

## Experiential Learning Experience Activity Diabetes: Non-Insulin Agents

This document is a suggested learning activity for pharmacy learners (APPE, PGY1, PGY2 residents) to complete during their ambulatory care rotation block. Consider using as a pre-test/post-test or as a topic discussion with preceptor.

**Optional Recommended Reading:**

- ADA Standards of Care – These guidelines are updated yearly; please ensure you are using the most updated guidelines
  - Link: <https://professional.diabetes.org/content-page/practice-guidelines-resources>
  - **Recommended Sections:**
    - **Section 9.** Pharmacologic Approaches to Glycemic Treatment
    - **Section 10.** Cardiovascular Disease and Risk Management

**Objectives:**

1. Describe the place in therapy, mechanism of action, administration, dosing, efficacy, and adverse effects for non-insulin agents for the treatment of type 2 diabetes
2. Review key clinical trials related to cardiovascular disease utilizing SGLT2-inhibitors and GLP-1 receptor agonists.
3. Evaluate existing drug therapy and modify regimen according to patient specific goals, lab parameters, adverse effects, comorbid conditions, and patient preference

**Search the Guidelines – Starter Questions:**

1. What agent is generally recommended first-line agent in the absence of comorbidities and contraindications?
2. Which classes are preferred if cost/affordability is an issue?
3. Which class would you want to avoid in patients with a history of hypoglycemia?
4. Fill in the chart with the non-insulin agents and their effect on weight. (Hint: ADA guidelines Table 9.1)

Decrease weight	Weight neutral	Increase weight

**Non-insulin Agents Chart:**

	Agents in this Class	Mechanism of Action	Administration Frequency and Pearls	Renal dose adjustments? *	Approximate A1C reduction (%)	Cardiovascular and Renal benefits? †	Common side effects/ Clinical considerations
<b>Biguanides</b>	Metformin						
<b>SGLT-2 inhibitors (Sodium glucose co-transporter 2)</b>	Canagliflozin (Invokana®)						
	Dapagliflozin (Farxiga®)						
	Empagliflozin (Jardiance®)						
	Ertugliflozin (Steglatro®)						
<b>GLP-1 receptor agonists (injectable)</b>	Exenatide IR (Byetta®)						
	Liraglutide (Victoza®)						
	Lixisenatide (Adlyxin®)						
	Exenatide ER (Bydureon BCise®)						
	Semaglutide (Ozempic®)						
	Dulaglutide (Trulicity®)						

<b>GLP-1 receptor agonist (oral agent)</b>	Semaglutide (Rybelsus <sup>®</sup> )						
<b>GLP-1 and GIP receptor agonist</b>	Tirzepatide (Mounjaro <sup>™</sup> )						
<b>DPP-4 inhibitors</b>	Alogliptin (Nesina <sup>®</sup> )						
	Linagliptin (Tradjenta <sup>®</sup> )						
	Saxagliptin (Onglyza <sup>®</sup> )						
	Sitagliptin (Januvia <sup>®</sup> )						
<b>Thiazolidinediones</b>	Pioglitazone						
	Rosiglitazone						
<b>Sulfonylureas (2<sup>nd</sup> generation)</b>	Glimepiride						
	Glipizide						
	Glyburide						

\* Check drug information resource for most up-to-date information on renal dose adjustments

± Check drug information resource for most up-to-date information on non-diabetic related FDA approvals

**Select Cardiovascular Clinical Trial Charts:**

	EMPA-REG	CANVAS	DECLARE-TIMI	DAPA-HF	EMPEROR-Reduced	LEADER	SUSTAIN-6	REWIND
Drug Studied	Empagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin	Liraglutide	Semaglutide	Dulaglutide
Participants Enrolled								
Inclusion Criteria								
Median follow-up (years)								
Mean age (years)								
Baseline A1c (%)								
Duration of DM (years)								
Baseline prevalence of CVD/HF (%)								
Primary composite outcome*								
Cardiovascular death*								
Fatal or non-fatal MI*								
Fatal or non-fatal stroke*								
All-cause mortality*								
Heart failure hospitalization*								
Worsening nephropathy								

Strengths								
Limitations								
Key Take Away								

\*Reported as HR (95% CI). ASCVD: atherosclerotic cardiovascular disease; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; NR: not reported. <sup>1</sup>Percentage of individuals with diabetes = 45% (includes those with diagnosed diabetes and those previously undiagnosed at baseline). <sup>2</sup>Primary outcome: a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death. <sup>3</sup> Demonstrated statistical superiority to standard of care.

## **Case-Based Questions:**

### **Case #1: JJ**

JJ is a 55-year-old male with a PMH of type 2 diabetes, hypertension, hyperlipidemia, myocardial infarction (1 year ago), and tobacco use disorder, who presents to your clinic for diabetes management. His current medications include metformin 1 g PO twice daily, lisinopril 40 mg PO once daily, carvedilol 12.5 mg PO twice daily, furosemide 40 mg PO once daily, atorvastatin 80 mg PO daily, and aspirin 81 mg PO daily.

#### **Vital signs:**

- Height: 72 inches
- Weight: 217 lb
- BMI: 29.4 kg/m<sup>2</sup>
- Blood pressure: 134/86 mmHg
- Heart rate: 72 bpm

#### **Today's laboratory values:**

- Plasma glucose: 205 mg/dL
- A1C: 8.9%
- Serum creatinine: 1 mg/dL
- eGFR: 89 ml/min/1.73 m<sup>2</sup>
- Total cholesterol: 162 mg/dL
- Triglycerides: 125 mg/dL
- HDL cholesterol: 50 mg/dL
- LDL cholesterol: 87 mg/dL
- Non-HDL cholesterol: 112 mg/dL

#### **Question 1**

What is JJ's A1C goal? \_\_\_\_\_

#### **Question 2**

What is the best medication to start for JJ's diabetes, given his recent cardiac history?

- A. Sitagliptin
- B. Glyburide
- C. Liraglutide
- D. Pioglitazone

#### **Question 3**

JJ wants to know more about his once-weekly options for a GLP-1 receptor agonist. Which of the following is *not* a once-weekly GLP-1 receptor agonist?

- A. Semaglutide
- B. Exenatide ER
- C. Dulaglutide
- D. Lixisenatide

**Question 4**

Which of the following once-weekly GLP-1 receptor agonists takes the shortest amount of time to prepare for administration?

- A. Dulaglutide
- B. Exenatide ER
- C. Semaglutide
- D. All of the products have the same administration instructions

**Question 5**

What is the most common side effect observed with GLP-1 receptor agonists that often limits its dose titration?

- A. Lower-limb amputation
- B. Hypertension
- C. Gastrointestinal disturbances
- D. Fractures

**Question 6**

JJ started the medication you recommended in question 2 and has titrated to the maximum dose; however, his A1C is still above target. What would be the next change you would recommend for JJ's diabetes?

- A. Canagliflozin
- B. Glyburide
- C. Pioglitazone
- D. Sitagliptin

## Case 2: MK

MK is a 42-year-old female with a PMH of hypertension, type 2 diabetes, hyperlipidemia, heart failure (HF) with ejection fraction 40%, and chronic kidney disease (CKD) stage G3aA3. She presents to your primary care clinic for her quarterly visit. She is hypervolemic on exam. Her current medications include rosuvastatin 20 mg PO daily, metformin 500 mg PO twice daily, furosemide 40 mg PO twice daily, losartan 100 mg PO once daily, metoprolol XL 100 mg PO twice daily, and spironolactone 25 mg PO once daily.

### Vital signs:

- Height: 68 inches
- Weight: 190 lb
- BMI: 28.9 kg/m<sup>2</sup>
- Blood pressure: 142/90 mmHg (140/90 mmHg at last visit)
- Heart rate: 66 bpm

### Laboratory values:

- Plasma glucose: 214 mg/dL
- A1C: 9.5%
- Serum creatinine: 1.5 mg/dL
- eGFR: 48 ml/min/1.73 m<sup>2</sup>
- Urine microalbumin: 402 mg/g
- Total cholesterol: 154 mg/dL
- Triglycerides: 152 mg/dL
- HDL cholesterol: 44 mg/dL
- LDL cholesterol: 99 mg/dL
- Non-HDL cholesterol: 110 mg/dL

### **Question 1**

What is MK's A1C goal? \_\_\_\_\_

### **Question 2**

What would you recommend regarding MK's metformin at this time?

- A. Continue metformin 500 mg twice daily
- B. Reduce dose to metformin 500 mg once daily
- C. Discontinue metformin 500 mg twice daily
- D. Titrate metformin to 1000 mg twice daily

### **Question 3**

What changes to MK's diabetes regimen would you recommend at this time?

- A. Add dapagliflozin 5 mg once daily
- B. Add liraglutide 0.6 mg once daily
- C. Add saxagliptin 2.5mg once daily
- D. Add glipizide 5mg once daily with breakfast



**Question 4**

What laboratory parameter would be most important to monitor with the medication change you recommended in question 3?

- A. SCr
- B. Albumin
- C. Calcium
- D. White blood cells

**Question 5**

What adverse effect of the medication you recommended in question 3 is most pertinent to counsel MK on?

- A. Genital mycotic infections
- B. Hypoglycemia
- C. Weight gain
- D. Diarrhea

**Question 6**

If MK were to add on a SGLT2 inhibitor and experience hypovolemia, which medication may need to be adjusted?

- A. Furosemide
- B. Losartan
- C. Metoprolol
- D. Rosuvastatin

**Question 7**

If MK were to add-on a DPP-4 inhibitor, which one would be a good choice to recommend because it does not require renal dose adjustment?

- A. Saxagliptin
- B. Alogliptin
- C. Linagliptin
- D. Sitagliptin

### Case 3: CS

CS is a 48-year-old male with a PMH of type 2 diabetes (x1 year), hypertension, hyperlipidemia, and obesity, who presents to your clinic for diabetes management. His current medications include metformin 1 g PO twice daily, lisinopril/hydrochlorothiazide 20 mg/12.5 mg PO once daily, and atorvastatin 40 mg PO daily.

#### Vital signs:

- Height: 72 inches
- Weight: 245 lb
- BMI: 31.5 kg/m<sup>2</sup>
- Blood pressure: 132/78 mmHg
- Heart rate: 76 bpm

#### Today's laboratory values:

- Plasma glucose: 192 mg/dL
- A1C: 8.2%
- Serum creatinine: 0.8 mg/dL
- eGFR: 109 ml/min/1.73 m<sup>2</sup>

#### **Question 1**

What changes to CS's diabetes regimen would you recommend at this time?

- A. Add empagliflozin 10 mg once daily
- B. Add tirzepatide 2.5 mg once weekly
- C. Add pioglitazone 15mg once daily
- D. Add glimepiride 2mg once daily

#### **Question 2**

What counseling points would you provide CS based on your recommendation in Question 1?

- A. Eat smaller portions compared your norm
- B. Increase intake of full fat foods
- C. Incorporate more spices and seasonings into meals
- D. Take an antacid to each meal

#### **Question 3**

You learn CS does not have prescription drug coverage. What changes to CS's diabetes regimen would you recommend at this time? (open-ended question)