

FDA Safety Warnings and Prescribing Updates: Fluoroquinolones, SGLT2 Inhibitors, and Metformin

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Goal. The goal of this lesson is to provide a review of select and pertinent U.S. Food and Drug Administration (FDA) safety warnings and associated prescribing updates that were recently issued regarding fluoroquinolone antibiotics and serious side effects, the safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors, and metformin use in patients with renal impairment.

Objectives. At the completion of this activity, the participant will be able to:

1. demonstrate an understanding of the safety warning and associated prescribing changes issued, if applicable, for each of the entities discussed;
2. identify the patient populations at risk for adverse events in relation to the safety warnings for the entities discussed; and
3. list fundamental patient counseling points secondary to the safety warnings and associated prescribing changes, if applicable, for the entities discussed.

Fluoroquinolone Antibiotics

In 2016, the Food and Drug Administration (FDA) released two related drug safety communications on the disabling effects of fluoroquinolones (FQs). In May 2016,

FDA stated there may be higher risk of serious adverse reaction, questioning the benefit of fluoroquinolone use in patients with acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), or uncomplicated urinary tract infections (UTIs). In July, FDA released a stronger warning stating that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

Manufacturers were required to update the Black Box Warning, the strongest warning of the FDA in the drug labeling and *Medication Guides* to reflect these new recommendations. Additionally, the *Indications and Usage* section contains new limitation-of-use statements to reserve fluoroquinolones for patients who do not have other available treatment options for the infectious diseases previously mentioned.

These are not the first post-marketing concerns raised regarding fluoroquinolone use. Over the past nine years, FDA has posted four drug safety communications regarding FQs and their potentially disabling adverse reactions, and continued to monitor the adverse effects of FQs which has led up to the most recent and serious warnings.

The drug safety communica-

tions discussed in this lesson were founded on two main principles. First, the adverse reaction profile for fluoroquinolones has a higher prevalence of rare but serious adverse reactions when compared to other antibiotic classes. Second, in select infectious diseases where antibiotics are needed and commonly treated with fluoroquinolones, effective alternative treatment options may be available.

Antibiotics are one of the most frequently prescribed medications in the United States. Of those, fluoroquinolones is a class of antibiotics used to treat a variety of bacterial infectious diseases. Levofloxacin, ciprofloxacin, and moxifloxacin are among the top 300 most prescribed drugs in the U.S. In 2014, approximately 22 million patients received prescriptions for selected oral fluoroquinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin) from U.S. outpatient retail pharmacies.

Fluoroquinolones are indicated in adults ages 18 and older with infections caused by designated, susceptible bacteria. FDA-approved indications vary for each agent, and may include pneumonia, sinusitis, exacerbation of chronic bronchitis, skin and soft tissue infections, prostatitis, urinary tract infections, and pyelonephritis.

At the time of approval, common side effects (occurring more frequently than 1 percent) included nausea, vomiting, diarrhea, abdominal pain, dyspepsia, insomnia,

headache, and dizziness. Examples of less common side effects (occurring less frequently than 1 percent) included electrolyte imbalances, anxiety, agitation, tremors, convulsions, palpitations, and arrhythmias. The labels of fluoroquinolone antibiotics previously had a boxed warning for tendinitis, tendon rupture, and worsening of myasthenia gravis; and warnings about the risks of peripheral neuropathy and central nervous system (CNS) effects. Other serious risks described in the labeling include cardiac, dermatologic, and hypersensitivity reactions. Post-marketing adverse reaction reporting indicated that fluoroquinolones are associated with tendinopathies, CNS effects, and peripheral neuropathies, which may be irreversible in some cases. This finding resulted in appropriate revisions to the original drug labeling and *Medication Guide*.

Post-marketing review and reporting has indicated that the frequency of some rare but serious adverse reactions were initially underestimated. In a study by Owens and Ambrose focusing on the safety profile of fluoroquinolones in comparison to other antibiotics, a difference was found in the rate of serious adverse reactions like tendinopathy, peripheral neuropathy, and CNS effects, which were shown to be more prevalent in fluoroquinolones than in other antibiotic classes.

A search of FDA's Adverse Event Reporting System (AERS) database from November 1997 to May 2015 identified 178 U.S. cases of apparently healthy patients who took an FQ to treat ABS, ABECB, or uncomplicated UTIs and developed disabling and potentially irreversible adverse reactions that appeared as a constellation of symptoms. Although the risk of peripheral neuropathy is described in the drug labels of each FQ, the potential rapid onset and risk of permanence were not adequately described.

The patients included in this evaluation reported adverse reactions lasting longer than one

month and involved two or more body systems. The majority of reactions affected the musculoskeletal and peripheral nervous systems, and the CNS. Seventy-four percent of the patients were 30 to 59 years of age, and many described having serious disability. The reported negative impact on their lives included job loss, resulting in lack of health insurance, a large financial burden, and family tension. Among reported cases, the side effects occurred within hours to weeks after starting the fluoroquinolone. Several cases reported that some side effects dissipated or improved after discontinuation of the medication; others reported the side effects worsened or continued. The data indicated that the mean duration of the disabling effect from the adverse reactions was 14 months, with the longest duration reported as nine years.

When prescribed a fluoroquinolone, some patients may be at a higher risk of developing potentially disabling adverse reactions than others. Patients with decreased renal function are at a higher risk due to impaired elimination. More adverse reactions were reported in older adults as well. For tendinitis and tendon rupture specifically, age greater than 60 years, active lifestyle, diabetes mellitus, peripheral vascular disease, gout, hyperparathyroidism and concomitant corticosteroid use all showed an increased risk of adverse reaction. Concomitant use of fluoroquinolones and other medications that may cause tendinopathies should be avoided due to an escalated risk of adverse reaction. No other risk factors have been identified for disabling peripheral neuropathy.

The fluoroquinolone drug label changes and *Medication Guide* recommendations are class-wide. However, the prevalence of serious adverse reactions might not be the same class-wide. In one study that looked at serious adverse reactions reported for multiple fluoroquinolones, levofloxacin had the most adverse reactions reported. When the results were adjusted for total

prescriptions dispensed, moxifloxacin had the highest incidence. It is unknown which of the FQs pose the highest associated risk.

In spite of fluoroquinolone FDA-approved indications to treat sinusitis, exacerbations of chronic bronchitis and urinary tract infections, their clinical utility may be limited due to resistance patterns and role in treatment. According to the Infectious Disease Society of America's (IDSA) guidelines for the treatment of uncomplicated urinary tract infections, fluoroquinolones should only be used if other options, like nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin, are contraindicated. The resistance patterns for common urinary tract bacteria indicate that they are also becoming more resistant to fluoroquinolones because of their high use. IDSA guidelines recommend not using a fluoroquinolone if local resistance in the community has been reported.

For acute upper respiratory infections, like sinusitis and exacerbations of bronchitis, the most common etiology is viral. In acute sinusitis, bacterial infections only account for 2 to 10 percent of all infections, whereas viruses account for 90 to 98 percent. Of all acute exacerbations of bronchitis, viruses cause 85 to 95 percent. These statistics call into question the appropriateness of antibiotic use in these infectious diseases, regardless of antibiotic choice.

In cases where antibiotics are indicated and alternative agents are not an option, patients who are prescribed FQs should be monitored and counseled for potentially serious adverse reactions, including tendinitis, tendon rupture, peripheral neuropathy and CNS effects. Patients should be counseled to report any new muscle or tendon pain, tingling or loss of feeling in the arms or legs, dizziness, insomnia, or headache. The benefits of treatment with fluoroquinolones should be questioned when using them in older adults, in patients with decreased renal function and in patients with active lifestyles,

Table 1
Selected information for
patients taking
fluoroquinolone
antibiotics

- Fluoroquinolone antibiotics are associated with disabling and potentially permanent serious side effects and should not be used to treat certain uncomplicated infections such as acute bacterial sinusitis (ABS), acute worsening of bacterial chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTIs).

- These side effects can involve the tendons, muscles, joints, nerves, and the CNS, and can occur within hours to weeks after starting a fluoroquinolone. These include swelling or inflammation of the tendons, tendon rupture, tingling or prickling sensation (like pins and needles), numbness in arms or legs, muscle pain, muscle weakness, joint pain, or joint swelling.

- Other serious CNS side effects include depression, hallucinations, suicidal thoughts, confusion, or anxiety.

- Other side effects include abnormally rapid or irregular heart beat, ringing or buzzing in the ears, vision problems, skin rash, sensitivity of skin to sunlight, headache, trouble falling asleep, and fatigue.

- Contact your health care professional immediately if you experience any serious side effects while you are taking your fluoroquinolone.

since they are at an increased risk of these serious adverse reactions. Patients should be advised to rest at the first sign of tendinitis or tendon rupture. Patients should contact their health care provider regarding the possibility of a change to a non-fluoroquinolone antibiotic if any signs or symptoms of serious adverse reactions occur. Table 1 lists additional information for patients regarding possible side effects with FQ use.

Risks Associated with SGLT2 Inhibitors

Between September 2015 and June 2016, FDA issued several safety communications regarding adverse reactions and possible risks asso-

ciated with the use of the SGLT2 inhibitors canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance) when prescribed for the treatment of type 2 diabetes. As a result, the *Warnings and Precautions* sections of the product inserts have been revised to reflect these prescribing updates which include a strengthened risk for kidney injury, ketoacidosis, urinary tract infections, and bone fractures.

Canagliflozin was the first SGLT2 inhibitor approved in 2013 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Dapagliflozin was approved in 2014, followed by empagliflozin shortly after. These agents are available as single entities or in combination with metformin and other diabetic medications. The introduction of SGLT2 inhibitors offered a novel mechanism and site of action in comparison to previous treatments for reducing serum glucose levels. The SGLT2 inhibitors exert their effect in the kidney by lowering renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion. Common side effects associated with these agents, at the time of initial approval, included genital yeast infections, urinary tract infections, and hypotension. The risk of hypoglycemia is low unless co-administered with insulin or an insulin secretagogue.

The 2016 treatment guidelines of the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) for T2DM recommend the use of SGLT2 inhibitors as an option for monotherapy. The AACE and the ADA treatment algorithms consider SGLT2 inhibitors as an option for patients with contraindications or intolerance to metformin. They may also be used as a component of dual and triple therapy. Approximately 1.7 million patients received prescriptions for SGLT2 inhibitors (as a single ingredient or combination product) in the outpatient retail pharmacy

setting from October 2014 to September 2015.

In a meta-analysis of SGLT2 inhibitors published in 2013, Vasylakou *et al.* assessed the efficacy and safety of these agents systematically by reviewing randomized trials comparing SGLT2 inhibitors with placebo or other medications for type 2 diabetes. The authors concluded that SGLT2 inhibitors reduced HbA1c levels in comparison to placebo when used as monotherapy or add-on. The inhibitors were estimated to reduce HbA1c by 0.66 percent. This is similar to the glycemic efficacy of other anti-diabetic agents such as dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) like sitagliptin (Januvia). They also had a favorable effect on body weight and blood pressure, along with risk of hypoglycemia similar to metformin, but less than that with sulfonylureas. The authors also noted that, in patients with moderate renal impairment, use of dapagliflozin or high doses of canagliflozin was associated with increased incidence of renal-related adverse events. Data on cardiovascular outcomes and death were inconclusive. Finally, the authors concluded that while SGLT2 inhibitors may improve short-term outcomes, further research is necessary to clarify long-term clinical outcomes, diabetic complications, and safety.

Renal Warnings. From March 2013 to October 2015, FDA received reports of 101 confirmable cases of acute kidney injury in patients receiving canagliflozin or dapagliflozin, some requiring hospitalization and dialysis. According to the safety communication, about half of the cases occurred within the first month of initiating the drug, and most patients improved after stopping it. Some cases occurred in patients who were younger than 65 years, dehydrated, had low blood pressure, or were taking other medications affecting the kidneys.

The activity of SGLT2 inhibitors is dependent upon renal function, particularly the glomerular

Table 2
Dosing recommendations
for SGLT2 inhibitors in
the presence of renal
impairment

Canagliflozin (Invokana)

- Dose is limited to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73m².
- Dose can be increased to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73m² or greater.
- Initiation or use is not recommended if eGFR is below 45 mL/min/1.73m².

Dapagliflozin (Farxiga)

- Initiation is not recommended in patients with an eGFR less than 60 mL/min/1.73m².
- If renal function declines to persistently under eGFR of 30 to 60 mL/min/1.73m² after initiation, dapagliflozin should be discontinued.

Empagliflozin (Jardiance)

- Do not initiate if eGFR is below 45 mL/min/1.73m².
- Discontinue if eGFR falls below 45 mL/min/1.73m².

filtration rate (GFR), with a pharmacodynamic response directly related to SGLT2 inhibition (i.e., urinary glucose excretion). Therefore, as renal function declines, this class of antiglycemic agents is expected to be less effective. Consequently, the product inserts of SGLT2 inhibitors include restrictions for use in patients with renal impairment. Table 2 lists the dosing recommendations for each of the SGLT2 inhibitors in the presence of renal impairment.

Because SGLT2 inhibition leads to osmotic diuresis with possible intravascular volume depletion and subsequent renal impairment, it is vital that health care professionals assess volume status and correct it prior to initiation of therapy. Patients with impaired renal function, elderly patients, patients on diuretics or medications that interfere with the renin-angiotensin-aldosterone system (RAAS) or patients with low systolic

blood pressure are predisposed to acute kidney injury and should be monitored for signs and symptoms. Discontinuing SGLT2 inhibitors in settings of reduced oral intake, such as acute illness or fasting or fluid losses such as gastrointestinal illness, should be considered. Prompt discontinuation of the drug is warranted should kidney injury occur, along with treatment for renal impairment. Patients should be counseled to seek medical attention immediately if they experience signs or symptoms of kidney injury which includes decreased urine output or swelling in the legs or feet.

Ketoacidosis and Urinary Tract Infections (UTIs). From March 2013 to May 2015, the FDA adverse event reporting system identified 73 cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors. In all of these cases, patients were hospitalized or treated in an emergency department. The safety communication released in December 2015 also included a warning about the potential of serious urinary tract infections. Nineteen cases of urosepsis and pyelonephritis were reported that started as UTIs.

The increased risk of urinary tract infections with SGLT2 inhibitors was stated as a potential adverse reaction in the product insert, as an increased incidence of infections was documented in the literature. However, the associated serious risk of UTIs was less consistent. Systematic reviews evaluating the data from 13 randomized, controlled trials (RCTs) reported a greater incidence of UTIs among those receiving canagliflozin (ranging 3 to 13.5 percent) versus placebo (6 to 6.7 percent). In studies where canagliflozin was used in combination therapy against a control group, the ranges were similar (4 to 8.3 percent versus 5 to 7.8 percent). No clear increased incidence in events consistent with UTI with empagliflozin was observed in pooled safety evaluation of RCTs. A pooled safety evalua-

tion of 12 placebo-controlled Phase IIb/III studies of dapagliflozin also reported an increased rate of UTIs in patients receiving dapagliflozin versus placebo. Complicated UTIs and pyelonephritis were reported in low rates in randomized controlled studies for both empagliflozin and dapagliflozin.

Hence, the revised product labeling advises prompt evaluation of UTIs if signs or symptoms occur, as urosepsis and pyelonephritis have been reported. Additionally, increased urination, including polyuria, nocturia and other urinary events, is also commonly reported, occurring in ≥2 percent of patients treated with SGLT2 inhibitors.

Patients should be advised of the signs and symptoms of a UTI which include a feeling of burning when urinating or the need to urinate frequently or urgently; pain in the lower part of the stomach area or pelvis; fever; or blood in the urine.

Ketoacidosis is a potentially life-threatening complication of diabetes that mainly occurs in patients with type 1 diabetes mellitus (T1DM), but can occur in some patients with T2DM. While diagnostic criteria can vary, typically patients present with hyperglycemia (blood glucose >250 mg/dL), serum and urinary ketones (serum level >5 mEq/L), and decreased arterial pH (pH <7.3). Usual causes of ketoacidosis in patients with diabetes include infection, missed or disrupted insulin treatment, and the presentation of a newly diagnosed case of diabetes.

Ketoacidosis secondary to SGLT2 inhibitors has occurred at a higher incidence than expected, as reported in post-marketing safety reporting. Many cases occurred in patients without significant hyperglycemia. This atypical presentation is termed “euglycemic ketoacidosis.” In 15 of the reported cases, SGLT2 inhibitors were utilized to treat T1DM, an indication for which they are not currently FDA-approved. The median time from SGLT2 inhibitor initiation or dose increase to onset of reported

ketoacidosis was 43 days, with a range of one day to one year. A concurrent event associated with ketoacidosis occurred in 53 cases and included dehydration, infection, and changes in insulin dose.

Ketoacidosis was reported in low frequencies among the clinical trials conducted for canagliflozin, dapagliflozin, and empagliflozin which were comprised of over 48,000 patients. It is noteworthy that the number of cases of euglycemic ketoacidosis reported remains small in comparison to the total number of patients exposed to SGLT2 inhibitors. AACE and the American College of Endocrinology (ACE) issued a position statement in 2016 on SGLT2 inhibitor-associated ketoacidosis. They concluded that the frequency of ketoacidosis was low, and the risk-benefit ratio overwhelmingly favored the continued use of SGLT2 inhibitors with no changes in the current recommendations.

Potential diabetic ketoacidosis triggering factors identified in some cases included acute illness (e.g., UTI, urosepsis, gastroenteritis, influenza, or trauma), reduced caloric or fluid intake, and reduced insulin dose. FDA is advising health care professionals to consider these risk factors prior to prescribing these agents and to discontinue SGLT2 inhibitors if ketoacidosis is suspected. Proper evaluation of the patient is warranted followed by appropriate treatment which may include insulin, fluids, and carbohydrate replacement. The product inserts for all FDA-approved SGLT2 inhibitors have been revised to reflect this.

Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and trouble breathing. FDA is advising patients to stop taking SGLT2 inhibitors if they have any symptoms of ketoacidosis or UTI.

Bone Fracture Risk and Decreased Bone Mineral Density. Additionally, new information is now available regarding decreased bone mineral density and increased risk of bone fractures associated

with canagliflozin. The additional data confirm the finding that fractures occur more frequently with canagliflozin than with placebo, and may occur as early as 12 weeks after starting the drug. These data were derived from a clinical trial in which FDA required the canagliflozin manufacturer to assess the impact of the drug on cardiovascular risk, which also evaluated changes to bone mineral density. The study revealed that among 714 elderly participants followed for two years, canagliflozin caused greater bone mineral density loss at the hip and lower spine when compared to placebo. At the time of writing this lesson, a similar warning for dapagliflozin- or empagliflozin-containing products has not been reported, although FDA is continuing to evaluate this risk in these agents.

Patients with T2DM are at increased risk of fractures, and this risk increases with advancing age. Comprehensive meta-analyses report an increased risk of hip fractures in patients with T2DM. Factors that contribute to elevated fracture risk include antihyperglycemic and blood-pressure lowering medications, and diabetes complications that might increase fall risk such as hypoglycemic events, peripheral and autonomic neuropathy, neuromuscular impairment, nephropathy, and retinopathy.

Pooled data from nine RCTs of canagliflozin, including separate analyses of a single trial containing patients with history/risk of cardiovascular disease (Canagliflozin Cardiovascular Assessment Study, CANVAS) and a pooled population of eight non-CANVAS studies, were evaluated to assess the effects of canagliflozin in bone fracture. The mean age was higher in CANVAS versus non-CANVAS studies. Also, the mean drug exposure was higher in CANVAS studies. The incidence of bone fracture in the pooled non-CANVAS studies was similar for canagliflozin versus comparator. However, a significant increase in bone fractures was observed with canagliflozin versus placebo in

Table 3 Warnings and precautions for all SGLT2 inhibitors

- *Hypotension.* Monitor blood pressure. Assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics.
- *Ketoacidosis.* Assess patients who present with signs and symptoms of metabolic acidosis, regardless of blood glucose level.
- *Acute Kidney Injury and Impairment in Renal Function.* Monitor renal function during therapy. Consider temporarily discontinuing during periods of reduced oral intake or fluid losses.
- *Urosepsis and Pyelonephritis.* Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.
- *Hypoglycemia.* In patients taking insulin or an insulin secretagogue with an SGLT2 inhibitor, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.
- *Genital Mycotic Infections.* Monitor and treat if indicated.
- *Increased LDL-C.* Monitor and treat per standard of care.

Additional warnings and precautions for **Canagliflozin**:

- *Hyperkalemia.* Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia.
- *Hypersensitivity Reactions.* Discontinue the drug.
- *Bone Fracture.* Consider factors that contribute to fracture risk before initiating.

Additional warnings and precautions for **Dapagliflozin**:

- *Bladder Cancer.* Dapagliflozin should not be used in patients with active bladder cancer, and used with caution in patients with a prior history of bladder cancer.
- *Macrovascular Outcomes.* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction.

CANVAS. The incidence of reported fall-related adverse events (AEs) was low, but was significant-

ly higher in the CANVAS study with canagliflozin. This observed increase in fall-related AEs may be potentially related to volume-depletion. Clinicians should be aware of the increased potential of bone fractures in patients treated with canagliflozin, especially in individuals who are at an elevated baseline risk of fracture. These individuals include the elderly, smokers, and those with osteoporosis, and a history of non-traumatic fracture and long-term glucocorticoid therapy.

In a review conducted by Carlson and Santamarina, the authors concluded that, while serious safety issues have been detected with SGLT2 inhibitors such as bladder cancer (not discussed in this lesson), bone fractures, pyelonephritis, urosepsis and ketoacidosis, these events have been uncommon. Furthermore, SGLT2 inhibitors are a valuable addition to the treatment of T2DM due to cardiovascular risk reduction.

Table 3 summarizes the product insert warnings statement for the SGLT2 inhibitors. Furthermore, it is important to note that other safety communications by FDA, as well as published literature, highlight safety challenges and associated risk with other antidiabetic medications such as, but not limited to, pioglitazone, sulfonylureas, and DDP-4 inhibitors which are not discussed in this lesson.

Metformin: Revised Labeling for Use in Renal Impairment

FDA is requiring labeling changes regarding the recommendations for metformin-containing products for diabetes to expand metformin's use in certain patients with reduced kidney function. Since FDA approval of metformin in 1995, its labeling has included that it is contraindicated in patients with renal dysfunction because of the concern of metformin-associated lactic acidosis. Specifically, the label utilized the value of a single serum creatinine (SCr) to guide the

decision to prescribe, rather than the estimated glomerular filtration rate (eGFR), which is a more accurate description of renal function. Metformin use is contraindicated in females with a serum creatinine of ≥ 1.5 and in males with a value ≥ 1.4 . However, the use of SCr instead of eGFR may lead to misclassification of kidney function. It is unknown how well current SCr parameters reflect elimination of metformin.

Metformin, a biguanide, has a unique mechanism of action in suppressing hepatic gluconeogenesis; enhancing glucose uptake by muscle and adipose tissue; and delaying intestinal glucose absorption. Benefits of metformin include effectively reducing HbA1c by 1 to 2 percent; neutral or potential weight loss; low or no risk for hypoglycemia; low cost; and greater reduction in cardiovascular disease and all-cause mortality compared with sulfonylureas and insulin.

Metformin is recommended as a treatment of choice in patients with T2DM. It is unanimously recommended in treatment guidelines as first-line therapy, either as monotherapy or combination therapy, in patients with T2DM in the absence of contraindications. Metformin use is desirable because of its ability to improve fasting and postprandial glycemic control, and the potential to reduce microvascular and macrovascular complications.

Nevertheless, metformin-associated lactic acidosis (MALA) can occur. It is a rare but potentially life-threatening complication with a mortality rate of 30 to 50 percent. The mechanism is complex and not fully understood, but is likely related to accumulation of metformin which suppresses biological oxidation and enzymes of the citric acid cycle. Metformin promotes the conversion of glucose to lactate in the splanchnic bed of the small intestine. It also inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine. This results in addi-

tional lactate and substrate for lactate production. In the absence of acute overdose, metformin-associated lactic acidosis rarely develops in patients without comorbidities such as renal or hepatic insufficiency or acute infection. A systematic review found the incidence of such lactic acidosis to be fewer than 5.1 cases per 100,000 patient-years. MALA is thought to be triggered by an acute primary tissue hypoxia as found in septic shock or cardiovascular failure.

In addition to renal insufficiency, clinically significant lactic acidosis accumulation almost always occurs in the presence of comorbid conditions such as concurrent liver disease or alcohol abuse, heart failure, history of lactic acidosis, decreased tissue perfusion or hemodynamic instability, hypoxic states or serious acute illness. Therefore, the metformin product label also includes contraindications for use in these patient populations. Additionally, those undergoing iodinated contrast or surgical procedures and the elderly are at a higher risk requiring close monitoring.

Literature reports that metformin is often used in clinical practice outside of the current labeling indications, and is prescribed for patients with mild to moderate chronic kidney disease (CKD) despite the presence of contraindications in 22 to 94 percent of patients. In fact, prior to the FDA safety communication and labeling change, most clinical guidelines were already recommending the use of eGFR to determine the lower limit of metformin use. The National Institute for Health and Care Excellence (NICE) recommends that an eGFR < 30 mL/min/1.73m² should be a contraindication for metformin use. The guidelines further suggest a review of the metformin dose if SCr > 1.5 mg/dL or eGFR is < 45 mL/min/1.73m², and discontinuation if SCr > 1.7 mg/dL or eGFR < 30 mL/min/1.73m². The AACE has a general recommendation to avoid metformin use in CKD stages 4 and 5. The ADA guideline

**Table 4
Labeling recommendations
on kidney function
monitoring with
metformin use**

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

in 2009 reported that metformin seems safe unless eGFR <30 mL/min/1.73m².

Hence, FDA was asked to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate kidney function impairment, and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. Upon review, FDA is concluding that metformin can be safely used in patients with mild to moderate chronic kidney disease. Continued recommendations include metformin interruption if acute changes in renal function occur or are anticipated because of an acute major illness or prior to procedures that may involve administration of

iodinated contrast media.

Table 4 lists the labeling recommendation that will be included on the revised product label for medications containing metformin.

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The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings. Disclosure: The OPF trustees and other individuals responsible for planning OPF continuing pharmacy education activities have no relevant financial relationships to disclose.

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continuing education quiz

FDA Safety Warnings and Prescribing Updates: Fluoroquinolones, SGLT2 Inhibitors, and Metformin

- Recent FDA safety communications regarding fluoroquinolones call attention to all of the following EXCEPT:
 - serious adverse reactions.
 - effective alternative treatment options may be available.
 - caution in patients with acute liver disease.
- Post-marketing adverse reaction reporting indicated that fluoroquinolones are associated with all of the following disabling and potentially irreversible side effects EXCEPT:
 - tendinopathies.
 - CNS effects.
 - ketoacidosis.
 - peripheral neuropathies.
- Patients with decreased renal function are at a higher risk of adverse reactions from fluoroquinolones due to impaired elimination.
 - True
 - False
- For acute upper respiratory infections such as sinusitis and bronchitis, the most common etiology is:
 - bacterial.
 - viral.
- According to the FDA safety communication, FQs should not be used to treat all of the following infectious diseases if alternatives are available EXCEPT:
 - community-acquired pneumonia.
 - uncomplicated UTIs.
 - acute bacterial bronchitis.
 - acute bacterial sinusitis.
- Common side effects associated with SGLT2 inhibitors include all of the following EXCEPT:
 - genital yeast infections.
 - hypotension.
 - urinary tract infections.
 - tendinitis.

Completely fill in the lettered box corresponding to your answer.

- | | | |
|--------------------|--------------------|---------------------|
| 1. [a] [b] [c] | 6. [a] [b] [c] [d] | 11. [a] [b] |
| 2. [a] [b] [c] [d] | 7. [a] [b] [c] [d] | 12. [a] [b] [c] [d] |
| 3. [a] [b] | 8. [a] [b] [c] [d] | 13. [a] [b] [c] [d] |
| 4. [a] [b] | 9. [a] [b] [c] [d] | 14. [a] [b] [c] [d] |
| 5. [a] [b] [c] [d] | 10. [a] [b] [c] | 15. [a] [b] [c] |

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 yes no If no, why? _____
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 yes no
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- Comments/future topics welcome.

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**Return quiz and payment (check or money order) to
Correspondence Course, OPA,
2674 Federated Blvd, Columbus, OH 43235-4990**

- Which of the following patients are not considered predisposed to acute kidney injury with SGLT2 inhibitors?
 - Those taking diuretics
 - The elderly
 - Those with active lifestyles
 - Those with low BP
- Signs and symptoms of urinary tract infections include all of the following EXCEPT:
 - fever.
 - diarrhea.
 - pelvic pain.
 - burning on urination.
- Potential triggers for ketoacidosis include all of the following EXCEPT:
 - infection or acute illness.
 - reduced fluid intake.
 - reduced insulin dose.
 - obesity.
- Which of the following SGLT2 inhibitors has an FDA warning for increased risk of bone fracture?
 - Empagliflozin
 - Dapagliflozin
 - Canagliflozin
- Metformin labeling has included a contraindication in patients with renal dysfunction because of the concern of metformin-associated lactic acidosis.
 - True
 - False
- Metformin is recommended in patients with T2DM:
 - only in combination.
 - with complications.
 - as first-line therapy.
 - after insulin fails.
- Clinically significant lactic acidosis accumulation almost always occurs in the presence of all of the following comorbid conditions EXCEPT:
 - heart failure.
 - liver disease.
 - lung disease.
 - decreased tissue perfusion.
- NICE recommends that an eGFR below which of the following is a contraindication for metformin use?
 - 60 mL/min/1.73m²
 - 50 mL/min/1.73m²
 - 40 mL/min/1.73m²
 - 30 mL/min/1.73m²
- FDA concludes that metformin can be safely used in patients with:
 - moderate chronic kidney disease.
 - severe kidney disease.
 - acute kidney disease.

To receive CPE credit, your quiz must be received no later than March 15, 2020. A passing grade of 80% must be attained. CPE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CPE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.