks (or more) to take effect and requires insulin (endogenous or exogenous)

DPP4 Inhibitors (gliptins)

- Sitagliptin (Januvia ®)
  - 25 mg, 50 mg, 100 mg
  - Once-daily dosing
  - Dose adjustment in renal impairment

- Saxagliptin (Onglyza ®)
  - 2.5 mg & 5 mg
  - Once-daily dosing
  - Dose adjustment in renal impairment

- Linagliptin (Tradjenta ®)
  - 5 mg
  - Once-daily dosing

- Alogliptin (Nesina ®)
  - 6.25 mg, 12.5 mg, & 25 mg
  - Once-daily dosing
  - Dose adjustment in renal impairment

DPP4 Inhibitors (gliptins)

- Inhibits DPP-4 enzyme in the GI tract that breaks down GLP-1 resulting in ↑ endogenous GLP-1.
  - Glucagon suppression (from pancreatic alpha cell) results in ↓ fasting glucose production
  - Enhances appropriate insulin and amylin secretion from the pancreatic beta cells
  - Can be used thru duration provided insulin is present
  - Promising durability

- Lowers postprandial glucose
  - Decrease A1c by 0.5 to 0.7% (~15-20 mg/dl, most postprandial)

- Most common side effects:
  - Stuffy, runny nose
  - Headache
  - Upper respiratory tract infection
Sodium Glucose Co-Transporter-2 Inhibitors (SGLT-2i)

- **Canagliflozin**
  - *Invokana®*
  - 100mg & 300mg
  - taken once daily before first meal of the day.

- **Dapagliflozin**
  - *Farxiga®*
  - 5mg & 10mg
  - taken once daily (ideally, before first meal of the day).

- **Empagliflozin**
  - *Jardiance®*
  - 10mg & 25mg
  - taken once daily (ideally, before first meal of the day).

↓ renal glucose reabsorption in the early proximal tubule of the kidney

- Possibly reduces adipose fat—likely due to ↑ water and fat urination (elimination)

Lowers fasting glucose

- Decreases A1c by 0.7-1.1% (~20-30 mg/dl)

Most common side effects

- Weight loss
- Vaginal and male genital infections
- Rash
- UTI
- Frequent urination
- Increased thirst
- GI problems (when combined with metformin)


**SGLT2 Inhibitors: Comparisons**

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (A1c lowering)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>↓ 0.77 - 1.03%</td>
<td>↓ 0.8 - 0.9%</td>
<td>↓ 0.7 - 0.8%</td>
</tr>
<tr>
<td>Combination</td>
<td>↓ 0.79 - 0.94%</td>
<td>↓ 0.7 - 0.8%</td>
<td>↓ 0.7 - 0.8%</td>
</tr>
<tr>
<td>Dose and Frequency</td>
<td>100-300 mg once daily</td>
<td>5-10 mg once daily</td>
<td>10-25 mg once daily</td>
</tr>
</tbody>
</table>

Renal dose adjustment

<table>
<thead>
<tr>
<th>CCl &lt; 60 mL/min</th>
<th>Canagliflozin 100 mg once daily Use not recommended</th>
<th><em>No dosage adjustment</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl &gt; 45 mL/min</td>
<td>Use not recommended</td>
<td></td>
</tr>
</tbody>
</table>

Jardiance (empagliflozin) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.*
Injectable Agents

GLP-1 Agonists

**long-acting GLP-1 agonists**
- Liraglutide (Victoza ®)
  - 0.6 mg, 1.2 mg, & 1.8 mg
  - Once-daily dosing
- Exenatide (Bydureon ®)
  - 2 mg
  - Once-weekly dosing
- Albiglutide (Tanzeum ®)
  - 30 mg & 50 mg
  - Once-weekly dosing
- Dulaglutide (Trulicity ®)
  - 0.75 mg & 1.5 mg
  - Once-weekly dosing

**short-acting GLP-1 agonists**
- Exenatide (Byetta ®)
  - 5 mcg & 10 mcg
  - Twice-daily dosing
- Lixisenatide (Adlyxin ®)
  - 10 mcg & 20 mcg
  - Once-daily dosing

GLP-1 Agonists

- GLP-1 agonists "fix" 5 dysfunctional organs in T2DM
  - Glucagon suppression from the pancreatic alpha cell
  - Reverses or limits glucagon production
  - Enhances appropriate insulin and amylin secretion from the pancreatic beta cell
  - Regulates the cell to slow gastric emptying time
  - Can be used thru duration provided insulin is present
  - Promising durability
- Short acting agonists lowers postprandial glucose
  - Decreases A1c by 0.8-1.5% (~20-45 mg/dl, most postprandial)
- Long acting agonists lowers fasting and postprandial glucose
  - Decreases A1c by 0.8-1.8% (~20-50 mg/dl)

- Most common side effects
  - Weight loss
  - Gastric upset
  - Caution in patients at risk for pancreatitis
Differences in GLP-1 agonists

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>Exenatide</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Exenatide QW</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>5 &amp; 10 mcg BID (within 30-60 min of am/pm meal)</td>
<td>10 &amp; 20 mcg (within 60 min of same meal daily)</td>
<td>0.6 mg initial, then ↑ to 1.2 &amp; 1.8 mg (orally, any time)</td>
<td>2 mg weekly</td>
<td>0.75 mg &amp; 1.5 mg weekly</td>
<td></td>
</tr>
<tr>
<td>Max dose</td>
<td>10 mcg BID</td>
<td>20 mg daily</td>
<td>1.8 mg daily</td>
<td>2 mg weekly</td>
<td>50 mg weekly</td>
<td>1.5 mg weekly</td>
</tr>
<tr>
<td>Half-life</td>
<td>2-8 hours</td>
<td>2-6 hours</td>
<td>10 hours</td>
<td>5 days</td>
<td>5 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Homology to GLP-1</td>
<td>53%</td>
<td>52%</td>
<td>97%</td>
<td>53%</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td>Antibodies</td>
<td>44%</td>
<td>69.8%</td>
<td>8.6%</td>
<td>44%</td>
<td>2.5%</td>
<td>2%</td>
</tr>
<tr>
<td>FPG &amp; PPG effects</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial plasma glucase

High-Concentration or Low Volume Glargine (U300)

- Available only in a pen
  - U-300: 450 units/pen, max 80 units/inj
  - Can be used for patients on small and large volumes of insulin
- Offers a smaller depot surface area, leading to a reduced rate of absorption
- Provides flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
  - Half-life is ~23 hours
  - Steady state in 4 days
  - Duration of action ≤36 hours

PK and PD of U300 Insulin Glargine vs U100 Insulin Glargine

U-100 and U-200 Insulin Degludec

- Available only in a pen
  - U-200: 600 units/pen, max 160 units/inj
  - U-100: 300 units/pen, max 80 units/inj
- Can be used for patients on small and larger volumes of insulin
- Provides flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
  - Duration of action >42 hours
  - Half-life ~25 hours
    - Detectable for at least 5 days
    - Steady state in 3-4 days

1. Garber AJ. Diabetes Obesity Metab; published online 31 Oct 2013.

Basal Insulin Degludec
Flat, stable profile of both 100 unit/mL and 200 unit/mL formulations

Mean 24-Hour GIR Profile of the Two Insulin Degludec Formulations at Steady State

Glucose Infusion Rate

Side Effects and Contraindications
Frequently Reported ADEs in Patients Receiving a DPP-4i

Adverse Reaction

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sitagliptin 100 mg†1</th>
<th>Saxagliptin 2.5 mg‡2</th>
<th>Saxagliptin 5 mg‡2</th>
<th>Linagliptin 5 mg‡3</th>
<th>Alogliptin 25 mg‡§4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.1–5.9</td>
<td>6.5</td>
<td>6.5</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.2–6.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7.0</td>
</tr>
<tr>
<td>URTI</td>
<td>5.5–6.3</td>
<td>–</td>
<td>7.7</td>
<td>–</td>
<td>4.2</td>
</tr>
<tr>
<td>UTI</td>
<td>–</td>
<td>–</td>
<td>6.8</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

No differences in the overall safety profiles of the various DPP-4 inhibitors have so far emerged.

Pharmacologic and PK Characteristics of DPP-4i

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approximate In Vivo DPP-4 Inhibition, %</th>
<th>24 H Postdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>97</td>
<td>Not appreciably metabolized</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>80</td>
<td>Primarily renal (~79% excreted unchanged by kidney)</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>80</td>
<td>~90% eliminated unchanged; exposure decreased by strong CYP3A4 or P-gp inducers</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>90</td>
<td>Not appreciably metabolized</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; P-gp = P-glycoprotein.

Safety Issues with DPP-4i

- Rare cases of acute pancreatitis and HSRs have been reported during clinical trials and the postmarketing period
  - Acute pancreatitis: meta-analysis did not detect increased incidence vs comparators in core trials
  - Patients should be monitored for signs and symptoms, especially at start of therapy
  - If pancreatitis is suspected, DPP-4 inhibitor should be discontinued promptly and management initiated
  - HSRs: often occur within 1st 3 months of treatment
  - Discontinue agent and do not restart if serious HSR is suspected
  - Use caution when prescribing a DPP-4 inhibitor for a patient who had a HSR during treatment with a previous DPP-4 inhibitor

GLP-1 agonist: GI Adverse Events

<table>
<thead>
<tr>
<th>Head-to-Head Trial, Active Comparators</th>
<th>Incidence of Adverse Event, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td>LEAD-6: liraglutide 1.8 mg, exenatide 10 μg</td>
<td>26, 28</td>
</tr>
<tr>
<td>DURATION-1: exenatide extended release 2 mg, exenatide 10 μg</td>
<td>26, 35</td>
</tr>
<tr>
<td>DURATION-5: exenatide extended release 2 mg, liraglutide 1.8 mg</td>
<td>14, 33</td>
</tr>
<tr>
<td>DURATION-6: exenatide extended release 2 mg, liraglutide 1.8 mg</td>
<td>9, 21</td>
</tr>
<tr>
<td>HARMONY-7: albiglutide 50 mg, liraglutide 1.8 mg</td>
<td>10, 29</td>
</tr>
<tr>
<td>AWARD-1: albiglutide 0.75 &amp; 1.5 mg, exenatide 10 μg</td>
<td>16, 28, 28</td>
</tr>
<tr>
<td>AWARD-5: albiglutide 1.5 mg, liraglutide 1.8 mg</td>
<td>20, 18</td>
</tr>
</tbody>
</table>

In clinical practice, GI disturbances often resolve over time, but 5–10% of patients discontinue treatment due to adverse effects. Following dose titration instructions reduces risk of GI disturbances. Patients with preexisting severe GI disease (e.g., gastroparesis) should not use a GLP-1 agonist.

Pancreatic Safety for GLP-1 agonists

- Pancreatitis has been reported in association with GLP-1 agonist treatment
- Until more is known, providers should
  - Observe patients carefully for pancreatitis signs and symptoms
  - Discontinue agent if pancreatitis is suspected
  - Not restart treatment if pancreatitis is confirmed
  - Consider other glucose-lowering agents in patients with pancreatitis history

Thyroid C-Cell Tumors

- Currently unknown whether GLP-1 agonists cause thyroid C-cell tumors in humans
- Liraglutide, exenatide extended release, albiglutide, and dulaglutide
  - Have boxed warning on thyroid C-cell tumor risk
  - Are contraindicated in patients with personal or family history of MTC and in patients with MEN 2
- Prescribers should
  - Counsel patients about potential MTC risk
  - Inform them about thyroid tumor symptoms
- Stipulations do not apply to exenatide (twice daily)
Comparing the Effects of GLP-1 Agonists and DPP-4i

<table>
<thead>
<tr>
<th>Effect</th>
<th>GLP-1 Agonists</th>
<th>DPP-4i Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase beta-cell mass and proliferation</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Reduce beta-cell apoptosis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Enhance glucose-dependent insulin secretion</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Reduce hepatic glucose production</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Improve fasting glucose</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Improve postprandial glucose</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Delay gastric emptying</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Increase satiety and reduce food intake</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Promote weight loss</td>
<td>++</td>
<td>–</td>
</tr>
</tbody>
</table>

GLP-1 agonists are administered by subcutaneous injection; DPP-4i inhibitors are administered orally.

1. Cornell.

Most common side effects:
- Weight loss
- Vaginal and male genital infections
- Rash
- UTI
- Frequent urination
- Increased thirst
- GI problems (when combined with metformin)

SGLT-2 Inhibitors Adverse Effects

SGLT-2i - Weight Effects

<table>
<thead>
<tr>
<th>Mean difference</th>
<th>Upper 95% CI</th>
<th>Lower 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>-0.640</td>
<td>-0.768</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>-0.592</td>
<td>-0.692</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>-0.564</td>
<td>-0.745</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>-0.591 kg</td>
<td>-0.663</td>
</tr>
</tbody>
</table>

Mechanism: 1 gram glucose = 4 kcal Loss of potentially 200-300 kcal/day Maximum weight loss at approximately 6 months Weight loss is, in general, maintained

Mean difference Upper 95% CI Lower 95% CI
Canagliflozin -0.640 -0.768 -0.513
Dapagliflozin -0.592 -0.692 -0.491
Empagliflozin -0.564 -0.745 -0.384
SUMMARY -0.591 kg -0.663 -0.519 P<0.001
SGLT-2i – Blood Pressure Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2i vs. placebo</td>
<td>-3.77</td>
<td>-4.65 to -2.80</td>
</tr>
<tr>
<td>SGLT2i vs. active comparator</td>
<td>-4.45</td>
<td>-5.73 to -3.18</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2i vs. placebo</td>
<td>-1.75</td>
<td>-2.27 to -1.23</td>
</tr>
<tr>
<td>SGLT2i vs. other antidiabetics</td>
<td>-2.01</td>
<td>-2.62 to -1.39</td>
</tr>
</tbody>
</table>

- BP Lowering Mechanism
  - Not fully determined but likely due to osmotic diuresis
  - Orthostatic changes possible upon initiation
  - Early 24-48 hour increased sodium excretion
  - Caution in combination with other diuretics

CV Effects of DPP-4i, GLP-1 agonists and SGLT-2i

Results of CV Outcomes Trials in T2DM

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study</th>
<th>Drug vs. placebo</th>
<th>N</th>
<th>Results (year published)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4i</td>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>5400</td>
<td>Neutral (2013)</td>
</tr>
<tr>
<td></td>
<td>SAVOR TIMI</td>
<td>Saxagliptin</td>
<td>16500</td>
<td>Neutral (2013)</td>
</tr>
<tr>
<td></td>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>14000</td>
<td>Neutral (2015)</td>
</tr>
<tr>
<td></td>
<td>CARMELENA</td>
<td>Linagliptin</td>
<td>8300</td>
<td>Expected (2017)</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>EUA</td>
<td>Liraglutide</td>
<td>14000</td>
<td>Neutral (2015)</td>
</tr>
<tr>
<td></td>
<td>LEADER</td>
<td>Exenatide</td>
<td>16500</td>
<td>Positive (2016)</td>
</tr>
<tr>
<td></td>
<td>EXSCEL</td>
<td>Exenatide QW</td>
<td>5400</td>
<td>Expected (2018)</td>
</tr>
<tr>
<td></td>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>8300</td>
<td>Expected (2019)</td>
</tr>
<tr>
<td>SGLT-2i</td>
<td>EMPA-REG</td>
<td>Empagliflozin</td>
<td>7300</td>
<td>Positive (2015)</td>
</tr>
<tr>
<td></td>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>4300</td>
<td>Positive (2017)</td>
</tr>
<tr>
<td></td>
<td>DECLARE</td>
<td>Ibagliflozin</td>
<td>22200</td>
<td>Expected (2019)</td>
</tr>
</tbody>
</table>

- DPP4i = dipeptidyl peptidase 4 inhibitor
- GLP-1 = glucagon like peptide 1
- SGLT-2i = sodium glucose cotransporter 2 inhibitor

Adapted from: Handelsman Y. Endocrine Today. 2016
LEADER Results

• 9340 patients randomized and followed for 3.8 years.
  – Fewer patients died from CV causes in the liraglutide group (219 patients) than in the placebo group (278) P=0.007.
  – The rate of death from any cause was lower in the liraglutide group (381 patients) than in the placebo group (447) P=0.02.
  – The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group.

• Is this reproducible?
  – Is this a class effect? Will this change guideline recommendations?


EMPA-REG Results

• 7300 randomized to empagliflozin vs. placebo.
  – Primary outcome was 3-point MACE:
    Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
  – Key secondary outcome was 4-point MACE:
    Same as primary + hospitalization for unstable angina

• Treatment duration 2.6 years, Observation time 3.2 years

• Results were impressive and unexpected
  – ↓ CV death by 38%
  – ↓ all cause mortality by 32%
  – ↓ heart failure hospitalization by 35%
  – Number Needed to Treat to prevent one death in 3 years = 39

• Is this reproducible?
  – Is this a class effect? Will this change guideline recommendations?


Dosing Considerations
**Biguanides (Metformin)**

- Decreases liver glucose production
  - Can be used throughout duration of disease; if no contraindication
  - Good durability
- Lowers fasting glucose
- Decreases A1c by 1.5-2% (~45-60 mg/dl)
- Most common side effects
  - Stomach and intestine distress
  - May reduce B-12 levels after long-term use
  - Favorable lipid profile improvements
    - ↑ good cholesterol (HDL)
    - ↓ bad cholesterol (LDL) & ugly cholesterol (triglycerides)
- Caution in patients with renal & hepatic dysfunction
  - CrCl < 1.4 in women and < 1.5 in men

**Metformin: Labeling changes**

- eGFR between 30 to 45 mL/minute/1.73 m²
  - Not recommended
- eGFR below 30 mL/minute/1.73 m²
  - Contraindicated
- If a patient is already on metformin
  - eGFR falls below 45 mL/minute/1.73 m²
    - Weigh benefits of continuation versus discontinuation.
  - eGFR falls below 30 mL/minute/1.73 m²
    - Discontinue metformin

**Sulfonylureas**

- Stimulates insulin release from the pancreatic beta cell
  - Long acting stimulation (>6 hours)
  - Requires endogenous insulin to be affective; therefore better used early in the disease; if necessary
  - Short durability
- Most common side effects
  - Hypoglycemia
  - Weight gain
  - may inhibit ischemic pre-conditioning
Pharmacologic and Pharmacokinetic Differences among GLP-1 Agonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Frequency and Timing</th>
<th>Tmax (hr)</th>
<th>Half-life (hr)</th>
<th>Regular Dose (2 months)</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Serous dose: 9:00 a.m. and 9:00 p.m.</td>
<td>2-3 hours</td>
<td>2.4 hours</td>
<td>5 µg or 10 µg</td>
<td>Mainly renal, not recommended for patients with kidney disease</td>
</tr>
<tr>
<td>Naranolide QD</td>
<td>Dose: any time of day</td>
<td>2-3 hours</td>
<td>2.4 hours</td>
<td>5 µg or 10 µg</td>
<td>Renal</td>
</tr>
<tr>
<td>Liraglutide QD</td>
<td>Dose: any time of day</td>
<td>2-3 hours</td>
<td>2.4 hours</td>
<td>5 µg or 10 µg</td>
<td>Renal</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>Dose: timing not specified</td>
<td>2-3 weeks</td>
<td>4-7 days</td>
<td>2 mg or 4 mg</td>
<td>Renal</td>
</tr>
<tr>
<td>Albiglutide QW</td>
<td>Dose: timing not specified</td>
<td>3-5 days</td>
<td>6-7 days</td>
<td>0.75 mg or 1.5 mg</td>
<td>Renal</td>
</tr>
<tr>
<td>Dulaglutide QW</td>
<td>Dose: timing not specified</td>
<td>~2 hours</td>
<td>~4 days</td>
<td>0.75 mg or 1.5 mg</td>
<td>Renal</td>
</tr>
</tbody>
</table>

Pharmacokinetic Profile of Currently Available Basal Insulins

- **Intermediate (NPH)**
  - Onset: 1-2 hours
  - Peak: 4-10 hours
  - Duration: 14+ hours
  - Appearance: Cloudy

- **Long (detemir)**
  - Onset: 3-4 hours
  - Peak: 6-8 hours
  - Duration: >20-24 hours
  - Appearance: Clear

- **Ultra-long (degludec & glargine U-300)**
  - Onset: 0.5 – 1 flat
  - Peak: 2.3 hours
  - Duration: >24 hours
  - Appearance: Cloudy

**Insulin Comparison**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humalog U-100 &amp; U-200</td>
<td>0.5 – 1.5</td>
<td>0.5 – 3</td>
<td>3-5</td>
<td>Clear</td>
</tr>
<tr>
<td>Humalog mix 75/25</td>
<td>0.15 – 0.2</td>
<td>1 – 2</td>
<td>18-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Humalog mix 50/50</td>
<td>0.25 – 0.5</td>
<td>0.5 – 3</td>
<td>14-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Lente Ilet 75/25</td>
<td>1 – 1.5</td>
<td>1 – 3</td>
<td>18-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Lente Ilet 50%</td>
<td>0.5 – 1</td>
<td>0.5 – 2</td>
<td>18-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Lente Ilet 75%</td>
<td>0.5 – 1</td>
<td>0.5 – 2</td>
<td>18-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Lente Ilet 100%</td>
<td>0.5 – 1</td>
<td>0.5 – 2</td>
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<tr>
<td>Lente Ilet 200%</td>
<td>0.5 – 1</td>
<td>0.5 – 2</td>
<td>18-24</td>
<td>Cloudy</td>
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<tr>
<td>Lente Ilet 300%</td>
<td>0.5 – 1</td>
<td>0.5 – 2</td>
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<td>Cloudy</td>
</tr>
</tbody>
</table>

Note: Patient-specific onset, peak, and duration may vary from times listed above.

Regular U-500 30 min 2-4 Up to 24 hr Clear

Note: Patient-specific onset, peak, and duration may vary from times listed above.
Key Points

• Metformin is recommended as initial therapy for most patients with type 2 diabetes, but most patients require additional therapy, particularly as the disease progresses.

• Guidelines recommend several second-line treatment options including insulin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors.

• A patient-centered approach to decision making is recommended including an evaluation of the mechanism of action, efficacy, unique benefits and safety of each option.