Diabetes Mellitus

By Andrew S. Bzowyckyj, Pharm.D., BCPS, CDE

INTRODUCTION

The prevalence and incidence of type 2 diabetes (T2DM) continue to rise. An estimated 9.4% of the U.S. population has diabetes, with T2DM accounting for 90%–95% of cases. This figure includes 23.1 million individuals with diagnosed disease and 7.2 million individuals without diagnosed disease. An additional 84.1 million U.S. adults 18 and older had prediabetes in 2015 (CDC 2017). Compounding these statistics is the national obesity rate, which was 39.8% of all U.S. adults in 2015–2016, with higher rates noted in Hispanic (47%) and non-Hispanic black (46.8%) subgroups (NCHS 2017). As a result, pharmacists in all patient care settings should work to decrease the morbidity and mortality associated with diabetes in a cost-effective and patient-centered manner. This chapter focuses on updates and innovations in managing type 1 diabetes (T1DM) will also be discussed.

Ominous Octet and Egregious Eleven

In 2009, the pathophysiology of diabetes was introduced as the “omnious octet,” which challenged clinicians to think beyond impaired insulin secretion, increased hepatic glucose production, and decreased glucose uptake as the main drivers of hyperglycemia, by adding five additional pathophysiologic factors: (1) decreased incretin effect, (2) increased renal glucose reabsorption, (3) neurotransmitter dysfunction, (4) increased glucagon secretion, and (5) increased lipolysis. This broader approach to diabetes has contributed to the shift from sulfonylureas that only target one pathophysiologic process toward agents that target several areas (e.g., glucagon-like peptide-1 receptor agonists [GLP-1 RAs]). In 2016, three more pathophysiologic mechanisms were incorporated, creating the “egregious eleven”: (1) decreased beta cell function and mass, (2) abnormal microbiota, and (3) immune dysregulation/inflammation (Schwartz 2016).
These newly identified targets have shifted the approach of caring for individuals with diabetes toward a focus on patient-specific causes of hyperglycemia and tailoring treatment accordingly.

**CLINICAL GUIDELINE UPDATES FOR HYPERGLYCEMIA MANAGEMENT**

**2018 ADA/EASD Consensus Report**

The 2018 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) update to the 2015 position statement on managing hyperglycemia incorporates new evidence gathered since publication of the previous version. Whereas the previous consensus statements focused predominantly on efficacy in reducing hyperglycemia, tolerability, and safety, this update emphasizes the need to consider a patient’s concurrent medical conditions and other patient-specific factors when deciding on the right drug for a patient (Figure 1). This position statement heavily emphasizes the role of drugs that target several pathophysiologic processes for optimizing patient outcomes, relegating sulfonylureas and thiazolidinediones only to when cost is a significant barrier. More specific guidance for intensifying a patient’s regimen to injectable therapies is also available, starting with a consideration for adding a GLP-1 RA before insulin in most people with diabetes unless the A1C is over 11%, symptoms of catabolism are present (e.g., weight loss, polyuria, polydipsia) suggesting insulin deficiency, or if T1DM is a possibility. Additional guidance is provided on when to consider initiating basal and mealtime insulins and which oral drugs to discontinue when transitioning a patient to injectable therapies (Table 1).

**BASELINE KNOWLEDGE STATEMENTS**

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to hyperglycemia in diabetes mellitus
- A1C, fasting, and postprandial glycemic goals defined by leading diabetes guidelines
- Familiarity with the various oral and non-insulin injectable agents and insulins used to treat diabetes mellitus
- Consequences of not achieving glucose goals, including micro- and macrovascular complications

**ADDITIONAL READINGS**

The following free resources have additional background information on this topic:

Diagnosis of T2DM:
Metformin and comprehensive lifestyle
(including weight management and physical activity)

- Established ASCVD, HF, or CKD
  - ASCVD predominates
    - GLP-1 RA with proven ASCVD benefit
      (liraglutide > semaglutide > exenatide extended release; dulaglutide)
  - HF or CKD predominates
    - SGLT2i with evidence of reducing HF and/or CKD progression
      (if eGFR adequate)
    - If SGLT2i not tolerated or contraindicated, add
      GLP-1 RA with proven ASCVD benefit
      (liraglutide > semaglutide > exenatide extended release; dulaglutide)
- A1C above goal
  - Compelling need to minimize hypoglycemia
    - DPP-4i
    - GLP-1 RA
    - SGLT2i
  - Compelling need to minimize weight gain or promote weight loss
    - GLP-1 RA (semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide)
  - Cost is a major issue
    - Sulfonylurea (2nd generation) TZD
- No established ASCVD or CKD

Figure 1. Overall approach to selecting glucose-lowering drug in type 2 diabetes.

aThe medication classes within each individual box are listed in alphabetical order, not in order of preference.
bAt the time of printing, the American Diabetes Association had not yet incorporated the dulaglutide data from the REWIND trial into their treatment algorithm for patients with concurrent ASCVD.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; HF = heart failure; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose co-transporter-2 inhibitor; T2DM = type 2 diabetes; TZD = thiazolidinedione.


Table 1. Considerations When Combining Oral Therapy with Injectable Therapies

<table>
<thead>
<tr>
<th>Oral Therapy</th>
<th>Consideration (clinical judgment may supersede)</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>Continue metformin</td>
</tr>
<tr>
<td>TZD</td>
<td>Discontinue TZD when initiating insulin OR reduce TZD dose</td>
</tr>
<tr>
<td>SU</td>
<td>Discontinue or reduce dose of SU by 50% when basal insulin is initiated (if patient at risk of hypoglycemia) Discontinue SU if mealtime insulin initiated or on a premix regimen</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Continue SGLT2i</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Discontinue DPP-4i if GLP-1 RA initiated</td>
</tr>
</tbody>
</table>

DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

larger A1C reductions than the other GLP-1 RAs in head-to-head trials (Htike 2017; Orme 2017). In addition, the weight reduction with these drugs has been favorable. Liraglutide has a labeled indication for weight loss, even in individuals without diabetes, marketed as Saxenda. The dosage is 3 mg daily for weight loss versus 1.8 mg daily for diabetes. The other GLP-1 RAs have shown overall mean reductions in weight of 1–2 kg in randomized controlled trials compared with placebo, except for semaglutide (Htike 2017). In the SUSTAIN-3 and SUSTAIN-7 trials, semaglutide 1 mg weekly had a mean weight loss of 5.6 kg compared with 3 kg with exenatide XR 2 mg weekly and 6.5 kg compared with 3 kg with dulaglutide 1.5 mg weekly, respectively (Ahmann 2018; Pratley 2018). The order of magnitude from the most to the least weight loss is semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide (Davies 2018).

An additional benefit of some GLP-1 RAs is their ability to reduce the risk of major adverse cardiovascular events, a composite end point including cardiovascular death, non-fatal myocardial infarction, and nonfatal stroke (Table 3). Liraglutide and semaglutide may also prevent new or worsening nephropathy, according to secondary outcomes from their cardiovascular outcomes trials, with HRs of 0.78 (0.67–0.92) and 0.64 (0.46–0.88), respectively.

### Table 2. Overview of Recommendations for Initiating and Titrating Insulin

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>2019 ADA Standards of Care &amp; 2018 ADA/EASD Consensus Report</th>
<th>2019 AACE/ACE Comprehensive Diabetes Management Algorithm</th>
</tr>
</thead>
</table>
| Consider injectable combination (i.e., basal insulin + GLP-1 RA or bolus insulin) | A1C > 10% and/or 2% above target Consider insulin as first injectable if:  
• A1C very high (> 11%)  
• Symptoms or evidence of catabolism (e.g., weight loss, polyuria, polydipsia) that suggest insulin deficiency  
• Type 1 diabetes is a possibility | A1C > 9% and symptomatic |
| **Basal Insulin** | | |
| Starting dose | 10 units/day or 0.1–0.2 unit/kg/day | A1C < 8%: 0.1–0.2 unit/kg/day  
A1C > 8%: 0.2–0.3 unit/kg/day |
| Dose titration | • Set FBG target that correlates with A1C target  
• Advise patient to increase by 2 units every 3 days until FBG target reached | Reassess q2–3 days  
FBG 110–139 mg/dL: Increase by 1 unit  
FBG 140–180 mg/dL: Increase by 10% of total daily basal dose  
FBG > 180 mg/dL: Increase by 20% of total daily basal dose |
| **Hypoglycemia** | If no clear cause, lower dose by 10%–20% | BG < 70 mg/dL: Decrease by 10%–20% of total daily basal dose  
BG < 40 mg/dL: Decrease by 20%–40% of total daily basal dose |
| **Bolus/Prandial Insulin** | | |
| Starting dose | • 4 units or 10% of basal dose before largest meal  
• If A1C < 8%, consider lowering basal dose by 4 units/day or 10% of basal dose | 10% of basal dose or 5 units before largest meal |
| Dose titration | • Increase dose by 1–2 units or 10%–15% twice weekly  
• Stepwise addition of prandial insulin every 3 mo if A1C remains above target | Reassess q2–3 days  
2-hour postprandial or next premeal  
BG > 140 mg/dL consistently: Increase prandial dose by 1–2 units or 10% |

BG = blood glucose; FBG = fasting blood glucose; q = every; TDD = total daily dose.

Safety

The most common adverse effects with GLP-1 RAs are nausea, vomiting, diarrhea, and cholelithiasis, occurring in a dose-dependent manner (Bettge 2017; Hitke 2017; Monami 2017). The long-acting agents tend to be associated with less nausea and vomiting, but more diarrhea, although semaglutide does come with a considerable amount of nausea at the highest dose (Bettge 2017). Whether incretin-based therapies, including GLP-1 RAs, increase the risk of acute pancreatitis remains controversial. Recent analyses of large randomized controlled trials have not shown an increased risk of pancreatitis (Liu 2018; Sai sho 2018; Mon ami 2017). A post hoc analysis of the LEADER trial was unable to identify predictors for which patients taking liraglutide were more likely to develop pancreatitis (Steinberg 2017). Of interest, a history of pancreatitis was not a predictive factor because the incidence of pancreatitis in patients who entered the trial with a history of pancreatitis was 1.4% and 5% for liraglutide and placebo, respectively. However, because spontaneous postmarketing reports of pancreatitis have been submitted to the FDA, pancreatitis has been added as a precaution to the labeling of each GLP-1 RA. The risk, as well as the symptoms, of pancreatitis should be discussed with patients when initiating GLP-1 RAs. Common symptoms include excessive nausea, vomiting, and right upper quadrant stomach pain, and patients should be educated to seek medical attention if these symptoms occur.

Liraglutide, dulaglutide, semaglutide, and exenatide XR have been associated with thyroid C-cell tumors in animal studies. These drugs have a black box warning for the risk of developing thyroid C-cell tumors and are contraindicated in patients with a personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

An emerging area of concern is the increased risk of retinopathy complications with semaglutide. These include vitreous hemorrhage, onset of diabetes-related blindness, need for treatment with an intravitreal agent, and retinal photocoagulation, which all occurred at a higher incidence in the semaglutide group than in placebo in the SUSTAIN-6 trial (3% vs. 1.8%; HR 1.76; 95% CI, 1.11–2.78) (Marso 2016). Trials are under way to further investigate this finding.

GLP-1 RA Devices

In addition to efficacy, each pen’s specific characteristics should be considered to ensure the patient can successfully use the device. Liraglutide, lixisenatide, exenatide IR, and
semaglutide all come in multiuse pens that use the same pen needles as insulin pens. This may increase patient acceptance because patients may be more familiar with this type of pen needle. These needles must be attached immediately before and removed immediately after each dose, requiring a certain level of dexterity. A separate prescription should be sent for pen needles (or the current prescription updated) to use with liraglutide, lixisenatide, and exenatide IR so that the patient can administer the drug. Semaglutide is packaged such that each box already contains pen needles. Alternatively, dulaglutide and exenatide XR both come in single-use formulations. Dulaglutide was the first GLP-1 RA to come in an autoinjector pen, which automatically reconstitutes the drug and contains a built-in needle that is never

<table>
<thead>
<tr>
<th>Table 3. Overview of CV Outcomes Trials Focused on GLP-1 RAs and SGLT2i Agents</th>
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<tbody>
<tr>
<td>Trial</td>
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<tr>
<td>GLP-1 RA</td>
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<td>ELIXA</td>
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<td>LEADER</td>
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<tr>
<td>EXSCEL</td>
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<tr>
<td>SUSTAIN-6</td>
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<tr>
<td>REWIND</td>
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<tr>
<td>HARMONY</td>
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<tr>
<td>SGLT2i</td>
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<tr>
<td>CANVAS</td>
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<tr>
<td>EMPA-REG OUTCOME</td>
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<tr>
<td>DECLARE-TIMI 58</td>
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<tr>
<td>VERTIS-CV</td>
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</table>

* Labeled indication to reduce the risk of major adverse CV events in adults with type 2 diabetes and established CV disease.
* Removed from market in 2018 because of poor market penetration.
* Data expressed as mean.
* Labeled indication to reduce the risk of CV death in adults with type 2 diabetes and established CV disease.

ASCVD = atherosclerotic cardiovascular disease; CHF = chronic heart failure; CKD = chronic kidney disease; CV = cardiovascular; MACE = major adverse cardiovascular events; N/A = not applicable.

seen by the patient. This device can be a good option for patients with limited dexterity because it is easier to use than other GLP-1 RA devices. Finally, exenatide XR is available in two different single-use pens. The exenatide XR dual-chamber pen is quite bulky compared with similar devices and requires a series of steps to be completed before administering the drug, including tapping the pen 80 times or more to reconstitute the drug. The newest device, Bydureon BCise, incorporates an autoinjector technology similar to dulaglutide. Now, the patient is responsible for only one step—shaking the pen for at least 15 seconds before injecting. All exenatide XR pens require a 23-gauge needle because of the way the drug is formulated, which may be a significant drawback from the patient’s perspective. However, the BCise pen has a preattached needle that is never seen by the patient, which may help patient-perceived tolerability.

**Sodium-Glucose Cotransporter-2 Inhibitors**

Currently, the sodium-glucose cotransporter-2 (SGLT2) inhibitor class includes canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. These agents work directly on the SGLT2 receptors in the renal proximal tubules to inhibit glucose reabsorption. In individuals without diabetes, SGLT2 is responsible for ensuring glucose is appropriately reabsorbed, resulting in extremely low glucose concentrations in the urine. In the presence of longstanding hyperglycemia, the renal proximal tubules try to increase the SGLT2 transport maximum as a compensatory mechanism for preserving this energy source, not necessarily realizing the blood glucose concentrations are exceeding those necessary for normal physiologic processes (Mosley 2015; Cersosimo 2014). In addition, SGLT2 inhibition reduces the threshold for renal glucose reabsorption, thereby promoting glucose excretion and decreasing blood glucose concentrations.

**Efficacy**

In clinical trials, these drugs reduce the A1C by about 0.5%–1% (Zaccardi 2016). The resultant glycosuria may facilitate weight loss through an overall reduction in calories being metabolized. With 4 calories lost for each gram of glucose excreted in the urine, SGLT2 inhibitors can lead to a potential net loss of 160–320 calories/day (Ribola 2017; Bays 2014). However, weight loss with SGLT2 inhibitor use is not as much as what is expected, potentially because of an adaptive increase in the intake of calories (Ferrannini 2015). This risk may be mitigated using the SGLT2 inhibitor in combination with a GLP-1 RA. In addition to glucose-lowering and weight-loss benefits, these agents moderately reduce blood pressure. The hypothesized mechanisms for blood pressure reduction include osmotic diuresis, mild natriuresis, weight reduction, and indirect effects on nitric oxide release (Majewski 2015). Blood pressure reductions in clinical trials were 3–5 mm Hg in systolic blood pressure and 1–2 mm Hg in diastolic blood pressure (Zaccardi 2016).

Empagliflozin and canagliflozin have additional labeled indications for reducing cardiovascular death and major adverse cardiovascular events, respectively, in adults with T2DM and established cardiovascular disease (see Table 3). In each of the published SGLT2 inhibitor cardiovascular outcome trials, hospitalization for heart failure was reduced compared with placebo (canagliflozin HR 0.67; 95% CI, 0.52–0.87; empagliflozin HR 0.65; 95% CI, 0.50–0.85; dapagliflozin HR 0.73; 95% CI, 0.61–0.88) (Wiviott 2019; Neal 2017; Zinman 2015).

In CANVAS and DECLARE-TIMI 58, canagliflozin and dapagliflozin reduced renal secondary outcomes by 40% and 47%, respectively (a composite of renal effects, including a 40% reduction in estimated glomerular filtration rate [eGFR], initiation of renal replacement therapy, and renal death) (Wiviott 2019; Neal 2017). In EMPA-REG, empagliflozin was associated with a 46% reduction in the composite outcome of doubling of the SCR concentration accompanied by an eGFR of 45 mL/minute/1.73 m² or less, initiation of renal replacement therapy, or death from renal disease (Wanner 2016). Empagliflozin was also associated with a 39% reduction in incident or worsening nephropathy and a 38% reduction in progression to macroalbuminuria (Wanner 2016). In CREDENCE, canagliflozin was associated with a 34% reduction in the composite outcome of doubling of serum creatinine level, end-stage kidney disease, renal death, and cardiovascular death, in patients with a baseline eGFR of 30 to less than 90 mL/minute/1.73 m² and albuminuria (Perkovic 2019). The hypothesized naphroprotective mechanisms include improved glycemic management, normalization of glomerular hyperfiltration, diuretic effects, anti-inflammatory and antioxidative stress effects, improved endothelial function, diminished sympathetic nerve activity, and increased renal oxygen consumption and energy production through increases in Hct and β-hydroxybutyrate (Mima 2018). In populations with renal impairment, SGLT2 inhibition was consistently associated with an initial decrease in eGFR, followed by an increase and then a return to baseline, suggesting a benefit in patients with reduced renal function (Seidu 2018). However, SGLT inhibitor use in severe renal impairment is not recommended because the glucose-lowering effects do not occur at eGFR values below 30 mL/minute/1.73 m². The package labeling provides some guidance, noting these drugs are not recommended for use in patients with an eGFR less than 45 mL/minute/1.73 m² for canagliflozin, dapagliflozin, and empagliflozin or less than 60 mL/minute/1.73 m² for ertugliflozin. However, updated ADA recommendations recommend clinicians consider using an SGLT2 inhibitor in patients with type 2 diabetes and kidney disease as long as the eGFR is above 30 mL/minute/1.73 m² to reduce the risk of CKD progression, cardiovascular events, or both, especially if albuminuria is present.

**Safety**

**Euglycemic Diabetic Ketoacidosis**

Euglycemic diabetic ketoacidosis (DKA), characterized by an increased anion gap metabolic acidosis, ketonemia, and normal blood glucose concentrations, has been reported with
SGLT2 inhibitor use (Rawla 2017; Peters 2015). Individuals with euglycemic DKA have nausea, vomiting, and malaise but lack hyperglycemia, which often delays recognition because the symptoms are nonspecific (Lupsa 2018). Most euglycemic DKA episodes have occurred in individuals with T1DM using SGLT2 inhibitors off-label, but these episodes can also occur in people with T2DM (Palmer 2016; Peters 2015). Risk factors for developing euglycemic DKA include serious illness, surgical stress, alcohol binge, low carbohydrate intake, and decreased insulin production/availability (Lupsa 2018). An additional emerging high-risk group are those who deliberately restrict insulin in order to lose weight (Staite 2018).

Amputations
The risk of lower-extremity amputations has also emerged from clinical trials and population-based analyses, specifically with canagliflozin (including the addition of a black box warning). In the CANVAS trial, the incidence of amputation in the canagliflozin group was almost double that in the placebo group (6.3 per 1000 patient-years vs. 3.4 per 1000 patient-years, p<0.001) (Neal 2017). This increased incidence of amputation did not occur in the EMPA-REG and DECLARE-TIMI 58 trials, so it may not be a class effect. According to analyses of the CANVAS program data, the highest-risk populations include those with a history of amputation, peripheral vascular disease, neuropathy, or foot ulcers (FDA 2017).

Skeletal Fractures
Canagliflozin has also been associated with an increased risk of skeletal fractures, according to data from the CANVAS program (15.4 per 1000 patient-years vs. 11.9 per 1000 patient-years) in addition to a phase IV postmarketing study required by the FDA that showed a reduction in total hip bone mineral density over 104 weeks (placebo-subtracted change of -0.9% and -1.2% in 100- and 300-mg groups, respectively) (Neal 2017; Bilezikian 2016). The clinical significance of this finding is still unclear, given that a meta-analysis of trials involving canagliflozin, dapagliflozin, and empagliflozin did not support a harmful effect of SGLT2 inhibitors on bone (Tang 2016). The 2019 AACE and ACE consensus statement removed the warning for bone safety with all SGLT2 inhibitors, citing the lack of data supporting this association (Garber 2019).

Genitourinary Risks
The increased risk of bladder cancer was identified during early trials with dapagliflozin, but this increased risk has not occurred in subsequent studies or in clinical practice (Lupsa 2018). All the SGLT2 inhibitors have a warning about the risk of Fournier gangrene. The reported incidence of this condition is 55 cases over a nearly 6-year period of postmarketing reports, making the identification of specific risk factors difficult. Obesity, immunosuppressed states, smoking, alcohol abuse, and end-stage renal or liver failure may increase risk (Kumar 2017). Maintaining good hygiene in the perineum and genital regions is essential for avoiding this condition.

Risk Mitigation Strategies
A thorough medical history and medication review should be done before initiating an SGLT2 inhibitor, including asking about a history of UTIs, acute kidney injury, DKA, chronic genitourinary conditions (e.g., benign prostatic hypertrophy, urinary incontinence), and drugs that may cause hypovolemia (e.g., loop diuretics) or nephrotoxicity (e.g., NSAIDs). To minimize adverse effects, patients should maintain adequate hydration and avoid excessive hyperglycemia.

Thiazide-like diuretics are generally not an issue when adding an SGLT2 inhibitor; however, reducing the dose of a loop diuretic by 50% should be considered when adding an SGLT2 inhibitor (Lupsa 2018). To minimize the risk of acute kidney injury, avoid initiating a thiazide-like diuretic, angiotensin-converting enzyme inhibitor, and SGLT2 inhibitor at the same time, when possible. Finally, the patient’s blood pressure and volume status must be sufficient to accommodate the addition of an SGLT2 inhibitor. If tolerability is a concern, using half of the traditional SGLT2 inhibitor starting dose can mitigate this risk, as can more frequent follow-ups.

Non-Insulin Therapies in the Inpatient Setting
For noncritically ill patients receiving care in the hospital, insulin remains the preferred treatment. However, continuing a patient’s home regimen consisting of non-insulin therapies is sometimes appropriate. Metformin plays a limited role in the inpatient setting, especially if the patient is at high risk of dehydration or renal insufficiency or is likely to receive radiocontrast media or other nephrotoxic drugs. Similarly, SGLT2 inhibitors should generally be avoided, given the risk of euglycemic DKA during periods of prolonged fasting and surgical procedures (Lupsa 2018). Thiazolidinediones likely also do not play a role in the inpatient setting, especially if used concurrently with insulin. Sulfonylureas can increase the risk of hypoglycemia; however, if the patient’s diabetes is already well managed on a sulfonylurea, the patient is eating regularly scheduled meals and has a low risk of hypoglycemia, and a relatively short admission is planned, it may be appropriate to continue sulfonylureas.

The dipeptidyl peptidase-4 inhibitors may play a role in the inpatient setting, with recent literature supporting their use in combination with basal insulin, resulting in glucose management and frequency of hypoglycemia similar to a basal-bolus insulin regimen (Garg 2017a; Pasquel 2017). Given the recommendation to avoid saxagliptin or alogliptin in patients with heart failure, sitagliptin or linagliptin would be preferable for an inpatient formulary. Although GLP-1 RAs may also play a role in the inpatient setting, their GI-related adverse effects (e.g., nausea, vomiting, decreased appetite, early satiety) may be problematic in hospitalized patients because of appetite suppression from their concurrent illness (Umpierrez 2013). As these agents come off patent in the coming years, a lower cost may make them more appealing in the inpatient setting.
INSULIN UPDATES

Basal insulin analog options for patients have dramatically expanded with the addition of insulin degludec, resurgence of concentrated insulins, and introduction of biosimilar insulins.

Ultra-Long Acting Insulin Analogs

The triple-concentrated formulation of insulin glargine (U-300) results in a smaller depot surface area after injection, a flatter pharmacokinetic profile, and a longer duration of action than traditional insulin glargine (up to 36 hours). Another new basal insulin analog is insulin degludec, with an almost entirely flat pharmacokinetic profile and a duration of action lasting at least 42 hours, allowing for a flexible dosing schedule, consistent insulin concentrations throughout the day and night, and less hypoglycemia than other basal insulins. In the SWITCH trials, insulin degludec was associated with a lower incidence of hypoglycemia in T1DM (RR 0.89; 95% CI, 0.85–0.94) and T2DM (RR 0.70; 95% CI, 0.61–0.80), as well as a lower incidence of nocturnal symptomatic hypoglycemia in T1DM (RR 0.64; 95% CI, 0.56–0.73) and T2DM (RR 0.58; 95% CI, 0.46–0.74) compared with insulin glargine U-100 (Lane 2017; Wysham 2017).

These ultra-long acting insulin analogs are only available in pen form, with the exception of insulin degludec U-100, which is also available in vials for pediatric patients requiring less than 5 units each day (Table 4). Patients must be educated not to use an insulin syringe to obtain their insulin from the pen because of the risk of inaccurate dosing, especially with concentrated insulins (Bzowyckyj 2016).

Ultra-Rapid Insulin Analog

Fast-acting insulin aspart has the same molecular structure as traditional insulin aspart, with the addition of niacinamide (for faster absorption) and l-arginine (as a stabilizing agent) resulting in a quicker onset and the ability to administer a dose as late as 20 minutes after starting a meal. In the ONSET 1 trial, patients with T1DM were randomized to fast-acting insulin aspart at mealtime, fast-acting insulin aspart postmeal, or traditional insulin aspart at mealtime (all in addition to insulin detemir). Mealtime was defined as

<table>
<thead>
<tr>
<th>Table 4. Product Characteristics of Newer Insulin Products</th>
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<tbody>
<tr>
<td><strong>Generic Name</strong></td>
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<tr>
<td>------------------</td>
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<tr>
<td>Degludec</td>
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<td>Aspart</td>
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<td>Glulinsine</td>
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<tr>
<td>Fast-acting aspart</td>
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<td>Insulin human U-500</td>
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*aDosed in 2-unit increments.

*bDosed in 0.5-unit increments.

*cDosed in 5-unit increments.
respectively), but not when administered postmeal, with similar rates of hypoglycemia between all groups (Russell-Jones 2017). In the ONSET 2 trial, patients with T2DM were randomized to either fast-acting insulin aspart or traditional insulin aspart administered at mealtime, with insulin glargine and metformin used as adjunctive therapies. Compared with traditional insulin aspart, this trial found that fast-acting insulin aspart only improved 1-hour postprandial glucose (-10.63 mg/dL). In addition, postprandial hypoglycemia (0–2 hours) was higher in the fast-acting insulin aspart group (RR 1.60; 95% CI, 1.13–2.27; p=0.0082) (Bowering 2017). According to the results of the ONSET trials, fast-acting insulin aspart may be more useful in the T1DM population through better postprandial glucose management. Additional trials have been completed or are in the process of evaluating the usefulness of fast-acting insulin aspart in insulin pumps. Preliminary results are promising, but further investigation is warranted to evaluate the potential increased risk of hypoglycemia, infusion site reactions, and premature infusion-set changes compared with insulin aspart (Klonoff 2019; Zijlstra 2018).

At the time of publication, use of fast-acting insulin aspart in insulin pumps is considered off-label.

**Insulin Dosing Conversions**

With the increase in commercially available insulin products, additional complexity exists when changing between products. Most patients administering their basal insulin once daily can be converted to the same dose of the new basal insulin, with a few exceptions. In clinical trials, patients taking U-300 insulin glargine needed higher doses to achieve the same glycemic goals compared with patients taking U-100 insulin glargine. Therefore, patients changing from U-300 insulin glargine to an alternative basal insulin analog are advised to set their new basal insulin dose at about 80% of their current dose. Patients changing to U-300 insulin glargine or insulin degludec from a twice-daily dosing regimen of any basal insulin analog should decrease the dose by 20% and administer the new insulin once daily.

**Concentrated Insulins**

For patients requiring more than 200 units/day of insulin, U-500 insulin regular can be considered. The starting dose for U-500 depends on the patient’s current glucose concentrations. If the A1C is less than 8% or the mean self-monitored glucose concentrations within the past 7 days are less than 180 mg/dL, the patient’s total daily dose (TDD) of U-500 should start at 80% of his or her current TDD of insulin (Hood 2015). If the patient does not meet either criterion, the TDD of U-500 should be equal to his or her current TDD of insulin. The patient’s entire insulin regimen should be discontinued, and the recommended TDD of U-500 insulin should be divided out over two or three doses. If given twice daily, 60% of the TDD should be administered before breakfast, with the remainder administered before dinner. If given three times daily, 40% of the TDD should be administered before breakfast, 30% before lunch, and 30% before dinner. The pen formulation of U-500 insulin is preferred to eliminate the need for dose conversions. If a patient needs to use the vial formulation, the U-500 insulin syringes should be co-prescribed with it.

**Changing to NPH Insulin**

With the rising costs of insulin and changes in insurance coverage, the cost of insulin analogs has become increasingly out of reach for patients. Therefore, patients may need to change to neutral protamine Hagedorn (NPH) and regular insulin for their lower price tag and OTC access. Patients changing from a basal insulin analog to NPH insulin can likely be changed on a unit-per-unit basis. Usually, changing to NPH insulin requires a twice-daily dosing schedule and a 20% dose increase. However, the dose increase should be deferred during the transition to minimize the risk of hypoglycemia, especially for patients who are already achieving their glycemic goals. Similarly, patients and clinicians may choose to change to a premixed insulin formulation (e.g., 70/30). In this situation, one approach is to calculate the patient’s current TDD of insulin from all sources, reduce the dose by 10%–20% if the patient is at high risk of hypoglycemia, and divide that amount evenly into two doses (Bhattacharyya 2014). The first dose is administered before breakfast and the other before dinner. During these transitions between insulin regimens, more frequent blood glucose monitoring and follow-up is recommended to adjust doses accordingly.

**Changing from a Premixed Insulin Regimen**

If changing from 70/30 insulin to a typical multidose injection regimen using insulin analogs, calculate the TDD of each insulin separately and convert to their respective insulin doses. For example, if a patient is taking 60 units of 70/30 twice daily, this would equate to 84 units of NPH insulin and 36 units of mealtime insulin (either rapid or regular). From there, a 20% reduction in NPH insulin is warranted because the patient will be changing from twice-daily NPH to a once-daily basal analog, resulting in a dose of 67 units once daily. The patient’s mealtime dose should then be divided evenly between three meals, resulting in a bolus dose of 12 units three times daily with meals.

**Subsequent Dose Adjustments**

Questions have arisen regarding whether insulin detemir and U-100 insulin glargine are truly comparable on a unit-per-unit basis. If changing from U-100 insulin glargine to insulin detemir, a one-to-one dose conversion is advised, but note that an eventual dose increase may be warranted to achieve the same glycemic goals (Wallace 2014). In addition, insulin...
Diabetes Mellitus

therapy varies depending on the product and patient’s regimen at baseline (Table 5).

Currently, the only drugs approved for helping patients achieve glycemic goals in T1DM are insulin and pramlintide. However, one study evaluating several T1DM exchange regimens found that 5.4% of patients were using an adjuvant agent for their diabetes including metformin (3.5%), GLP-1 RAs (0.91%), and SGLT2 inhibitors (0.63%), with the use of adjuvant therapy associated with older age, a higher BMI, and a longer duration of diabetes (Lyons 2017). Reasons for using non-insulin therapies in T1DM include the desire to provide insulin-sparing effects, combat weight gain, and reduce glycemic variation throughout the day.

**Metformin**

In the REMOVAL trial, patients 40 and older with T1DM for at least 5 years and three or more cardiovascular risk factors were randomized to metformin 2000 mg/day or placebo (Petrie 2017). After 3 years, patients’ insulin doses and A1C values were unchanged, and metformin did not significantly alter atherosclerosis progression. However, weight and LDL were significantly lower in the metformin group (-1.17 kg and -5.03 mg/dL, respectively) and eGFR was increased (4 mL/minute/1.73 m²) compared with placebo, suggesting that metformin’s role in T1DM is long-term weight management and renal benefits rather than glucose management (Petrie 2017).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Insulin Glargine and Lixisenatide (Soliqua 100/33)</th>
<th>Insulin Degludec and Liraglutide (Xultophy 100/3.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin concentration</td>
<td>100 units/mL</td>
<td>100 units/mL</td>
</tr>
<tr>
<td>GLP-1 RA concentration</td>
<td>33 mcg/mL</td>
<td>3.6 mg/mL</td>
</tr>
<tr>
<td>Insulin amount per pen</td>
<td>300 units</td>
<td>300 units</td>
</tr>
<tr>
<td>GLP-1 RA amount per pen</td>
<td>99 mcg</td>
<td>10.8 mg</td>
</tr>
<tr>
<td>Starting dose (naive to basal insulin or GLP-1 RA)</td>
<td>15 units/5 mcg</td>
<td>10 units/0.36 mg</td>
</tr>
<tr>
<td>Starting dose (currently on basal insulin or GLP-1 RA)</td>
<td>15 units/5 mcg (if current basal insulin dose &lt; 30 units daily) 30 units/10 mcg (if current basal insulin dose = 30–60 units daily)</td>
<td>16 units/0.58 mg (regardless of current basal insulin dose)</td>
</tr>
<tr>
<td>Dose titrations</td>
<td>Increase/decrease by 2–4 units every week</td>
<td>Increase/decrease by 2 units every 3–4 days</td>
</tr>
<tr>
<td>Max insulin dose per day</td>
<td>60 units</td>
<td>50 units</td>
</tr>
<tr>
<td>Max GLP-1 RA dose per day</td>
<td>20 mcg</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>Shelf-life (open and unrefrigerated)</td>
<td>28 days</td>
<td>21 days</td>
</tr>
</tbody>
</table>

detemir may need to be administered twice daily to achieve 24-hour basal coverage, especially with doses of less than or equal to 0.4 unit/kg/day in T1DM (Wallace 2014).

When changing insulin regimens, the patient should be notified that subsequent dose changes may be necessary. People may respond to insulin products differently, so getting the dose “right” on the first try is unlikely. The highest priorities when changing insulin regimens are to get the patient comfortable and to balance the risks of hypoglycemia or hyperglycemia. Patients must be advised that subsequent dose adjustments may be necessary so that they do not think their diabetes is suddenly worsening or perceive their new drug to be ineffective. Finally, clinical judgment should always be used when changing the patient’s regimen. If patients are currently experiencing a consistent pattern of hyperglycemia, they are at low risk of developing hypoglycemia and may not need a dose reduction during the transition. Conversely, patients with unexplained hypoglycemia may need an even larger dose reduction than what was recommended during the transition to maximize patient safety.

**Basal Insulin/GLP-1 RA Fixed-Ratio Combinations**

For patients looking to minimize their number of injections or copays, a once-daily fixed-ratio combination product is a potential solution. This product provides benefit to patients who require lower amounts of basal insulin with the synergistic effects of a GLP-1 RA. However, unlike insulin, GLP-1 RAs have maximum daily doses, which limits the amount of drug that can be administered each day. The approach to initiating therapy varies depending on the product and patient’s regimen (Table 5).

**NON-INSULIN THERAPIES IN T1DM**

Currently, the only drugs approved for helping patients achieve glycemic goals in T1DM are insulin and pramlintide. However, one study evaluating several T1DM exchange registries found that 5.4% of patients were using an adjuvant agent for their diabetes including metformin (3.5%), GLP-1 RAs (0.91%), and SGLT2 inhibitors (0.63%), with the use of adjuvant therapy associated with older age, a higher BMI, and a longer duration of diabetes (Lyons 2017). Reasons for using non-insulin therapies in T1DM include the desire to provide insulin-sparing effects, combat weight gain, and reduce glycemic variation throughout the day.
GLP-1 RA Agents

In the ADJUNCT ONE treat-to-target trial comparing liragludide with placebo, insulin doses after 1 year were reduced by 5% and 2% in the 1.8- and 1.2-mg groups, respectively, compared with a 4% increase in the 0.6-mg and placebo groups (Mathieu 2016). Liraglutide 1.8 mg daily also resulted in an average 4-kg weight loss compared with a 0.9-kg weight increase for the placebo group. Mean A1C was reduced in all groups, with no significant difference between the individual groups. However, liraglutide was also associated with an increase in symptomatic hypoglycemia, especially at higher doses. Finally, the risk of hyperglycemia with ketosis was significantly higher in the liraglutide 1.8-mg/day group (Mathieu 2016).

SGLT2 Inhibitors

Use of SGLT2 inhibitors in T1DM also holds promise as a potential therapeutic option, especially because of their insulin-independent mechanism of action. In the DEPICT 1 trial, dapagliflozin decreased A1C, total daily insulin dose, and glycemic variability (using continuous glucose monitoring to calculate the mean amplitude of glycemic excursions) compared with placebo. However, these benefits were accompanied by a numeric (but not statistical) increase in UTIs and severe hypoglycemia episodes, with similar rates of definite DKA (Dandona 2017). In the EASE trials, empagliflozin reduced weight, A1C, total daily insulin dose, and systolic blood pressure while increasing glucose time-in-range, all in a dose-dependent manner, in persons with T1DM. These benefits came with a similar rate of hypoglycemia, an increase in genital infections at all doses, and more DKA with the 10- and 25-mg doses, but not at 2.5-mg daily dosage (Rosenstock 2018).

Sotagliflozin

Sotagliflozin is a combined SGLT1/2 inhibitor, currently in development specifically for use as an adjunct to insulin in people with T1DM. In addition to inhibiting renal SGLT2 receptors, sotagliflozin inhibits glucose reabsorption through SGLT1 in the small intestine. The inTandem trials used a primary multi-component outcome of A1C lower than 7% with no episodes of severe hypoglycemia and absence of DKA after randomization. The inTandem3 trial was the largest of the three (n=1402) and lasted 24 weeks (Garg 2017b). More patients achieved the primary outcome when sotagliflozin 400 mg daily was added to insulin than when insulin alone was used (28.6% vs. 15.2%), with similar rates of severe hypoglycemia (around 3%). Decreases in mean total daily insulin dose (-5.25 units/day), weight (-2.9 kg), and systolic blood pressure (-3.5 mm Hg) also occurred in the sotagliflozin group compared with placebo. These benefits must be weighed against the higher incidence of DKA in the sotagliflozin arm (3% vs. 0.6%). The incidence of DKA also appeared to be higher in the patient subgroup that used an insulin pump (4.4% vs. 0.7%) than in patients using multiple daily injections of insulin (2.1% vs. 0.5%).

In March 2019, the FDA issued a complete response letter stating it would not approve the new drug application in its current form, citing an 8-fold increase in DKA risk compared with placebo (95% CI, 3.1–19.9). The risk of DKA was consistent across all subgroups studied but was highest in subjects with a history of DKA, young age, high baseline A1C, and insulin pump use (FDA 2019). Conversely, the European Medicines Agency Committee for Medicinal Products for Human Use has issued positive opinions for sotagliflozin and dapagliflozin as adjunctive treatments with insulin for certain adults with T1DM and under strict conditions, including patients with a BMI above 27 kg/m², high insulin requirements, following up with an endocrinologist, and closely monitoring their glucose concentrations to prevent ketosis.

Summary

General concerns related to using non-insulin therapies in T1DM include the additional costs, adverse effects, and treatment burden that comes with extra drugs. A proposed strategy for mitigating the DKA risk in patients with T1DM receiving adjunctive treatment with SGLT inhibitors is implementing the STICH protocol when patients have symptoms of DKA: stop the SGLT inhibitor, inject bolus insulin, consume 30 g of carbohydrates, and hydrate with water (Garg 2018). An additional factor to consider is how to adjust mealtimel insulin doses and insulin-carbohydrate ratios in the presence of these additional agents for patients who use customized mealtime doses or preprogrammed insulin pumps. This will be especially problematic as new closed-loop insulin pump systems are introduced to the market. The increased risk of hyperglycemia with ketosis is also cause for concern, given that the incidence would likely be higher in clinical practice when patients are not followed as closely as they would be in a clinical trial. Therefore, patients must be able to show that these drugs are being used adjunctively and do not replace their insulin. Finally, until these agents are labeled for use in T1DM, they will likely not be covered by insurance.

USE OF LANGUAGE IN DIABETES AND EDUCATION

The focus in diabetes care should be on the person living with diabetes. Because many individuals have difficulty attaining their diabetes-related goals, larger focus has been placed on the use of language and terminology when providing diabetes care and education. How health care professionals talk to and about people with diabetes plays an important role in engagement, conceptualization of diabetes and its management, treatment outcomes, and the individual’s psychosocial well-being (Dickinson 2017). As care providers, pharmacists must embrace strengths-based
Practice Points
The key updates in diabetes drug therapy include the following:

- Diabetes is a heterogeneous condition, which requires customizing therapy approaches and goals to the patient’s specific comorbidities and expectations.
- Although helping patients achieve their glycemic goals is still a priority, decreasing a patient’s overall cardiometabolic risk is essential.
- Sulfonylureas and thiazolidinediones have limited benefit in managing diabetes, and their role is limited to patients in whom drug cost is a significant barrier.
- GLP-1 RAs and SGLT2 inhibitors provide many benefits, including A1C reduction, weight loss, and reduced cardiovascular risk in patients with established atherosclerotic cardiovascular disease for some agents.
- Preliminary evidence shows promise for SGLT2 inhibitors to improve heart failure symptoms and renal outcomes.
- Despite the benefits of using GLP-1 RAs and SGLT2 inhibitors, confirm the individual patient has no absolute or relative contraindications to use of either class of drugs before they are initiated.
- Non-insulin therapies play a limited role in the inpatient setting; however, pharmacists should evaluate each patient’s diabetes regimen on admission and discharge.
- Off-label use of metformin, GLP-1 RAs, and SGLT inhibitors as adjunctive treatment for T1DM has had mixed results. Their use in T1DM is not widely recommended, though specific patients may benefit, and more frequent monitoring is required.

and person-first language to help achieve better health outcomes. An example of strengths-based language is, “Lee takes her insulin 50% of the time because of cost concerns,” which is much more helpful than “Lee is noncompliant/nonadherent” (Dickinson 2017). Similarly, person-first language encourages the statement “Lee has diabetes” rather than the commonly used disease-first phrase “Lee is diabetic” (Dickinson 2017).

CONCLUSION
Previously, the treatment regimen for an individual patient was based almost entirely on glycemic management. However, with new research and updated guidelines, the emphasis has shifted to more patient-specific treatments. With recent cardiovascular outcomes trial data, clinicians have more information on the cardiovascular and renal benefits of some GLP-1 RA and SGLT2 inhibitor classes.

REFERENCES


Self-Assessment Questions

1. A 54-year-old man with type 2 diabetes (T2DM) currently takes metformin 1000 mg twice daily and glipizide XR 10 mg 2 tablets before breakfast. His eGFR is 65 mL/minute/1.73 m², A1C is 7.4%, and A1C goal is less than 7%. In addition to T2DM, his medical history is significant for heart failure with reduced ejection fraction (New York Heart Association class II; American College of Cardiology/American Heart Association stage C) and gout. Which one of the following is best to recommend adding to manage this patient’s T2DM?
   A. Empagliflozin 10 mg daily
   B. Pioglitazone 15 mg daily
   C. Saxagliptin 5 mg daily
   D. Insulin glargine 10 units daily at bedtime

2. A 48-year-old man presents for a T2DM follow-up. He has been taking metformin 1000 mg twice daily for a few months now, but his A1C continues to be above his personal goal of less than 7% (most recent A1C was 7.5%), and his BMI is 25.3 kg/m². His medical history is non-significant, and he has a strenuous job as a garbage collector. Which one of the following is best to recommend adding as next-step therapy for this patient?
   A. Glipizide
   B. Sitagliptin
   C. Insulin glargine/lixisenatide
   D. Insulin detemir

3. A 49-year-old woman was referred for T2DM management, having been given a diagnosis of T2DM about 1 year ago. She has been taking metformin 1000 mg twice daily in addition to implementing lifestyle modifications for the past 6 months. Her A1C today is 10.6%, and her goal is less than 6.5%. She has occasional polyuria (about three or four times per week) but has not noticed any other symptoms of hyperglycemia. She has no other chronic medical conditions. Which one of the following is the best approach to intensifying this patient’s regimen?
   A. Add insulin detemir and glipizide.
   B. Add insulin degludec and insulin lispro.
   C. Add insulin aspart and dulaglutide.
   D. Add insulin glargine and semaglutide.

4. A 29-year-old man (weight 140 kg [308 lb]) has a medical history that includes T2DM; he currently takes metformin 1000 mg twice daily and liraglutide 1.8 mg daily. His most recent A1C was 9.4%, despite consistent use of his medications and after generally healthy eating and exercise plans. His physician wants to initiate insulin glargine and requests your advice on the most appropriate starting dosage for him. According to the AACE and ACE comprehensive diabetes management algorithm, which one of the following is the best insulin glargine dosage to recommend for this patient?
   A. 10 units daily
   B. 14 units daily
   C. 28 units daily
   D. 5 units twice daily

5. A 38-year-old woman (weight 120 kg) presents to the clinic for a T2DM follow-up. Basal insulin was added to her regimen 6 months ago, and her A1C has improved (current A1C is 7.4%; previously was 10.3%; goal is less than 6.5%). Almost all of her fasting blood glucose readings are at goal, although postprandial readings are almost always above her goal range. The patient’s current T2DM regimen consists of metformin 1000 mg twice daily, liraglutide 1.8 mg daily, and U-300 insulin glargine 140 units daily. Which one of the following is best to recommend for this patient?
   A. Initiate insulin aspart 14 units before her largest meal and decrease insulin glargine to 126 units daily.
   B. Initiate insulin aspart 14 units before her largest meal and increase insulin glargine to 154 units daily.
   C. Initiate sitagliptin 100 mg daily and continue insulin glargine 140 units daily.
   D. Initiate sitagliptin 100 mg daily and increase insulin glargine to 154 units daily.

6. A 72-year-old woman presents to the clinic for T2DM management. She currently takes insulin degludec 30 units daily and insulin aspart 12 units three times daily with meals. Prebreakfast and predinner glucose readings have generally been in her goal range (80–130 mg/dL), but she notes prelunch hypoglycemia (50s–70s) about three or four times per week. She denies any changes in eating habits or exercise patterns on those days and cannot identify a cause. Which one of the following is best to recommend for this patient’s hypoglycemia?
   A. Skip breakfast dose of insulin aspart.
   B. Decrease insulin degludec to 25 units daily.
   C. Decrease prebreakfast insulin aspart to 10 units.
   D. Change insulin aspart to fast-acting insulin aspart.

7. A 59-year-old woman presents for follow-up. She has a longstanding history of T2DM with A1C values previously over 10%. Her A1C has decreased to 8.1% recently, and her current weight is 110 kg (242 lb) (BMI 40.3 kg/m²). She takes metformin 1000 mg daily, insulin glargine 60 units daily, and insulin lispro 20 units three times daily with meals, missing doses about two or three times per
8. A 62-year-old woman with T2DM was admitted to the hospital yesterday for a heart failure exacerbation. Her home diabetes regimen consists of insulin glargine 48 units at bedtime, insulin lispro 10 units three times daily with meals, canagliflozin 300 mg every morning, and dulaglutide 1.5 mg weekly (last dose administered yesterday). Which one of the following is best to recommend holding during this patient’s inpatient hospitalization?

A. Insulin glargine
B. Canagliflozin
C. Insulin lispro
D. Dulaglutide

9. A 38-year-old man with T2DM has been referred for initiation of a glucagon-like peptide-1 receptor agonist (GLP-1 RA). The patient expresses a serious concern about needles. When asked for more specifics, he notes he is distressed when he needs to attach the needle and remove the cap before injection. Which one of the following GLP-1 RAs would be most appropriate to recommend for this patient?

A. Dulaglutide
B. Liraglutide
C. Semaglutide
D. Lixisenatide

10. A 43-year-old woman (weight 130 kg [286 lb]) recently lost her job and her insurance. She is concerned because she has been doing well with diabetes (fasting glucose readings of 80–100 mg/dL and most recent A1C was 6.4%), but now her current insulins will be too expensive and she will have to change to a less costly alternative. The patient currently takes insulin glargine 64 units daily and insulin aspart 15 units three times daily with meals for T2DM. Which one of the following regimens using 70/30 (NPH insulin/regular) would be best to recommend for this patient?

A. 35 units before breakfast and dinner
B. 45 units before breakfast and dinner
C. 55 units before breakfast and dinner
D. 60 units before breakfast and dinner

11. A 52-year-old man will be admitted to the hospital today for cardiac monitoring. His home regimen includes 40 units of 70/30 NPH insulin/aspart before breakfast and dinner. The comparable medications on your hospital formulary include insulin glargine and insulin lispro. Assuming the patient will have the same insulin needs in the hospital as he does at home, which one of the following is best to recommend for this patient?

A. Insulin glargine 45 units daily and insulin lispro 8 units three times daily with meals
B. Insulin glargine 56 units daily and insulin lispro 12 units three times daily with meals
C. Insulin glargine 22 units twice daily and insulin lispro 12 units three times daily with meals
D. Insulin glargine 28 units daily and insulin lispro 8 units three times daily with meals

12. A 28-year-old woman (BMI 53 kg/m²) presents with concerns about her insulin copays. She currently takes U-100 insulin glargine 80 units twice daily and insulin glulisine 66 units three times daily with meals. Her insurance formulary covers insulin regular U-500 in pen form at a lower copay than the insulin analogs. Her most recent A1C is 7.3% and preprandial glucose concentrations are all generally less than 150 mg/dL. Which one of the following is best to recommend for this patient?

A. Insulin regular U-500 215 units before breakfast and 145 units before dinner
B. Insulin regular U-500 140 units before breakfast and 140 units before dinner
C. Insulin regular U-500 115 units before breakfast and 85 units before lunch and dinner
D. Insulin regular U-500 215 units before breakfast and 105 units before lunch and dinner

13. A 63-year-old woman with T2DM and a history of a myocardial infarction 1 year ago currently takes metformin XR 500 mg 2 tablets twice daily and insulin glargine 24 units daily with no dosage changes in the past 6 months. Her current A1C is 8.3%. Which one of the following is best to recommend for changing the patient’s current insulin regimen to a basal insulin/GLP-1 RA fixed-ratio combination?

A. Insulin degludec/liraglutide 10 units daily
B. Insulin degludec/liraglutide 16 units daily
C. Insulin glargine/lixisenatide 15 units daily
D. Insulin glargine/lixisenatide 30 units daily
14. Which one of the following patients with type 1 diabetes (T1DM) is the best candidate for using an SGLT2 inhibitor as adjunctive therapy to insulin?

A. A 24-year-old man with a BMI of 23 kg/m$^2$, taking 0.6 unit/kg/day of insulin, and using continuous glucose monitoring

B. A 26-year-old woman with a BMI of 32 kg/m$^2$, taking 0.7 unit/kg/day of insulin, and checking glucose concentrations two or three times daily

C. A 39-year-old man with a BMI of 29 kg/m$^2$, taking 1.6 unit/kg/day of insulin, and using continuous glucose monitoring

D. A 41-year-old woman with a BMI of 31 kg/m$^2$, taking 1 unit/kg/day of insulin, and checking glucose concentrations two or three times weekly

15. A 34-year-old man (weight 82 kg) with a medical history of T1DM presents to be evaluated for adjunctive non-insulin therapy. He currently takes insulin degludec 40 units daily and insulin lispro 15 units three times daily with meals, does not miss any doses, and is using continuous glucose monitoring. He states that his glucose concentrations vary significantly throughout the day, with no identified cause. He believes this is contributing to his A1C of 7.6% because his fasting glucose concentrations are almost always within range. He denies an overactive appetite or snacking and reports consuming appropriate portions at his meals. However, he is concerned because he has experienced a gradual weight gain without any changes in exercise or eating patterns (current BMI is 23.8 kg/m$^2$, up from 21.7 kg/m$^2$ 1 year ago). Which one of the following is best to add to this patient’s regimen?

A. Liraglutide 0.6 mg daily, titrated to 1.8 mg daily

B. Metformin 500 mg daily, titrated to 1000 mg twice daily

C. Dapagliflozin 5 mg daily, titrated to 10 mg daily

D. Pioglitazone 15 mg daily, titrated to 45 mg daily