Diabetes: Setting the stride to improve glycemic control

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Abstract
The management of diabetes is a fast-moving field with constant changes in treatment guidelines, newly approved medications, and updates to existing treatments. The updates and similarities and differences in the main diabetes management guidelines in the United States are discussed. Recent changes in the efficacy and safety of diabetes medications and recently approved diabetes medications are also described.

Introduction
Diabetes remains highly prevalent throughout the United States and the world, often existing with comorbid conditions and complications such as hypertension and dyslipidemia. A mainstay of diabetes treatment is pharmacotherapy. As one of the healthcare professionals with the most access to patients living with diabetes, pharmacists need to be aware of the updates in diabetes medication management to optimize medication therapy management.

Changes to pharmacologic management of type 2 diabetes in 2017 ADA guidelines
The American Diabetes Association (ADA) Standards of Medical Care in Diabetes is an annually updated guideline providing comprehensive recommendations for all aspects of diabetes management. This section discusses the major changes made to the 2017 ADA guideline as these apply to pharmacists and medication therapy management. Additional changes can be found in Table 1.

Metformin and monitoring. Metformin is the first-line medication recommended for the management of hyperglycemia in patients with type 2 diabetes unless otherwise contraindicated. For many years, a contraindication to the use of metformin per FDA product labeling has been a serum creatinine greater than or equal to 1.4 mg/dL in women and 1.5 mg/dL in men, due to the rare but potentially fatal risk of lactic acidosis.
sis as metformin is cleared renally.2 These relatively arbitrary cutoffs, however, have met with debate over the years. The 2016 ADA guideline endorsed an expert opinion recommendation that metformin can be used in most patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m² unless there are additional risk factor(s) for lactic acidosis.3 This recommendation was changed with the publication of the 2017 ADA guideline to be consistent with the April 2016 FDA labeling change.1 The specifics of these FDA recommendations are:4

› Prior to initiating metformin, obtain patient’s renal function and annually thereafter
› In patients at increased risk of developing renal impairment, eg, the elderly, renal function should be assessed more frequently
› Metformin should not be started in patients with an eGFR ≤45 mL/min/1.73 m²
› In patients on metformin therapy whose eGFR falls <45 mL/min/1.73 m², assess risk versus benefit of continuing therapy
› Do not use in patients with an eGFR <30 mL/min/1.73 m²
› Metformin-containing products may be safely used in patients with mild-to-moderate renal impairment
› Metformin should be discontinued at or prior to the use of iodinated contrast dye in the following patients:
  › An eGFR between 30 and 60 mL/min/1.73 m²
  › Those with a history of liver disease, alcoholism, or heart failure
  › Patients who will receive intra-arterial iodinated contrast dye
› eGFR should be reevaluated 48 hours after contrast dye imaging procedure and may be restarted if renal function is stable.

The 2017 ADA guideline also added an emphasis on periodic measurements of vitamin B12 levels.5 A potential deficiency of vitamin B12 in metformin-treated patients due to decreased absorption is not a new discovery. For more than a decade, FDA product labeling has included the wording that measuring “vitamin B12 levels every 2 to 3 years may be useful” in patients with risk factors for vitamin B12 deficiency.2

The 2017 ADA guideline’s emphasis on vitamin B12 measurement was based on a recently published analysis from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS). The DPP/DPPOS found a low vitamin B12 (≤203 pg/mL) prevalence of 4.3% and 2.3% in the metformin and placebo arm, respectively, at year 5. The prevalence of combined low and borderline-low (≤298 pg/mL) vitamin B12 level was 19.1% (metformin) and 9.5% (placebo) at year 5 and 20.3% (metformin) and 15.6% (placebo) at year 13.6 Suboptimal vitamin B12 levels may lead to anemia, which, among other things, can complicate interpretation of the glycosylated hemoglobin (A1C) because the value may be falsely high.6 Vitamin B12 deficiency can also lead to peripheral neuropathy symptoms. Therefore, it is important to rule out metformin-induced vitamin B12 deficiency as a potential cause before attempting treatment of diabetic peripheral neuropathy. An annual hematologic evaluation is recommended in metformin-treated patients, with periodic (every 2–3 years) measurements of vitamin B12 levels in patients with predisposing risk factors such as inadequate vitamin B12 intake or absorption or inadequate calcium intake or absorption.2

**Premixed insulin.** Recommendations for use of premixed insulin therapy have also been updated in the 2017 ADA guideline. The 2016 guideline previously recommended that patients uncontrolled on twice-daily premixed insulin (NPH/Reg 70/30, aspart mix 70/30, lispro mix 75/25 or 50/50) should be initiated on basal-bolus therapy (≥2 rapid-acting insulin injections before meals + basal insulin).3 The 2017 guideline now recommends advancing to 3 times daily analog premixed insulin (aspart mix 70/30, lispro mix 75/25 or 50/50) as another treatment intensification option.1 A premixed insulin regimen is traditionally given at breakfast and dinner. Because premixed insulin contains not only a prandial insulin but also an intermediate-acting insulin component (NPH) with an approximate duration of effect of 12 hours, the addition of a third dose at lunchtime may increase the risk of hypoglycemia. Patients should be educated on the signs and symptoms of hypoglycemia as well as corrective actions prior to initiation of a third premix injection.

**Antiplatelet therapy.** The recommendations on aspirin use for primary prevention of cardiovascular events in adult patients with diabetes have changed over the last several years, with the 2015 ADA guideline having stratified aspirin therapy based on gender and age (eg, for men age >50 years, for women age >60 years) in addition to cardiac risk factors.7 The 2017 ADA guideline currently recommends considering use of aspirin for primary prevention
in men and women age 50 years or older with diabetes and at least one major cardiovascular risk factor (family history of premature atherosclerotic cardiovascular disease [ASCVD], hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria). Recommended dosing in this population is 75 to 162 mg/day. Patients at increased risk of bleeding and those younger than age 50 years without additional major risk factors should not receive aspirin for primary prevention.1

The 2017 ADA guideline also provides recommendations for secondary prevention with antiplatelet therapy in those with type 2 diabetes. Unlike primary prevention, secondary prevention (ie, in those with established ASCVD such as history of myocardial infarction [MI]) with aspirin therapy has clearly been shown to be effective in reducing cardiovascular mortality in diabetic patients. In those with ASCVD and diabetes, 75 to 162 mg/day of aspirin is recommended. Patients with a documented aspirin allergy may use 75 mg/day of clopidogrel as an acceptable alternative. In patients with a history of acute coronary syndrome, dual antiplatelet therapy is reasonable for up to a year, and may be beneficial beyond this timeframe.1

**ADA and AACE/ACE guidelines comparisons**

The 2017 ADA guideline and the 2017 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Comprehensive Diabetes Management Algorithm guidelines provide recommendations for hypertension and dyslipidemia management in patients with diabetes in addition to the management of hyperglycemia. Major differences in goals of therapy and preferred treatment options are discussed here. A summary of the major differences in statin therapy, lipid management, and hypertension management by these guidelines may be found in Tables 2, 3, and 4.1,8

**Differences in hyperglycemia management.** The 2017 ADA guideline and the 2017 AACE/ACE guideline recommend an A1C goal of lower than 7% and lower than or equal to 6.5%, respectively, for the majority of the population.1,8 In addition, the ADA and AACE/ACE guidelines also differ on the preferred agent of choice when initiating a second diabetic agent in uncontrolled patients. Both guidelines recommend metformin as the first-line oral medication for type 2 diabetes.1,8 When adding a second agent or when metformin is contraindicated, the 2017 ADA guideline recommends use of any of the following: sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin.1 In contrast, the 2017 AACE/ACE guideline provides a suggested hierarchy, with first preference given to GLP-1 receptor agonists, followed by SGLT-2 inhibitors, and then DPP-4 inhibitors.8 GLP-1 receptor agonists are considered the preferred second-line agents due to their significant A1C reduction potential (up to 1.9% with once-weekly formulations), ability to reduce weight and blood pressure, and low risk for hypoglycemia.8 As with all treatment decisions, patient-specific factors should be taken into account in the selection of a diabetic agent.

ADA and AACE/ACE 2017 guidelines also differ in the management of hyperglycemia based on A1C value. The AACE/ACE guideline recommends that patients with an A1C less than 7.5% should be started on monotherapy and those with an A1C of 7.5% or higher should be started on dual therapy. Patients who remain uncontrolled on initial therapy may escalate (monotherapy to dual therapy, dual therapy to triple therapy) until achievement of glycemic control. Patients with an entry A1C more than 9% may proceed directly to insulin therapy with or without addition of other diabetes medications if symptomatic, while those without significant symptoms may start dual or triple therapy, typically with noninsulin medications.8 In contrast, the 2017 ADA guideline places the threshold for starting insulin therapy in newly diagnosed type 2 diabetes patients who are symptomatic at an A1C of 10% or higher and/or blood glucose of 300 mg/dL or higher while an A1C of 9% or higher calls for initiation of dual therapy.1

**Lipid management differences.** ADA and AACE/ACE 2017 recommendations also differ on deciding whether or not to target a specific lipid goal. The AACE/ACE guide-
line provides specific lipid values to which patients should be treated, whereas the ADA guideline treats solely on risk factors and does not recommend laboratory testing to determine if a patient has reached a predetermined lipid numerical value (Table 3).1,8 Patients with diabetes have a significantly increased risk of ASCVD when compared to those without. ASCVD risk factors include age, sex, race, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, use of blood-pressure-lowering medications, diabetes status, and smoking status.9 HMG-CoA reductase inhibitors (ie, statins) are a major part of the risk reduction strategy. High-intensity statin therapy is defined as statin doses capable of decreasing low-density lipoprotein cholesterol (LDL-C) by 50% or more from untreated baseline, while moderate-intensity statin therapy is defined as statin doses capable of reducing LDL-C by 30% to 49% from untreated baseline.9

ADA and AACE/ACE guidelines differ on statin treatment intensity recommendations. The 2017 ADA guideline stratifies the need for statin therapy by both age and cardiovascular risk (Table 2).1 The 2017 AACE guideline stratifies patients with diabetes into 3 discrete ASCVD risk groups: high, very high, and extremely high. High risk is defined as diabetes with no additional risk factors, very high risk is defined as those with diabetes and additional risk factors, and extremely high risk is defined as those with confirmed cardiovascular disease.8 Table 3 highlights major differences in lipid management between the guidelines. At this time of this article’s writing, AACE/ACE has a draft version of their lipid guideline in press.10

ADA and AACE/ACE guidelines recommend additional agents in combination with statin therapy for different patient populations. Both guidelines recommend adding ezetimibe to statin therapy based on the Improved Reduction Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). IMPROVE-IT evaluated the addition of ezetimibe to moderate-intensity simvastatin therapy in patients age 50 years or older, with an acute coronary syndrome within the past 10 days and an LDL-C 50 mg/dL or higher. The rate of adverse cardiovascular events was significantly decreased in the ezetimibe-simvastatin group. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are also recommended by both guidelines in patients at high risk of adverse cardiovascular events who need additional LDL-C lowering therapy. Recommendations for additional lipid-lowering agents, however, vary per guideline. The AACE/ACE guideline recommends use of niacin to lower LDL-C, non-HDL-C, triglycerides, and apo B, while the ADA guidelines state that statin-niacin combination therapy is not recommended due to lack of efficacy on major ASCVD outcomes in diabetes patients.1,8

Hypertension management differences. Blood-pressure goal recommendations and first-line medications also vary between the ADA and the AACE guidelines. Per the 2017 ADA guideline, antihypertensive therapy should be initiated at a blood pressure of greater than 140/90 mm Hg and the goal blood pressure is lower than 140/90 mm Hg in the majority of patients.2 For patients with high ASCVD risk, a blood pressure goal of lower than 130/80 mm Hg may be prudent.1 First-line recommended medications include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazide-like diuretics, and dihydropyridine calcium channel blockers (DHP-CCBs).4 By contrast, a blood-pressure goal of lower than 130/80 mm Hg is recommended by the 2017 AACE guideline.6 Recommended first-line antihypertensive therapy is similar to the ADA’s recommendation, and includes ACE inhibitors, ARBs, thiazide-like diuretics, and DHP-CCBs. AACE, however, also includes the use of beta blockers as first-line agents and recommends an ACE inhibitor or ARB as a preferred initial agent when initiating hypertension medication management.6

Diabetes medication updates
Recently published cardiovascular data from 2 clinical trials provided medication recommendations in patients with type 2 diabetes at high risk of cardiovascular disease (CVD) and for those with existing CVD. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) clinical trial evaluated this SGLT2 inhibitor versus placebo in over 7000 patients with a mean follow-up of 3.1 years.11 The composite primary outcome was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. This primary outcome occurred in 10.5% of the empagliflozin patients compared to 12.1% in the control group (hazard ratio [HR] 0.86, P = .04). Although no difference was found in rates of MI and stroke, the trial found empagliflozin significantly reduced cardiovascular death when compared to placebo (3.7% vs 5.9%, respectively). This translates to a relative risk reduction with the use of empagliflozin of 38%. In addition, all-cause mortality and heart failure hospitalization was reduced by 32% and 35%, respectively.11 In December 2016, FDA approved an additional indication for empagliflozin to reduce the risk of cardiovascular death in adult patients with type 2 diabetes and established CVD.12 At the time of writing, it is the only diabetes medication with this FDA indication.

Additional data demonstrating the reduction of cardiovascular death in type 2 diabetes
2 diabetes were published for liraglutide, a GLP-1 agonist. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide versus placebo was evaluated in adult patients with type 2 diabetes and high cardiovascular risk. The composite primary endpoint was death from cardiovascular causes, nonfatal MI, and nonfatal stroke. Over 9000 patients underwent randomization, with a mean follow-up of 3.8 years. The mean age and duration of diabetes were 64 years and 13 years, respectively. The composite primary outcome occurred in 13% of the liraglutide-treated patients compared to 14.9% in the placebo group (95% confidence interval, 0.78–0.97; HR 0.87). The rate of death from cardiovascular causes and all causes was 22% and 15% lower, respectively, in the liraglutide group compared to placebo. Additionally, the rates of nonfatal MI, hospitalization for heart failure, and nonfatal stroke were nonsignificantly lower in the liraglutide group. At the time of writing, FDA has not revised the product labeling to reflect this data.

FDA has also recently approved a new GLP-1 receptor agonist, lixisenatide, indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Lixisenatide decreases A1C by approximately 0.7% compared to placebo. Contraindications and precautions are similar to the other GLP-1 receptor agonists and include hypersensitivity and pancreatitis. Adverse drug reactions are also similar to the other GLP-1 receptor agonists, with the most common being nausea, vomiting, diarrhea, headache, dizziness, and hypoglycemia. Rare but serious adverse drug reactions include pancreatitis, acute kidney injury and worsening of chronic renal failure, immunogenicity, and hypersensitivity reactions. The renal impairment is likely due to dehydration from gastrointestinal (GI) adverse reactions, and patients should be educated to avoid dehydration and contact a healthcare professional if significant GI side effects occur. Drug–drug interactions are also similar to the other GLP-1 receptor agonists and relate to the medication’s mechanism of action. One effect of GLP-1 receptor agonists is delayed gastric emptying; therefore, absorption of concomitantly administered oral medications may be affected. Product labeling recommends orally administered medications that are significantly affected by decreased absorption and therefore decreased concentrations (eg, antibiotics, drugs with narrow therapeutic index) or delayed onset of effect (eg, pain medications) be administered 1 hour prior to lixisenatide. Oral contraceptives should be taken at least 1 hour prior or 11 hours after lixisenatide administration. Additionally, due to its effect on stimulation of glucose-dependent insulin secretion, concomitant administration with an insulin secretagogue or with basal insulin may lead to additive hypoglycemia and the dose of these medications may need to be lowered. Lixisenatide has not been studied with prandial insulin.

Lixisenatide is administered subcutaneously (abdomen, thigh, or upper arm) within 1 hour prior to the first meal of the day and initiated at 10 mcg once daily for 14 days, increasing to 20 mcg once daily thereafter. It is available as a prefilled pen that, unlike some of the other GLP-1 receptor agonists, does not require reconstitution before administration. Two different pen dosage strengths are available: the starter pen containing 50 mcg/mL of lixisenatide that delivers 14 of the 10-mcg doses and the maintenance pen containing 100 mcg/mL of lixisenatide that delivers 14 of the 20-mcg doses. Two different packages are available: a starter pack containing 1 prefilled 10-mcg pen and 1 prefilled 20-mcg pen and a maintenance pack containing 2 prefilled 20-mcg pens. Pens should be stored in the refrigerator between 36°F and 46°F prior to first use and in the original packaging to protect from light. After first use, pens may be kept below 86°F with the cap on after each use to protect from light and discarded after 14 days.

FDA has also approved 2 long-acting basal insulin/GLP-1 receptor agonist combinations. This combination treatment has been gaining in popularity over the last several years and has been endorsed by the ADA since 2015. The use of a GLP-1 receptor agonist in addition to basal insulin is associated with a lower potential for additive hypoglycemia and weight gain compared to a basal-bolus insulin regimen. Approved in November 2016, insulin glargine and lixisenatide injection is indicated to improve glycemic control in adult patients with type 2 diabetes uncontrolled on basal insulin (<60 units) or lixisena-

### TABLE 4

Hypertension Drug Therapy Management Recommendations in Adult Patients with Diabetes by Major US Guidelines

<table>
<thead>
<tr>
<th>When to initiate antihypertensive drug treatment</th>
<th>ADA 2017 GUIDELINE</th>
<th>AACE/ACE 2017 GUIDELINE</th>
</tr>
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<tbody>
<tr>
<td>Initiate antihypertensive treatment at blood pressure of &gt;140/90 mm Hg.</td>
<td></td>
<td>Initiate antihypertensive treatment at blood pressure of &gt;130/80 mm Hg.</td>
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<table>
<thead>
<tr>
<th>Goal blood pressure</th>
<th>ADA 2017 GUIDELINE</th>
<th>AACE/ACE 2017 GUIDELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The goal blood pressure for majority of patients is &lt;140/90 mm Hg. For patients at high risk of CVD, the goal is &lt;130/80 mm Hg.</td>
<td></td>
<td>A blood-pressure goal of &lt;130/80 mm Hg is recommended for most patients.</td>
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<thead>
<tr>
<th>Antihypertensive medication of choice</th>
<th>ADA 2017 GUIDELINE</th>
<th>AACE/ACE 2017 GUIDELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive medications of choice include ACE inhibitor, ARB, thiazide-like diuretic, DHP-CCB. ACE inhibitors and ARBs are preferred initial agents in patients with urinary albumin-to-creatinine ratio ≥30 mg/g.</td>
<td></td>
<td>Antihypertensive medications of choice include ACE inhibitor, ARB, thiazide-like diuretic, CCB, beta blocker. ACE inhibitors and ARBs are preferred initial agents.</td>
</tr>
</tbody>
</table>
Food, Drug, and Cosmetic Act. Licensed approval process under the Federal glargine injection was through an abbreviation.

Approval of the follow-on U-100 insulin classified as a “follow-on” product. The U-500 pen formulation. The U-500 pen includes confusion between the prescribed dose of units a patient is to receive. A dose written as “50 units” on the prescription may be interpreted as to draw up to either: the 50-units marking on the U-100 syringe (equaling 250 units of the U-500 insulin), the 10 units (equaling 50 units of the U-500 insulin) on the U-100 syringe, or the 0.1 mL (equaling 50 units of the U-500 insulin) on the tuberculin syringe. The U-500 pen avoids this dosing misinterpretation. The U-500 pen formulation may be stored at room temperature (up to 86 °F) for 28 days after opening and should not be refrigerated, in contrast to the U-500 vial formulation, which may be used for 40 days at room temperature after opening. An additional measure of decreasing errors with the U-500 insulin is the availability of a dedicated syringe for the vial formulation. As of July 2016, FDA approved a U-500 syringe that begins at the 5-unit mark with each line marking equaling 5 units. The syringe delivers a maximum of 250 units and has a needle length of 6 mm x 31 gauge. These syringes are designed to emphasize their use for the U-500 vial only, with a green cap to match the green cap of the U-500 vial and a red U-500 marking on the barrel. FDA emphasizes that this syringe is the only device approved for administration with the U-500 vial. The development of both the U-500 syringe and the U-500 KwikPen will allow for safer, more-accurate dosing in patients needing high doses of insulin.

In December 2016, FDA approved an additional indication for empagliflozin to reduce the risk of cardiovascular death in adult patients with type 2 diabetes and established CVD."
approved medications in this class are currently canagliflozin, dapagliflozin, and empagliflozin. Applicable to the entire class, FDA added a warning for an increased risk of diabetic ketoacidosis (DKA) in the product labeling. Notably, ketoacidosis associated with SGLT-2 inhibitors can occur even when blood glucose levels are not extremely elevated (<250 mg/dL; sometimes referred to as euglycemic DKA), unlike classical DKA. Routine measurement of urine ketones is not recommended, however, and blood ketones should be measured instead to confirm the diagnosis if DKA is suspected. Symptoms include nausea, vomiting, abdominal pain, and dyspnea. In clinical trials, the incidence of DKA with SGLT-2 inhibitors in type 2 diabetic patients was 0.2 to 0.8 cases per 1000 patient-years. However, the majority of cases that have been reported have come from real-world settings. Incidence of DKA was up to 6% in type 1 diabetic patients in clinical trials. Use of SGLT-2 inhibitors is off-label in type 1 patients.

Risk factors for the development of DKA while taking an SGLT-2 inhibitor include: 1,2,4,25
- Pancreatic insulin deficiency from any cause
- Frequent alcohol use or “binge” drinking
- Surgery
- Eating less due to surgery, dieting (esp. low-carbohydrate diets), or any other reason
- Strenuous/extensive physical activity
- Severe infections, MI, stroke, or any other stressful medical conditions
- Essentially, any stressful metabolic event can be considered a risk factor for precipitation of DKA in SGLT-2 inhibitor-treated patients. The AACE/ACE published a position statement in June 2016 and recommends the following preventive and management measures:
  - Stop SGLT-2 inhibitor at least 24 hours prior to “elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon”
  - Stop the drug immediately during “emergency surgery or any extreme stress events”
  - SGLT-2 inhibitor-treated patients should avoid “excess alcohol intake and very-low-carbohydrate/ketogenic diets”
  - Consider not automatically lowering insulin dose when SGLT-2 inhibitor is initiated in a patient treated with insulin
- Pharmacists should educate patients about the signs and symptoms of DKA and to seek emergency medical care if they suspect they are experiencing a DKA episode, even if the blood glucose is lower than 250 mg/dL.
- In the same MedWatch announcement, FDA reiterated that all SGLT-2 inhibitors are associated with urinary tract infections, including urosepsis and pyelonephritis. Subsequently, FDA also strengthened the existing warning of acute kidney injury with canagliflozin and dapagliflozin.
- In June 2016, FDA stated that the number of acute kidney injury cases reported with these latter medications warranted a revised labeling reflecting the risk and added recommendations for minimization of this risk. Risk factors include patients with decreased blood volume, chronic kidney insufficiency, congestive heart failure, and the use of ACE inhibitors, ARBs, or nonsteroidal anti-inflammatory drugs. Most cases of acute kidney injury occurred within a month of initiation of therapy, and the majority occurred in patients age 65 years or older. Temporary discontinuation of these drugs may be considered in the setting of reduced oral intake (such as fasting) or fluid losses (GI illness or excessive heat exposure).
- Canagliflozin also had an existing warning of increased risk of bone fracture when compared to placebo. FDA has now strengthened this warning and added an additional warning of decreased bone mineral density (BMD), as a result of findings in several postmarketing clinical trials conducted by the manufacturer. Increased fracture was seen with use of canagliflozin as early as 12 weeks after initiation of therapy, and occurred most frequently in low trauma situations (minor falls from no more than standing height). BMD was evaluated in 714 elderly patients over the course of 2 years. When compared to a placebo, patients in the canagliflozin arm had a greater loss of BMD at the hip and lower spine. Patient-specific factors that may contribute to risk of fracture should be taken into consideration when utilizing this medication, such as age, history of previous falls, and concomitant medications. Further studies are being performed to determine whether this adverse event applies to other medications in this class.
- Finally, in May 2016, FDA issued a report stating that they are investigating the potential increased risk of foot and leg amputations with use of canagliflozin. Interim results of the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) indicated a 2-fold increased risk of foot and leg amputations in those taking canagliflozin compared to placebo. Patients in the CANVAS trial had been followed for an average of 4.5 years at that time, and the majority of amputations has been amputations of the toes. Patients taking canagliflozin should report any new tenderness, sores, ulcers, or infections of their legs and feet to their healthcare providers. Although the CANVAS trial found an increased number of amputations, FDA has not yet definitively linked use of canagliflozin to increased risk of amputations. Another clinical trial (CANVAS-R), with a shorter duration of follow-up of 9 months as of May 2016, has not found the same association.

Conclusion
Diabetes is among the most common chronic conditions encountered by pharmacists in all settings. Its management is complex, multifaceted, and rapidly changing. It is important to remain current with recommendations and new products to provide the optimal level of patient care.

References are available online at www.drugtopics.com/cpe.
TEST QUESTIONS FOR PHARMACISTS

1. The use of metformin is not recommended in patients with:
   a. An eGFR <30 mL/min/m²
   b. An eGFR <60 mL/min/m²
   c. In men with a serum creatinine of 1.4 mg/dL
   d. In women with a serum creatinine of 1.5 mg/dL

2. The AACE/ACE guidelines recommend the following A1C goal for the majority of the population:
   a. <5.5%
   b. ≤6.5%
   c. <7%
   d. ≤7.5%

3. The AACE/ACE guideline has a preferred hierarchy when adding a second diabetic agent to metformin therapy. The preferred medication class according to the AACE/ACE guideline is:
   a. Sulfonylureas
   b. SGLT-2 inhibitors
   c. GLP-1 agonists
   d. DPP-4 inhibitors

4. Which of the following is true:
   a. Patients with diabetes should interrupt prolonged sitting every 90 minutes.
   b. Metformin is safe in all patients regardless of kidney function.
   c. There are no syringes available specifically for U-500 human insulin regular.
   d. Clinically significant hypoglycemia is now defined as glucose <54 mg/dL.

5. The two diabetes medications with proven cardiovascular benefits are:
   a. Empagliflozin and liraglutide
   b. Empagliflozin and lixisenatide
   c. Canagliflozin and liraglutide
   d. Canagliflozin and lixisenatide

6. Lixisenatide is a GLP-1 agonist capable of reducing A1C by approximately:
   a. 0.5%
   b. 0.7%
   c. 1.0%
   d. 1.5%

7. In patients taking an SGLT-2 inhibitor, it is important to know that:
   a. Diabetic ketoacidosis may occur in patients with lower than usual blood glucose values (<250 mg/dL).
   b. There is evidence to support empagliflozin for the use of cardiovascular risk reduction in adult patients with type 2 diabetes and established cardiovascular disease.
   c. Canagliflozin is currently being investigated for an increased risk of leg amputations.
   d. All of the above

8. Which of the following is a concern with the DPP-4 inhibitor drug class?
   a. Diabetic ketoacidosis
   b. Joint pain
   c. Foot amputations
   d. Acute kidney injury

9. The insulin glargine follow-on product:
   a. Is available only in a pen formulation
   b. Is available in both U-100 and U-200 concentrations
   c. Must always be stored in the refrigerator
   d. All of the above

10. When dispensing a prescription for dapagliflozin, which of the following is not a counseling point pharmacists may consider telling the patient:
    a. Their prescriber may ask them to hold their medication at least 24 hours prior to extreme strenuous activity (i.e., running a marathon).
    b. They should take their medication on an empty stomach.
    c. They should avoid binge drinking while on this medication.
    d. They should consult their provider about continued use of this medication if they need to fast for any reason.

11. Metformin may cause:
    a. Amputations
    b. Arthritis
    c. Decreased bone mineral density
    d. Vitamin B12 deficiency

12. SGLT-2 inhibitors may cause:
    a. Acute kidney injury
    b. Diabetic ketoacidosis
    c. Decreased bone mineral density
    d. All of the above

13. According to the 2017 ADA guideline, aspirin therapy is definitively recommended in which of the following diabetes patients?
    a. A woman age 60 years with diabetes and no other comorbidities
    b. A woman age 40 years with diabetes and hypertension
    c. A man age 40 years with diabetes and hypertension
    d. None of the above

14. The ADA and AACE/ACE guidelines differ in which facet of diabetes management?
    a. Preferred second-line medications for type 2 diabetes
    b. Hypertension management
    c. Dyslipidemia management
    d. All of the above

15. Which of the following insulin is available in a concentrated formulation?
    a. Insulin glargine
    b. Insulin detemir
    c. Insulin glulisine
    d. Insulin aspart

16. Risk factors for DKA associated with SGLT-2 inhibitors include:
    a. Strenuous physical activity
    b. Surgery
    c. Low-carbohydrate/ketogenic diets
    d. All of the above

17. When dispensing U-500 human regular insulin vials, patients should also receive:
    a. U-100 syringes
    b. Tuberculin syringes
    c. U-500 syringes
    d. All of the above

18. The insulin degludec-liraglutide product:
    a. Is supplied in a 1.5-mL pen
    b. Has dosing instructions listed as the insulin degludec units
    c. Has a maximum dose of 60 units
    d. All of the above

19. Blood-pressure goals for most adult patients with diabetes according to the 2017 ADA and AACE/ACE guidelines are:
    a. <140/90 mm Hg and <130/80 mm Hg, respectively
    b. <130/90 mm Hg and <140/80 mm Hg, respectively
    c. <150/90 mm Hg and <130/80 mm Hg, respectively
    d. None of the above

20. The 2017 ADA guideline recommends that patients age 40–75 years with diabetes and additional ASCVD risk(s) should consider which of the following in addition to lifestyle modification?
    a. High-intensity statin therapy
    b. Moderate-intensity statin therapy
    c. Low-intensity statin therapy
    d. Moderate-intensity statin therapy plus niacin