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

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

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Search the Guidelines – Starter Questions:

1. What agent is generally recommended first-line agent in the absence of comorbidities and contraindications?
   - Metformin

2. Which classes are preferred if cost/affordability is an issue?
   - Sulfonylureas
   - TZDs

3. Which class would you want to avoid in patients with a history of hypoglycemia?
   - Sulfonylureas

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
• GLP-1 RA • Dual GLP/GIP Receptor Agonist (tirzepatide) • SGLT-2 inhibitors	• DPP-4 inhibitors • Metformin	• Sulfonylureas • TZDs

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
Biguanides	Metformin	Inhibits hepatic glucose production; increase insulin sensitivity by tissue & fat cells	Daily to BID	eGFR 30-45: use is not recommended for initiation; if already on & GFR falls <45 during therapy, consider 50% dose reduction eGFR < 30: use contraindicated	1.5 - 2%	CV: Yes (UKPDS study) Renal: No	• Boxed Warning: lactic acidosis • Side effects: diarrhea, nausea, vomiting • May cause B12 deficiency with long-term use
SGLT-2 inhibitors (Sodium glucose co-transporter 2)	Canagliflozin (Invokana®)	Inhibits SGLT-2 in the proximal tubule; decreases reabsorption of filtered glucose	Daily	eGFR 30-60: 100 mg daily eGFR <30: Not recommended for initiation; if already on & GFR falls <30, may continue 100 mg daily Contraindicated in dialysis	0.5 - 1%	CV: canagliflozin, empagliflozin Heart failure: dapagliflozin, empagliflozin Renal: canagliflozin, dapagliflozin	• Side effects: hypotension, increased urination/volume depletion, genital mycotic infections, urinary tract infections • May result in euglycemic DKA
	Dapagliflozin (Farxiga®)		Daily	eGFR <25: Not recommended for initiation; if already on & GFR falls <25, may continue 10 mg daily Contraindicated in dialysis			
	Empagliflozin (Jardiance®)		Daily	eGFR <30: Not recommended for initiation; if already on & GFR falls <30, may continue 10 mg daily Contraindicated in dialysis			
	Ertugliflozin (Steglatro®)		Daily	eGFR <45: Not recommended			
GLP-1 receptor agonists (injectable)	Exenatide IR (Byetta®)	Agonist at GLP-1 receptors, resulting in glucose-dependent insulin secretion, inhibition of glucagon secretion, reduced gastric emptying, and increased satiety	BID 1 hour before meals	eGFR <30: Not recommended	~1 – 1.7%	CV: liraglutide, semaglutide, dulaglutide Renal: No	• Boxed Warning: risk of thyroid C-cell tumors • Side effects: nausea, vomiting, diarrhea (N/V/D), headache, pancreatitis (rare) • Avoid use in patients with gastroparesis or patients with multiple endocrine neoplasia syndrome type 2 • Do not use in combination with DPP-4 inhibitors
	Liraglutide (Victoza®)		Daily	No dosage adjustment necessary; use with caution in mild-severe impairment due to limited clinical evidence			
	Lixisenatide (Adlyxin®)		Daily	eGFR <15: Not recommended			
	Exenatide ER (Bydureon BCise®)		Weekly - shake for 15 sec.	eGFR 30-45: use with caution eGFR <30: Not recommended			
	Semaglutide (Ozempic®)		Weekly - lead in of 0.25mg x 4 weeks	No dosage adjustment necessary; use with caution in mild-severe impairment due to limited clinical evidence			
	Dulaglutide (Trulicity®)		Weekly – never see needle!	No dosage adjustment necessary; use with caution in mild-severe impairment due to limited clinical evidence			
GLP-1 receptor agonist (oral agent)	Semaglutide (Rybelsus®)	Agonist at GLP-1 receptors, resulting in glucose-dependent insulin secretion, inhibition of glucagon secretion, reduced	Daily - >30 min before food/drinks	No dosage adjustment necessary; use with caution in mild-severe impairment due to limited clinical evidence	0.9 – 1.4%	CV: No Renal: No	• Boxed Warning: risk of thyroid C-cell tumors • Side effects: N/V/D, headache, pancreatitis (rare) • Dose titration to minimize side effects and increase tolerability

		gastric emptying, and increased satiety					• Avoid use in patients with gastroparesis or h/o multiple endocrine neoplasia syndrome type 2 • Do not use in combination with DPP-4 inhibitors
GLP-1 and GIP receptor agonist	Tirzepatide (Mounjaro™)	Agonist at GLP-1 and GIP receptors	Weekly – never see needle!	No dosage adjustment necessary; use with caution in mild-severe impairment due to limited clinical evidence	2.0-2.3%	CV: No Renal: No	• Boxed Warning: risk of thyroid C-cell tumors • Side effects: N/V/D, dyspepsia, pancreatitis (rare), gallbladder disease (rare) • Dose titration to minimize side effects and increase tolerability • Avoid use in patients with gastroparesis or patients with multiple endocrine neoplasia syndrome type 2 • May decrease effectiveness of oral contraceptives • Do not use in combination with GLP-1 RAs or DPP-4 inhibitors • Dual mechanism of action results in significant weight loss
DPP-4 inhibitors	Alogliptin (Nesina®)	Enhances body's natural incretin system; increase insulin secretion; decrease glucagon secretion	Daily	CrCl ≥30 to <60: 12.5 mg daily CrCl ≥15 to <30: 6.25 mg daily	0.7 – 1%	CV: No Renal: No	• Side effects: upper respiratory tract infection, headache, GI distress • Do not use in combination with GLP-1 receptor agonists
	Linagliptin (Tradjenta®)		Daily	None			
	Saxagliptin (Onglyza®)		Daily	eGFR <45: 2.5 mg daily			
	Sitagliptin (Januvia®)		Daily	eGFR ≥30 to <45: 50 mg daily eGFR <30: 25 mg once daily			
Thiazolidinediones	Pioglitazone	Increases sensitivity of adipose tissues & muscles to insulin via activation of PPAR-γ resulting in decreased levels of free fatty acids thus increased glucose uptake by cells; suppresses hepatic glucose output	Daily	None	1 - 1.5%	CV: No Renal: No	• Boxed Warning: congestive heart failure • Side effects: weight gain, fluid retention, bone fractures
	Rosiglitazone		Daily	None			
Sulfonylureas (2nd generation)	Glimepiride	Increase insulin secretion from pancreatic β-cells; Bind to sulfonylurea receptor and block ATP-dependent K+ channels thus reduce K+ efflux to enable β-cell depolarization, calcium influx and secretion of insulin	1-2 div. doses w/ first meal	eGFR 15-60: initiate at low dose and titrate cautiously eGFR <15: avoid use	1.5 - 2%	CV: No Renal: No	• Side effects: hypoglycemia, weight gain • Use in caution with older adults and in patients with kidney disease
	Glipizide		1-2 div. doses IR: 30 min before 1st meal ER: w/ 1st meal	eGFR 10-50: initiate at low dose and titrate cautiously eGFR <10: avoid use			
	Glyburide		1-2 div doses with meals	Not recommended in chronic kidney disease			

* 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	7,020	10,142	17,160	4,744	3,730 (total); 1,856 (with diabetes)	9,340	3,297	9,901
Inclusion Criteria	T2Dm + pre-existing CVD	T2DM + pre-existing CVD if ≥ 30 YO or >2 CV risk factors if ≥50 YO	T2DM + established ASCVD or multiple ASCVD risk factors	NYHA class II-IV HF + EF ≤40% with or w/o diabetes	NYHA class II-IV HF + EF ≤40% with or w/o diabetes	T2DM + pre-existing CVD, CKD, or HF at ≥50 YO or CV risk at ≥60 YO	T2DM + pre-existing CVD, CKD, or HF at ≥50 YO or CV risk at ≥60 YO	T2DM + prior ASCVD event or risk factors for ASCVD
Median follow-up (years)	3.1	2.4	4.2	1.5	2.2	3.8	2.1	5.4
Mean age (years)	63.1	63.3	64.0	66	67.2 (total), 66.5 (with diabetes)	64.3	64.6	66.2
Baseline A1c (%)	8.1	8.2	8.3	NR[1]	NR	8.7	8.7	7.4
Duration of DM (years)	10+ years	13.5	11	NR	NR	12.8	13.9	10.5
Baseline prevalence of CVD/HF (%)	100/11	72/14	41/10	NR/100	100% with HF	81/18	60/24	32/9
Primary composite outcome*	3-point MACE 0.86 (0.74-0.99)	3-point MACE 0.86 (0.75-0.97)	3-point MACE *0.93 (0.84-1.03)	Worsening HF or CV death 0.74 (0.65–0.85)[2]	CV death or HF hospitalization 0.75 (0.65-0.86)	3-point MACE 0.87 (0.78-0.97)[3]	3-point MACE 0.74 (0.58-0.95)[3]	3-point MACE 0.88 (0.79-0.99)[3]
Cardiovascular death*	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.82 (0.69–0.98)	0.92 (0.75-1.12)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.91 (0.78-1.06)
Fatal or non-fatal MI*	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	NR	NR	0.86 (0.73-1.00)	0.74 (0.51-1.08)	0.96 (0.79-1.16)
Fatal or non-fatal stroke*	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	NR	NR	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.76 (0.61-0.95)
All-cause mortality*	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.71–0.97)	0.92 (0.77-1.10)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.90 (0.80-1.01)
Heart failure hospitalization*	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.70 (0.59–0.83)	0.69 (0.59-0.81)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.93 (0.77-1.12)
Worsening nephropathy	0.61 (0.53-0.70	0.60 (0.47-0.77)	0.53 (0.43-0.66)	0.71 (0.44-1.16)	Composite renal 0.50 (0.32-0.77)	0.78 (0.67-0.92)	0.64 (0.46-0.88)	0.85 (0.77-0.93)
Strengths	• In pts with established CVD • Time to benefit occurred earlier than LEADER • CV outcomes regardless of dose & baseline characteristics • Added to standard of care	• Large trial • Long duration • Included pts with & without established CVD	• Large trial • Included larger % of patient without ASCVD – just had to have 1 risk factor • Consistent response across BMI • Decrease BP	• Included pts without DM, too • Pts had lower BMI, SBP, and mean eGFR • Included analysis of dapagliflozin based on use of other medications, including those specific for HF • Benefits seen regardless of whether pt had	• Included pts without DM, too • Pts had lower BMI, SBP, and mean eGFR • Pts with "more advanced but stable heart failure"	• Included pts with higher baseline A1C	Included: • High percentage of pts with ASCVD	Included: • pts w/ and w/out ASCVD • longer f/u than other CVOTs • lower baseline A1C than other CVOTs • mgmt. of T2D using background treatment – could help external validity

				diabetes or not; pt's age, risk, health, or baseline use of diuretic, or sacubitril/valsartan				
Limitations	• Pts did not reach their A1C targets	• Pts had a greater risk of amputation – toe or metatarsal • Limited number of events for certain outcomes – difficult to interpret/apply	• Excluded pts with CrCl < 60 ml/min • Differences in pts vs. other SGLT2i CVOT	• Limited diversity (ethnic/race) • Older pts • Very limited number of pts NYHA functional class IV • Limited number of pts on sacubitril/valsartan		• Length of follow-up (3.5 – 5yrs) – limits safety and efficacy • High risk of CV events and baseline A1C >/ 7%	• Length of follow-up (2.1 years) • Increase in diabetic retinopathy complications – thought to be related to rapidly decreasing glucose	• 25% of participants not taking their study drug at their last visit • Many of the strengths could also be limitations as far as thinking of applicability
Key Take Away	NNT of 39 over 3 years Pts at high risk for CV events have lower rate of CV outcomes and death when empagliflozin is added Can use in T2DM if ASCVD • empagliflozin has indication to reduce risk of CV death in T2DM and established CVD	Pts at high risk for CV events have lower rate of CV outcomes and death when canagliflozin is added Can use in T2DM if ASCVD • canagliflozin has indication to reduce risk of MACE in T2D if established CVD	Pts with ASCVD or at risk for ASCVD events have lower rate of CV death or hospitalization when dapagliflozin is added Can use in T2DM if ASCVD or risk factors • dapagliflozin has indication to reduce risk of hospitalization for heart failure in T2D if established CVD or multiple CV risk factors	Dapagliflozin is beneficial in patients with symptomatic HFrEF regardless of whether the pt has diabetes. Can use in T2DM if ASCVD, ASCVD risk factors, or HFrEF • dapagliflozin has indication to reduce risk of CV death and HF hospitalization in adults with HFrEF	Benefit in pts with HF regardless of whether pt had diabetes – reduced risk of CV death or hospitalization for HF • Empagliflozin has indication to reduce the risk of CV death and hospitalization for heart failure in adults with heart failure	Can use in T2DM if ASCVD • liraglutide has indication to reduce risk of MACE in T2D if established ASCVD	In pts with high CV risk, semaglutide injection was noninferior to placebo regarding MACE • semaglutide injection has indication to reduce MACE if T2DM if and ASCVD	Can use in T2DM if ASCVD or ASCVD risk factors • Dulaglutide has indication to reduce risk of MACE in T2D if ASCVD or ASCVD risk • Potential to decrease BG, weight, and BP and minimize hypoglycemia

*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. [1]Percentage of individuals with diabetes = 45% (includes those with diagnosed diabetes and those previously undiagnosed at baseline). [2]Primary outcome: a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death. [3] 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^2
- 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^2
- 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? _____

Answer/Explanation: According to the ADA, JJ's A1C goal should be ≤ 7%. Although he has multiple comorbidities, nothing in his PMH indicates a shorter life expectancy and he does not have a history of hypoglycemia.

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

Answer: C

Explanation: Based on evidence of JJ's established ASCVD, a GLP-1 receptor agonist or SGLT2 inhibitor would be preferred. Of the above choices, answer C is the best option because it is a GLP-1 receptor agonist. Remember that liraglutide does have FDA-approval "to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease."

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

Answer: D

Explanation: The once-weekly GLP-1 receptor agonists currently available (August 2022) in the United States are semaglutide (Ozempic), exenatide ER (Bydureon), and dulaglutide (Trulicity). These agents may be given once weekly, as opposed to the other GLP-1 receptors agonists that are dosed at least once daily. These agents include exenatide (Byetta), which must be given twice daily within 60 minutes before the morning and evening meals; liraglutide (Victoza), which is given once daily at any time of day; and lixisenatide (Adlyxin), which is administered once daily 60 minutes before the morning meal.

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

Answer: A

Explanation: Although all of the once-weekly GLP-1 receptor agonists are administered via pen injection once weekly into subcutaneous tissue (abdomen, thigh, or back of arm), their administration instructions differ. Dulaglutide has the fewest steps for administration. Dulaglutide comes has a pre-filled, single-use pen. To use it, patients must *1*) remove the base cap, *2*) twist the other end of the pen to unlock it, *3*) place the flat base side against the injection site, *4*) press and hold the green injection button until they hear a loud click and then continue holding until a second click is heard, *5*) remove the pen from the skin, and *6*) dispose of the pen. Dulaglutide enables patients to inject their medication without seeing the needle, which is inside the pen. Because the pens are for single use, there should be no need to keep them out of the refrigerator for prolonged periods of time; however, if patients need to take pens with them for vacation or out of town trips, the pens may be stored out of the refrigerator at room temperature (<86°F [30°C]) for 14 days. Unused pens should be stored in the refrigerator (36–46°F [2–8°C]).

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

Answer: C

Explanation: The most observed side effects of GLP-1 receptor agonists are nausea, vomiting, and diarrhea. The incidence of nausea may be less with the long-acting GLP-1 receptor agonists (dulaglutide, semaglutide, and exenatide ER) compared to daily GLP-1 receptor agonists (exenatide [immediate release], liraglutide, and lixisenatide) and may subside over time. Because of the mechanisms of action of slowed gastric emptying and increased early satiety, patients should be counseled to stop eating as soon as they feel full, which may result in their eating smaller portions than they did previously. Patients should be counseled that if the gastrointestinal disturbances do not improve, they should call their provider for further guidance. Rarely, severe abdominal pain may be a sign of pancreatitis.

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

Answer: A

Explanation: Based on evidence of JJ's established ASCVD, a GLP-1 receptor agonist or SGLT2 inhibitor would be preferred. Since JJ is already on a GLP-1 receptor agonist (liraglutide was selected in question 2), evidence supports adding a SGLT2 inhibitor with proven benefit on reducing cardiovascular disease. Canagliflozin and empagliflozin have both been shown to reduce ASCVD. Remember that canagliflozin and empagliflozin have FDA-approval "to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease."

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^2
- 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^2
- 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? _____

Answer/Explanation: According to the ADA, MK's A1C goal should be ≤ 7%.

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

Answer: A

Explanation: Evidence still supports metformin as a first-line therapy option. However, it is important to consider MK's current renal function. Her eGFR of 48 ml/min/1.73 m^2 is still within the range of 45 – 60 ml/min/1.73 m^2 and metformin can be continued. Some clinicians may choose to increase metformin to the max dose of 1g BID at this point since MK's renal function is still >45ml/min/1.73 m^2. A more conservative approach would be to continue at the current dose, closely monitor MK's renal function, and consider other adjunctive therapy with evidence for MK's other co-morbidities.

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

Answer: A

Explanation: Due to the history of HF and hypervolemic status, an SGLT2 inhibitor with evidence of reducing heart failure is the preferred medication option. To improve cardiovascular (CV) outcomes in type 2 diabetes and high cardiovascular risk, patients should consider an SGLT2 inhibitor or a GLP-1 receptor agonist. If HF predominates, then an SGLT2 inhibitor is preferred (according to the ADA and ACC). GLP-1 receptor agonists would be considered for HF if a patient were unable to tolerate an SGLT2 inhibitor. Saxagliptin, a DPP-4 inhibitor, has been shown to worsen HF and should be avoided in a patient with HF, like MK. The same precaution should be taken with the DPP-4 inhibitor, alogliptin. You should also avoid TZDs, rosiglitazone and pioglitazone, in heart failure. Glipizide, a sulfonylurea, is not recommended (although not contraindicated) in heart failure patients given the potential for weight gain. Other first-line options, pending medication affordability, should be utilized first.

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

Answer: A

Explanation: SGLT2 inhibitors have an impact on kidney function. To ensure that these medications are not causing harm, such as leading to acute kidney injury, monitoring SCr and eGFR in patients taking them is advised. In renal outcomes trials, there is an initial drop in eGFR, but the eGFR remains more stable over time compared to placebo.

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

Answer: A

Explanation: Due to the mechanism of action leading to increased glucose excretion via the urinary tract, SGLT2 inhibitors have a risk for increased genital mycotic infections. The magnitude of absolute risk for women ranges from ~3% in placebo trials up to ~18% in active comparator trials with women. To help mitigate these effects, men and women should be counseled on the importance of keeping the genital area clean and dry. Hypoglycemia risk is low with SGLT-2 inhibitors. SGLT-2 inhibitors have a mild weight loss effect. Diarrhea is not an expected side effect of SGLT-2 inhibitors, but is common with metformin (biguanide).

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

Answer: A

Explanation: Due to the mechanism of action of SGLT2 inhibitors, the hypovolemic effect of SGLT2 inhibitors may enhance the hypovolemic and hypotensive effects of loop diuretics like furosemide. MK should be monitored closely for her response to these medications. The dose of her furosemide may need to be adjusted.

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

Answer: C

Explanation: All DPP-4 inhibitors require renal dose adjustment with the exception of linagliptin.

Maximum Doses of DPP-4 Inhibitors Based on eGFR

eGFR (mL/min/1.73 m^2)	Sitagliptin, mg	Saxagliptin, mg	Linagliptin, mg	*Alogliptin, mg
≥45^	100 once daily (No dose adjustment)	5 once daily (No dose adjustment)	5 once daily (No dose adjustment)	25 once daily (>60 mL/min) -- 12.5 (<60 mL/min)
≥30 to <45	50 once daily	2.5 once daily	5 once daily	12.5 once daily
<30	25 once daily	2.5 once daily	5 once daily	6.25 once daily

*Cut-offs based on CrCl
^Dose adjustment for alogliptin at <60 mL/min

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^2
- 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^2

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

Answer: B

Explanation: A dual GLP1/GIP RA would be the best option for CS given their history of obesity with a BMI >30 kg/m^2. Tirzepatide (Mounjaro™) 6 doses available (at 2.5mg increments up to 15mg). The patient should be on each dose for 4 weeks before titrating up to the next dose, considering tolerability and glycemic response. You may also consider other commonly utilized GLP1 RAs for this patient, such as dulaglutide, semaglutide, liraglutide.

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

Answer: A

Explanation: Both dual GLP/GIP agonists and GLP1 receptor agonist can cause GI disturbances, such as nausea, diarrhea, decreased appetite, vomiting, constipation, indigestion, and stomach pain. To mitigate these effects, it is generally recommended to: (1) Eat smaller meals. You may break up your typical 3 meals into 4 or more smaller portions per day; (2) Stop eating when full; (3) Avoid fatty foods; (4) Eat bland foods, like rice or crackers. The most GI disturbances are seen at medication initiation and dose escalations. Should the disturbances become severe, the patient should contact their care provider.

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)

Answer/Explanation: There are many options available here! First, for patients who are prescribed a brand medication, the manufacturer's website can be searched for a Patient Assistance Program that the patient can apply for. These are often limited to patients without government insurance or those who have Medicare but do not qualify for Low-Income Subsidy (also known as "Extra Help"). Some medications will also offer discount cards or other savings for those with or without insurance. The free resource, Needymeds.org, is a great place to search for coverage options for medications. For those who are not eligible for these programs, the ADA recommends the use of a TZD or sulfonylurea due to their low costs. Both classes come with weight gain side effects, as well as some precautions specific to each class, thus a thorough overview of the patient's profile and the specific medication to be added are extremely important.

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