PHARMACIST AND PHARMACY TECHNICIAN OBJECTIVES

- Identify new treatment options available to diabetic patients
- Identify the difference between previously available diabetes treatment options and new treatment options
- Discuss the initial and maximum doses, available formulations, and optimal administration techniques for the new treatment options for diabetes.

QUESTION #1

(SELECT ALL THAT APPLY) Which of the following medications have received additional FDA indication for reducing cardiovascular events?

A. Liraglutide (Victoza)
B. Empagliflozin (Jardiance)
C. Saxagliptin (Onglyza)
D. Metformin (Glucophage)

QUESTION #2

Which of the following is true regarding insulin glargine/lixisenatide initiation?

A. FDA approved for as first-line initial therapy for DMII
B. If the patient is not controlled on <30 units of long acting insulin daily, the initial dose of insulin glargine/lixisenatide should be 30 units insulin glargine/5mcg lixisenatide.
C. If the patient is not controlled on 30 units to 60 units of long acting insulin daily, the initial dose of insulin glargine/lixisenatide should be 30 units insulin glargine/10mcg lixisenatide.

QUESTION #3

True/False: GLP-1RAs reduce the A1C to a greater extent than SGLT-2 inhibitors?

QUESTION #4

SR is a 56yr WM 6’2”, weighing 186lbs who has a significant medical history that includes CVD with history of PCI with 4 DES, DPN, peripheral neuropathy and depression. He is currently taking metformin 1000mg PO BID, verapamil XR 150mg PO daily, lyric 75mg PO QHS, PO BID, clopidogrel 75mg PO BID, aspirin 81mg. His most recent A1C was 8.1% two weeks ago. Due to his swing shift work schedule, his meals are unpredictable and at times, he may go an entire day without eating. Which of the following is the most effective way to improve glycemic control in this patient?

A. Assess adherence, discontinue glyburide 10mg po bid, initiate Victoza 1.8 SC daily
B. Assess adherence, discontinue glyburide 10mg po bid, initiate Victoza 0.6mg SC daily
C. Assess adherence, continue glyburide 10mg po bid, initiate insulin therapy Bumet QHS
STANDARDS OF MEDICAL CARE IN DIABETES

- Last updated in January 2018
- Recommendations for treatment are based upon an Evidence Grading System – A, B, C, D, E
- American Diabetes Association Professional Practice Committee (PPC) conducts annual review

DIABETES PREVALENCE BASED UPON RACE AND ETHNICITY

PERCENTAGE OF US ADULTS ≥ 18 YR OLD BY EDUCATION LEVEL

TYPE II DIABETES AMONG US CHILDREN AGED 10-19 YRS OLD BY RACE/ETHNICITY

PERCENTAGE OF US ADULTS ≥ 18 YR OLD BY STATE
PREVENTION – NATIONAL DIABETES PREVENTION PROGRAM

- Public and private organizations working together to prevent or delay progression to Type II Diabetes
- State and local health departments
- National and community organizations
- Employers
- Public and private insurers
- Health care professionals
- University community education programs
- Emphasizes evidence-based, affordable and high quality lifestyle changes to improve overall health and reduce risk of Type 2 Diabetes


CURRENT TREATMENT OPTIONS FOR TYPE II DIABETES TREATMENT

- Biguanides - Metformin
- Sulfonylureas
- DPP-4 inhibitors (-gliptins)
- SGLT-2 inhibitors (-flozins)
- GLP-1 Receptor Agonists (-tides)
- Insulin

PHARMACOLOGIC THERAPY FOR T2DM: RECOMMENDATIONS

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01

PHARMACOLOGIC THERAPY FOR T2DM: RECOMMENDATIONS

- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed T2DM who are symptomatic and/or have A1C >10% and/or blood glucose levels ≥300 mg/dL
- Consider initiating dual therapy in patients with newly diagnosed T2DM who have A1C >9%

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01

DRUG-SPECIFIC AND PATIENT FACTORS

- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include:
  - Efficacy
  - History of ASCVD
  - Potential side effects
  - Renal effects, impact on weight, hypoglycemic risk
  - Delivery method
  - Cost
  - Patient preferences

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01

TREATMENT RECOMMENDATIONS BASED UPON OTHER FACTORS

- In patients without atherosclerotic cardiovascular disease (ASCVD), 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

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01
### TREATMENT RECOMMENDATIONS: COMORBIDITIES

- In patients with T2DM and established ASCVD, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse CV events and CV mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors.

- In patients with T2DM and established ASCVD, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce major adverse CV events, based on drug-specific and patient factors.

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01

### TREATMENT RECOMMENDATIONS: THERAPY INTENSIFICATION

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

- For patients with T2DM who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed.

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

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01

### Antihyperglycemic Therapy in Adults with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Antihyperglycemic Therapy</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>BP</th>
<th>Weight Change</th>
<th>Cost</th>
<th>Oral/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td></td>
<td></td>
<td>$</td>
<td>Oral</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>Medium</td>
<td>No</td>
<td>$$$</td>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>High</td>
<td>No</td>
<td>$$$</td>
<td></td>
<td></td>
<td>SC</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Medium</td>
<td>No</td>
<td>$$$</td>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>TZDs</td>
<td>High</td>
<td>No</td>
<td>$</td>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>High</td>
<td>Yes</td>
<td>$</td>
<td></td>
<td></td>
<td>SC</td>
</tr>
<tr>
<td>Insulin</td>
<td>Highest</td>
<td>Yes</td>
<td>$$$</td>
<td></td>
<td></td>
<td>SC</td>
</tr>
</tbody>
</table>

### Lifestyle Management + Metformin + Additional Agent

- Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with “Y” on p. 575 and Table 8.1).

- Additional agent after consideration of drug-specific effects and patient factors (see Table 8.1).

Diabetes Care 2018 Jan; 41 (Supplement 1): S1-S159. https://doi.org/10.2337/dc18-in01
**New indications/Precautions**

**Cardiovascular Disease and Risk Management**

- **ASCVD** is the leading cause of morbidity & mortality for those with diabetes.
- Largest contributor to direct/indirect costs
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for ASCVD.
- Diabetes itself confers independent risk
- Control individual cardiovascular risk factors to prevent/slow CVD in people with diabetes.
- Systematically assess all patients with diabetes for cardiovascular risk factors.

---

**Progression of DKD**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>CI with eGFR &lt;30ml/min</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>Canagliflozin and empagliflozin</td>
</tr>
<tr>
<td>Canagliflozin and empagliflozin</td>
<td>Caution eGFR &lt;45ml/min</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>saxagliptin and alogliptin</td>
</tr>
<tr>
<td>TZDs</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
</tbody>
</table>

---

**Cardiovascular Disease and Diabetes**

- ASCVD is the leading cause of morbidity & mortality for those with diabetes.
- Largest contributor to direct/indirect costs
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for ASCVD.
- Diabetes itself confers independent risk
- Control individual cardiovascular risk factors to prevent/slow CVD in people with diabetes.
- Systematically assess all patients with diabetes for cardiovascular risk factors.

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**Dipeptidyl Peptidase Inhibitors**

- **Saxagliptin** and **alogliptin**
- **Linagliptin** (exception)
- **Liraglutide**, **Exenatide**, **Lixisenatide**: Caution eGFR <30ml/min
- Increased risk of ADE with renal impairment
- DPP-4 inhibitors: Renal dosing adjustments required. Exception: Linagliptin
- TZDs: Caution: Potential fluid retention
- Sulfonylureas: Do not use glyburide. Glipizide and glimepiride preferred.
- Insulin: Titrate per clinical response

---

**Review of Newer Indications/New Combination Agents/New Precautions**

- Biguanides
- Sulfonylureas
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 Receptor Agonists
- Insulin
DIPEPTIDYL PEPTIDASE-4 (DPP4) INHIBITORS

- Sitagliptin (Januvia ®) FDA Approved on 10-17-2006
- Saxagliptin (Onglyza ®)* FDA Approved on 7-31-2009
- Linagliptin (Tradjenta ®)
  - 5-2-2011 – Original FDA Approval
  - 8-17-2012 – FDA Approved for use with insulin in adults with T2DM
- Alogliptin ( Nesina ®)* FDA Approved on 1-25-2013
- **Vildagliptin (Galvus ®, Zomelis ®) – European Commission Approved 2011. Also available in India and Japan. It is currently not an FDA approved medication in the US

CONTROVERSIES BETWEEN DPP-4 INHIBITORS AND PRODUCT LABELING

- Two dipeptidyl peptidase-4 (DPP-4) inhibitors demonstrated a negative association with heart failure hospitalizations in their respective cardiovascular outcomes trials:
  - SAVOR study with saxagliptin
  - EXAMINE trial of alogliptin

- In response, Merck published the TECOS trial results in June 2015 in hopes of being able to remove the cardiovascular warning OFF of sitagliptin’s product labeling:
  - Showed no signal for heart failure
  - Overall the trial was neutral for cardiovascular outcomes

SAXAGLIPTIN (ONGLYZA®) – SAVOR-TIMI 53 TRIAL

- The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes-Thrombolysis in Myocardial Infarction (SAVOR-TIMI)
- The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53)
  - Primary endpoints: composite of CV death, nonfatal MI, nonfatal ischemic stroke
  - CV endpoints was similar in the saxagliptin and placebo groups (7.3% vs 7.2%)
  - Hazard Ratio 1.09 (95% CI 0.89-1.32)
  - No difference in the primary endpoint.

SAVOR-TIMI 53: Design

- Double-blind, placebo-controlled trial
- Randomization to saxagliptin or matched placebo
- Duration: 3 years
- Patients: 20,143
- Secondary endpoints: CV death, nonfatal MI, nonfatal ischemic stroke
- Metabolism: Fasting blood glucose, lipids
- Follow-up: 3 years

* Denotes FDA approved in the US

** European Commission Approved 2011
SAFETY CONCERNS

On April 5, 2016, FDA announced that a safety review has found 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, we are adding new warnings to the drug labels about this safety issue.


THEORETICAL CAUSE FOR DPP4-INHIBITOR ASSOCIATED HEART FAILURE

Theoretical cause for DPP4-inhibitor associated heart failure

- Worsening Heart Failure During the Use of DPP-4 Inhibitors
  - Pathophysiological Mechanisms, Clinical Risks, and Potential Influence of Concomitant Antidiabetic Medications
  - Toyoaki Murohara JACC 2012;59:277-279
  - American College of Cardiology Foundation
ALOGLIPTIN ACCORDING TO THE FDA – EXAMINE TRIAL (2016)
- In the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE)
  - 7.9% of alogliptin-treated patients were hospitalized for heart failure versus 3.3% in the placebo group
  - Since then, several statistical analysis reviews have occurred to refute the claim that DPP-4 inhibitors increase the risk of heart failure.

SITAGLIPTIN – TECOS TRIAL – CARDIOVASCULAR OUTCOMES
- The Trial Evaluating Cardiovascular Outcomes with Sitagliptin
  - Assessed the effect of sitagliptin compared to placebo across 673 centers in 38 countries.
  - Primary endpoint: Composite of death from CV events, non-fatal MI, non-fatal stroke and hospitalizations for unstable angina.
  - Secondary endpoints: Heart Failure Hospitalization.
  - Median follow-up was 3 years.
  - Primary Outcome: No difference between sitagliptin and placebo groups (11.4% vs 11.6%).
  - Secondary endpoints: No increase in the rates of hospitalization for heart failure (3.1% vs 3.1%, p=0.98).

ALOGLIPTIN (NESINA®)
- Can be used as monotherapy or in combination with metformin, insulin, glyburide, pioglitazone, pioglitazone plus metformin.
- Available strengths: 6.25mg, 12.5mg, 25mg
- Assess renal function at baseline: Dose must be adjusted for patients with moderate to severe renal dysfunction
  - Normal or mild renal function – 25mg PO Daily
  - CrCl 30-60ml/min – 12.5mg PO Daily
  - CrCl <30ml/min or ESRD – 6.25mg PO Daily

WARNINGS/PRECAUTIONS
- Pancreatitis
- Heart failure
- Hypersensitivity
- Hepatic effects
- Acute hypoglycemic effects
- Arthralgia
- Bullous pemphigoid

ALOGLIPTIN – EXAMINE TRIAL
- The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
  - Assessed the effect of alogliptin compared to placebo in 898 centers in 49 countries.
  - The median follow-up was 18 months.
  - Primary endpoint: Composite of death from CV events, nonfatal MI, and nonfatal stroke.
  - Secondary endpoints: Primary composite and patients with the need for any urgent revascularization.
  - This study found similar CV event rates in alogliptin and placebo groups (11.3% vs 11.8%).
  - There were no differences in any of the secondary outcomes assessed.
  - Glycemic control and hemoglobin A1c (HbA1c) was significantly better in the alogliptin group but by only 0.14%.
  - Even though the incidence of hospitalization was not initially reported, the EXAMINE study investigators later published that alogliptin did not increase the rates of hospitalization for heart failure (1.1 vs 1.9%, p=0.67).

ALOGLIPTIN-CONTAINING PRODUCTS – NEW WARNING

**Important Safety Information**

**WARNING for OSENI (saxagliptin and alogliptin): RISK OF HEART FAILURE**
OSENI can cause heart failure and cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Before you start taking OSENI, tell your doctor if you have ever had heart failure or have problems with your kidneys. Call your doctor right away if you experience edema of hands or ankles (swelling especially when you lie down), weight gain, feeling faint or dizzy while standing, difficult or labored breathing, or swelling in your abdomen or fluid retention (especially in the feet, ankles or legs). These may be symptoms of heart failure.

**Comparison of DPP4 Inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>ALLOGLIPTIN</th>
<th>SITAGLIPTIN</th>
<th>LINAGLIPTIN</th>
<th>SAXAGLIPTIN</th>
<th>VILDAGLIPTIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical Phase III dose</strong></td>
<td>100mg Daily</td>
<td>5mg Daily</td>
<td>5mg Daily</td>
<td>50mg Twice Daily</td>
<td></td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12.4 h</td>
<td>12.5-21.1 h</td>
<td>2.2-3.8 h</td>
<td>1.3 – 2.4 h</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Kidney</td>
<td>Kidney</td>
<td>Liver and Kidney</td>
<td>Kidney &gt; Liver</td>
<td></td>
</tr>
<tr>
<td><strong>Renal dosage adjustments</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes for mod-severe impairment</td>
<td></td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Low</td>
<td>Low</td>
<td>Strong CYP3A4/3A5 inhibitor</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Food effects</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

* Non-FDA approved in the US

**SGLT-2 RECEPTOR AGONIST**

- Empagliflozin (Jardiance®)
- New FDA Indication-12-6-2016 – To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease (EMPA-REG Outcome)
- Dapagliflozin (Farxiga®)
- Canagliflozin (Invokana®)
- Ertugliflozin (Steglatro™) – FDA Approved 12-20-2017

**SODIUM-GLUCOSE TRANSPORTER 2 INHIBITOR**

**ERTUGLIFLOZIN (STEGLATRO®) AND SITAGLIPTIN (JANUVIA®) COMBO STEGLUJAN® APPROVED 12/20/2017**

- SGLT2 inhibitor plus a DPP-4 inhibitor
- Oral: Initial: Ertugliflozin 5 mg/sitagliptin 100 mg once daily; if further glycemic control needed dose may be increased to ertugliflozin 15 mg/sitagliptin 100 mg once daily (max: ertugliflozin 15 mg/sitagliptin 100 mg/day)
- Dosing: Renal Impairment: Adult
  - eGFR ≥60 mL/minute/1.73 m²: No dosage adjustment necessary
  - eGFR 30 to <60 mL/minute/1.73 m²: Not recommended for initiation or in continuation
  - eGFR <30 mL/minute/1.73 m²: Use is contraindicated
  - ESRD or dialysis (use is not recommended)
- Dosing: Hepatic Impairment: Adult
  - Mild or moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary
  - Severe impairment (Child-Pugh class C): Use is not recommended (has not been studied)
DAPAGLIFLOZIN (FARXIGA) AND SAXAGLIPTIN (ONGLYZA) COMBO QTERN® APPROVED 2/28/2017

- SGLT-2 inhibitor plus a DPP-4 Inhibitor
- Diabetes mellitus, type 2
- Oral: Dapagliflozin 10mg/saxagliptin 5 mg once daily

Concomitant use with strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, ritonavir, saquinavir, telithromycin): Do not use

Concomitant use with insulin or insulin secretagogues: Reduced dose of insulin or insulin secretagogues (e.g., sulfonylurea) may be needed

Renal Impairment dosing:
- eGFR ≥ 60 mL/minute/1.73 m²: No dosage adjustment necessary
- eGFR 45 to <60 mL/minute/1.73 m²: Use is contraindicated
- eGFR <45 mL/minute/1.73 m²: Use is contraindicated

EMPAGLIFLOZIN (JARDIANCE®) – NEW INDICATION

- (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)
- N=7000 trial involving more than 7000 patients with established CVD and being treated with statin, ACE inhibitors and aspirin
- 38% relative risk reduction in cardiovascular mortality
- 32% risk reduction in all-cause mortality compared with placebo among the patients with type 2 diabetes, all of whom had established cardiovascular disease and were already being treated with statins, angiotensin-converting inhibitors, and aspirin.

EMPAGLIFLOZIN: EMPA-REG OUTCOME TRIAL – INCLUSION CRITERIA

- Type II DM patients >18yrs
- BMI ≤ 45.0kg/m²
- eGFR > 30ml/min/1.73m²
- Entry A1C 7-9% (drug-naïve) or 7-10% (stable anti-diabetes regimen)
- Established CVD
- History of MI or CVA > 2 months prior to informed consent
- Evidence of multi-vessel CAD
- Evidence of incompletely treated single-vessel CAD
- Unstable angina > 2months prior to consent with evidence of CAD
- Documented exclusion peripheral artery disease

Canagliflozin Cardiovascular Assessment Study
- It did not reduce risk of cardiovascular death like EMPA-REG OUTCOME
- CANVAS was also responsible for the addition of “lower extremity amputations” as a precaution for its use. This risk was double that of placebo.

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- History of MI or CVA > 2 months prior to informed consent
- Evidence of multi-vessel CAD
- Evidence of incompletely treated single-vessel CAD
- Unstable angina > 2months prior to consent with evidence of CAD
- Documented exclusion peripheral artery disease

Comparative adverse effects of SGLT-2 inhibitors

- Reduction of cardiovascular events in DMII patients who have established cardiovascular disease
- Off-label indication based upon the results from CANVAS
- Canagliflozin Cardiovascular Assessment Study
- It did not reduce risk of cardiovascular death like EMPA-REG OUTCOME
- CANVAS was also responsible for the addition of “lower extremity amputations” as a precaution for its use. This risk was double that of placebo.

- Uses: Type II Diabetes as an adjunct to lifestyle modifications.
- December of 2016 – Received an FDA approved indication update:
- To reduce the risk of cardiovascular death in adult patients with Type II DM and cardiovascular disease.
- New Guideline recommendation: In patients with established atherosclerotic cardiovascular disease (ASCVD) on metformin, empagliflozin is a preferred add-on agent to reduce major adverse cardiovascular events

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GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Indication, Dosing, and Cardiovascular Risks

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONIST

- Also known as Incretin Mimetics
  - Exenatide
    - Byetta®
    - 4-28-05 – Original FDA approval
    - 11-2-09 – Expanded use as first-line treatment for T2DM
    - 10-20-11 – Approved for use with insulin glargine
  - Bydureon®
    - 1-27-2012 – Original FDA approval – First Once-Weekly treatment for T2DM
    - 3-3-2014 – FDA approval of Pen formulation
    - 10-23-17 – FDA approval of Once-Weekly Bcise formulation
  - 4-3-18 – FDA approval for use with basal insulin

- Liraglutide
  - Victoza®
    - FDA Approved on 1-25-2010
  - Saxenda®
    - FDA Approved on 12-23-2014
  - Albiglutide (Tanzeum®)
    - FDA Approved on 4-15-14
  - Dulaglutide (Trulicity®)
    - FDA Approved on 9-18-14
  - Lixisenatide (Adlyxin®)
    - FDA Approved on 6-26-2016
  - Semaglutide (Ozempic®)
    - FDA Approved on 12-5-2017

- August 25, 2017 receives new indication as a result of the LEADER trial.
  - New Indication: To reduce the risk of major adverse cardiovascular (CV) events, heart attack, stroke and CV death, in adults with type 2 diabetes and established CV disease.
  - LEADER trial demonstrated that Victoza® reduced the composite of cardiovascular death, nonfatal heart attack or nonfatal stroke by 13% vs placebo (p=0.01)
  - Reduced cardiovascular death by 22% reduction in cardiovascular death
  - Reduced all-cause death by 13%

- Week 1: Begin with 0.6 mg subcutaneously once daily
  - The 0.6 mg dose is a starting dose intended to reduce gastrointestinal (GI) symptoms during initial titration and is not effective for glycemic control.
  - Week 2: Increase the dose to 1.2 mg subcutaneously once daily if acceptable glycemic control not achieved, the dose can be increased to 1.8 mg subcutaneously once daily.
  - If a dose is missed, resume the once daily regimen as prescribed with the next scheduled dose. If more than 3 days have elapsed since the last dose, initiate at 0.6 mg
SEMAGLUTIDE (OZEMPIC®) GLP-1RA

- Why is semaglutide so special?
  - Produces a quicker and greater effect in reducing blood glucose levels and body weight in studies.
  - Reduces A1c by 1.2 to 1.8%

SC:
- Initial: 0.25 mg once weekly for 4 weeks then increase to 0.5 mg once weekly for at least 4 weeks, if further glycemic control is necessary increase to a maximum of 1 mg once weekly.
- Note: 0.25 mg dose is not effective for glycemic control and is intended only for therapy initiation. If changing the day of administration is necessary, allow at least 48 hours between 2 doses.
- Missed doses: Missed dose should be administered as soon as possible within 5 days; if greater than 5 days has elapsed, skip the missed dose and resume on the next regularly scheduled day.
- Can store up to 56 days!

NEW COMBINATION GLP-1RA AND LONG-ACTING INSULIN

GLP-1 receptor agonist + insulin Combination therapy:
- Insulin Glargine, Recombinant/ Lixisenatide (Soliqua 100/33) FDA Approved on 11-21-2016
- Insulin Degludec/Liraglutide (Xultophy ®) FDA Approved on 11-21-2016

Give all doses within the hour prior to the first meal of the day.
- Titrate (up or down) by 2 to 4 units every week based upon glycemic control goals
- If <15 dose units or > 60 dose units per day are needed, choose an alternate antihyperglycemic agent
- MAX DAILY DOSE: 60 dose units (60 units insulin glargine and 20 mcg lixisenatide)
- Not recommended as first-line initial therapy.

GLARGINE/LIXISENATIDE (SOLIQUA®)

Interesting interactions
- Acetaminophen: When 1,000 mg acetaminophen was given 1 or 4 hours after 10 mcg lixisenatide, acetaminophen Cmax was decreased by 29% and 31%, respectively and median Tmax was delayed by 2 and 1.75 hours, respectively.
- To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least one hour prior to lixisenatide subcutaneous injection.
- ACE inhibitors/ARBs – improve insulin sensitivity leading to potential hypoglycemia

LIXISENATIDE (ADLYXIN®) GLP-1RA – JULY 28, 2016

- Lixisenatide is initiated at 10 mcg once daily for 14 days.
- On day 15, the dose is increased to 20 mcg once daily
- Pen should be discarded 14 days after initial use.
DEGLUDEC/LIRAGLUTIDE (XULTOPHY®) – 12/21/2016

Initial: 16 units (insulin degludec 16 units/liraglutide 0.58 mg) once daily;
○ Titrate dose upward or downward every 3 to 4 days in increments of 2 units (insulin degludec 2 units/liraglutide 0.072 mg) per glycemic response.
○ Usual range: 16 units (insulin degludec 16 units/liraglutide 0.58 mg) to 50 units (insulin degludec 50 units/liraglutide 1.8 mg) once daily; if necessary, dose may be temporarily titrated down to 10 to 15 units (insulin degludec 10 to 15 units/liraglutide 0.36 to 0.54 mg) once daily.

Maximum dose: 50 units (insulin degludec 50 units/liraglutide 1.8 mg)/day
○ Missed dose: Resume with next regularly scheduled dose; do not administer an extra dose or increase dose to account for missed dose. If more than 3 days have elapsed since last dose, reinstate at the initial dosage (insulin degludec 16 units/liraglutide 0.58 mg) once daily.
○ Store up to 21 days after initial use.

DEGLUDEC/LIRAGLUTIDE (XULTOPHY®) – 12/21/2016

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COMPARATIVE EFFECTS OF DPP4 INHIBITORS, GLP1-RA, SGLT2-INHIBITOR

<table>
<thead>
<tr>
<th></th>
<th>DPP4-Inhibitor</th>
<th>GLP-1RA</th>
<th>SGLT2-Inhibitor</th>
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<tr>
<td>A1C reduction</td>
<td>0.5-0.7%</td>
<td>0.7-1.8%</td>
<td>0.5-1%</td>
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<td>Weight</td>
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<td>1-3kg (loss)</td>
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<td>Adverse Effects</td>
<td>Minimal</td>
<td>GI/GU</td>
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<tr>
<td>CV Outcomes</td>
<td>-</td>
<td>+/−</td>
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NEWER BIOSIMILAR TO INSULIN GLARGINE

- Glargine biosimilar (Basaglar)®

GLARGINE BIOSIMILAR (BASAGLAR)®

- KwikPen - Store it at room temperature up to 86°F (30°C) and throw it away after 28 days.
- Conversion to insulin glargine from other insulin therapies:
- Converting from once-daily NPH insulin to insulin glargine: May be substituted on an equivalent unit-per-unit basis.
- Converting from once-daily insulin glargine to other insulin glargine: Initial dose: Use 80% of the total daily dose of NPH (eg, 20% reduction) and administer once daily; adjust dosage according to patient response.

GLARGINE BIOSIMILAR (BASAGLAR)®

- Conversion between Toujeo, Lantus, and Basaglar:
  - Conversion from once-daily Toujeo to once-daily Lantus or once-daily Basaglar:
    - Initial dose: Use 80% of the dose of Toujeo (eg, 20% reduction) and adjust dosage according to patient blood glucose response.
  - Conversion from once-daily Lantus to once-daily Toujeo or once-daily Basaglar:
    - May be substituted on an equivalent unit-per-unit basis; however, generally a higher daily dosage of Toujeo will be required to achieve the same level of glycemic control as with Lantus.
  - Conversion between Toujeo SoloStar and Toujeo Max SoloStar: If previous dose was an odd number, the dose should be increased or decreased by 1 unit.
INSULIN GLARGINE (TOUJEO MAX SOLOSTAR®)

- Will begin distributing to retail pharmacies during Q3 2018
- One pen holds up to 900 units of insulin glargine potentially reducing the number of refills and copays.
- The maximum dose of up to 160 Units/mL may also help reduce the number of injections needed for doses
- Medication Access: Sanofi will offer a savings program for Toujeo that includes both the SoloStar pen and Max SoloStar pen. Eligible commercially insured patients will pay a $0 copay if they are new to Toujeo for their first three prescription fills, and a $10 copay for their next 12 fills.

PHARMACIST AND PHARMACY TECHNICIAN OBJECTIVES

- Identify new treatment options available to diabetic patients
- Identify the difference between previously available diabetes treatment options and new treatment options
- Discuss the initial and maximum doses, available formulations, and optimal administration techniques for the new treatment options for diabetes.

QUESTION #1

(SELECT ALL THAT APPLY) Which of the following medications have received additional FDA indication for reducing cardiovascular events?

A. Liraglutide (Victoza)
B. Empagliflozin (Jardiance)
C. Saxagliptin (Onglyza)
D. Metformin (Glucophage)

QUESTION #2

Which of the following is true regarding insulin glargine/lixisenatide initiation?

A. FDA approved for as first-line initial therapy for DMII
B. If the patient is not controlled on <30 units of long acting insulin daily, the initial dose of insulin glargine/lixisenatide should be 30 units insulin glargine/5mcg lixisenatide.
C. If the patient is not controlled on 30 units to 60 units of long acting insulin daily, the initial dose of insulin glargine/lixisenatide should be 30 units insulin glargine/10mcg lixisenatide.

QUESTION #3

True/False: GLP-1 RAs reduce the A1C to a greater extent than SGLT-2 inhibitors?

QUESTION #4

SR is a 54yr WM 6’2” weighing 96kg has a significant medical history that includes CVD with history of PCI with 4 DES, DMII, peripheral neuropathy and depression. He is currently taking metformin 1500mg PO BID, valvadilav XR 150mg PO daily, Lystica 75mg, PO BID, atorvastatin 40mg PO QHS, glyburide 10mg PO BID, Aspirin 81mg Daily, Clopoidagrnil 75mg daily. His most recent A1C was 8.1% two weeks ago. Due to his swing shift work schedule, his meals are unpredictable and at times, he may go an entire day without eating. Which of the following is the most effective way to improve glycemic control in this patient.

A. Assess adherence, discontinue glyburide 10mg po bid, initiate Victozza 1.8 SC daily
B. Assess adherence, discontinue glyburide 10mg po bid, initiate Victozza 0.6mcg SC daily
C. Assess adherence, continue glyburide 10mg po bid, initiate insulin therapy 10units QHS
REFERENCES

- Scheen. Drugs 2015; 75: 33-39
- Zinman et al. Diabetes Care 2014; doi:0.1056/NEJMoa1504720
- Zinman et al. Cardiomet. Diabete 2014; doi:0.1056/NEJMoa1504720