Diabetes Mellitus

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

Reviewed by: Christie Schumacher, Pharm.D., BCPS, BCACP, BC-ADM, CDE; and Heather L. Peterson, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Apply the current treatment guidelines to a specific patient with type 2 diabetes.
2. Evaluate the appropriateness of non-insulin therapies in patient-specific situations.
3. Construct a treatment plan for a patient needing to convert between different insulin regimens.
4. Design a patient-specific regimen incorporating a fixed-ratio combination of a basal insulin and glucagon-like peptide-1 receptor agonist.
5. Assess the safety and efficacy of non-insulin therapies in a patient with type 1 diabetes.

ABBREVIATIONS IN THIS CHAPTER

ADA	American Diabetes Association
DKA	Diabetic ketoacidosis
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
SGLT2	Sodium-glucose cotransporter-2
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
TDD	Total daily dose

Table of other common abbreviations.

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 emerging therapies in achieving glycemic goals in T2DM, though 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 "ominous 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).

Updates to Additional Diabetes-Specific References

In 2018, the annual ADA standards of care became a "living" document, with updates added as new evidence becomes available rather than waiting until the next year to incorporate timely recommendations. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) also publish a comprehensive T2DM management algorithm annually. All of these references provide useful algorithms and flowcharts for obesity management, prediabetes treatment, cardiovascular risk factor modifications, hyperglycemia management, and adding and intensifying insulin (Table 2).

UPDATES IN NON-INSULIN THERAPIES

Glucagon-like Peptide-1 Receptor Agonists

Six GLP-1 RAs are available in the United States: twice-daily exenatide immediate release (IR), once-daily liraglutide and lixisenatide, and once-weekly formulations exenatide extended release (XR), dulaglutide, and semaglutide. The GLP-1 RAs are injected subcutaneously, though a once-daily oral formulation of semaglutide is currently in development (Aroda 2018). These drugs act by increasing glucose-dependent insulin secretion, decreasing glucose-dependent glucagon secretion, slowing gastric emptying, and increasing satiety. Benefits of these agents include a low risk of hypoglycemia and the potential to facilitate weight loss or prevent further weight gain.

Efficacy

In clinical trials, GLP-1 RAs have reduced A1C values by 1%–1.5%, with liraglutide, dulaglutide, and semaglutide having

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

Table of common laboratory reference values

ADDITIONAL READINGS

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

- American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2019. Diabetes Care 2019;42(suppl 1):S61-S138.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes algorithm – 2019 executive summary. Endocr Pract 2019;25:91-100.
- Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.
- Schwartz SS, Epstein S, Corkey BE, et al. The time is right for a new classification system for diabetes: rationale and implications of the beta-cell-centric classification schema. Diabetes Care 2016;39:179-86.
- Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. Diabetes Care 2017;40:1790-9.

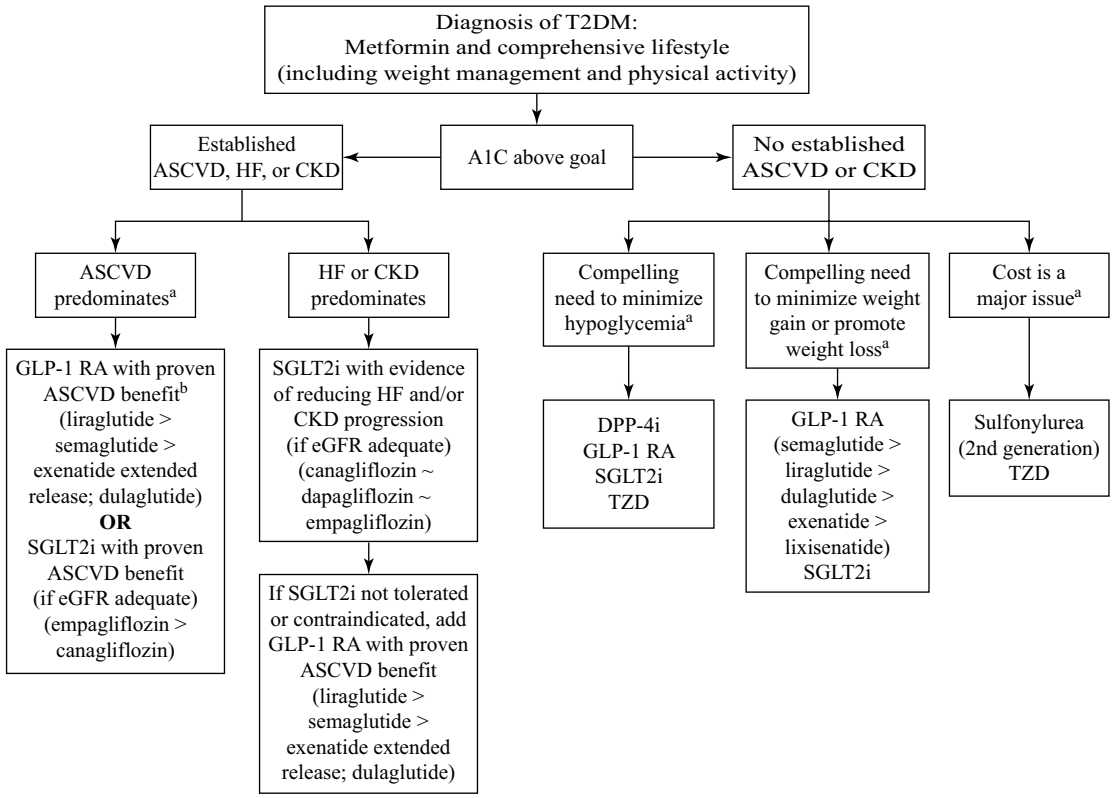

Figure 1. Overall approach to selecting glucose-lowering drug in type 2 diabetes.

[a]The medication classes within each individual box are listed in alphabetical order, not in order of preference.

[b]At 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.

Information from: American Diabetes Association (ADA). Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42(suppl 1):S90-S102; Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind randomised placebo-controlled trial. Lancet 2019;394:121-30.

Table 1. Considerations When Combining Oral Therapy with Injectable Therapies

Oral Therapy	Consideration (clinical judgment may supersede)
Metformin	Continue metformin
TZD	Discontinue TZD when initiating insulin OR reduce TZD dose
SU	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
SGLT2i	Continue SGLT2i
DPP-4i	Discontinue DPP-4i if GLP-1 RA initiated

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.

Information from: Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.

Table 2. Overview of Recommendations for Initiating and Titrating Insulin

Recommendation	2019 ADA Standards of Care & 2018 ADA/EASD Consensus Report	2019 AACE/ACE Comprehensive Diabetes Management Algorithm
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.

Information from: American Diabetes Association (ADA). Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42(suppl 1):S90-S102; Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the AACE and ACE on the comprehensive type 2 diabetes management algorithm – 2019 executive summary. Endocr Pract 2019;25:69-100.

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, nonfatal 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.

Patient Care Scenario

G.K. is a 68-year-old woman with newly diagnosed T2DM. She has had difficulty tolerating metformin, even at low doses of the XR formulation. She denies any overt symptoms of hyperglycemia. Her relevant clinical information includes A1C 10.8%, weight 128 kg (BMI 44.1 kg/m^2), blood pressure 132/78 mm Hg, and a history of hypertension, obesity, and a myocardial infarction 2 years ago. Her drug regimen consists of atorvastatin 80 mg daily, lisinopril 40 mg daily, carvedilol 25 mg twice daily, and aspirin 81 mg daily. Her physician has recommended an A1C target of less than 7%, and G.K. is in agreement. What is the most appropriate regimen for her T2DM?

ANSWER

Using the ADA/EASD algorithm, this patient is a candidate for the initial injectable combination, given her A1C above 10% and greater than 2% above her target. Options include a GLP-1 RA, basal insulin, and/or prandial insulin. With an A1C above 9%, she should be offered a once-daily basal insulin (at least in the short term) because there is likely some form of insulin insufficiency. Given her history of cardiovascular disease and obesity, she is also a candidate for a GLP-1 RA, preferably one with cardiovascular benefits. Bolus/prandial insulin is likely not needed at this time, given the relatively low likelihood that she has T1DM or insulin deficiency and the risk of further weight gain.

For her basal regimen, a starting dosage of 10 units once daily can be used, though a weight-based dose of 13–26 units once daily (0.1–0.2 unit/kg/day) is likely more appropriate, given her higher BMI. A GLP-1 RA with proven cardiovascular benefit would be preferred (i.e. liraglutide, semaglutide, dulaglutide), with the final decision made on the basis of the patient's preferred device characteristics and dosing frequency, in addition to insurance formulary. A fixed-ratio combination of basal insulin and GLP-1 RA can be used if not cost-prohibitive, with degludec/liraglutide preferred, given the cardiovascular benefit of liraglutide compared with lixisenatide. However, the patient's BMI suggests she needs more than 50 units/day of insulin, which makes using a fixed-ratio combination difficult.

Once the patient's glucose values are closer to target range and the GLP-1 RA is at maximum tolerated dose, a sodium-glucose cotransporter-2 (SGLT2) inhibitor with cardiovascular benefit can be added to her regimen if additional glucose lowering is still indicated, with the added benefit of providing additional cardiovascular risk reduction.

1. American Diabetes Association (ADA). Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42(suppl 1):S90-S102.
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the AACE and ACE on the comprehensive type 2 diabetes management algorithm – 2019 executive summary. Endocr Pract 2019;25:69-100.
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.

Safety

The most common adverse effects with GLP-1 RAs are nausea, vomiting, diarrhea, and cholelithiasis, occurring in a dose-dependent manner (Bettge 2017; Htike 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; Saisho 2018; Monami 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

Table 3. Overview of CV Outcomes Trials Focused on GLP-1 RAs and SGLT2i Agents

Trial	Agent	Study Population	No. of Patients	Median Trial Duration	MACE Outcomes (95% CI)
GLP-1 RA					
ELIXA	Lixisenatide	Age 30+ with ASCVD	6068	2.1 yr	HR 1.02 (0.89–1.17)
LEADER	Liraglutide[a]	Age 50+ with ASCVD; 60+ with 1+ CV risk factor	9340	3.8 yr	HR 0.87 (0.78–0.97)
EXSCEL	Exenatide XR	73.1% had ASCVD; 26.9% did not	14,752	3.2 yr	HR 0.91 (0.83–1.00)
SUSTAIN-6	Semaglutide	Age 50+ with ASCVD, CHF, or stage 3–5 CKD; 60+ with 1+ CV risk factor	3297	2 yr	HR 0.74 (0.58–0.95)
REWIND	Dulaglutide	Age 50+ with ASCVD; 55+ with ASCVD or 1 CV risk factor; 60+ with 2+ CV risk factors	9901	5.4 yr	HR 0.88 (0.79–0.99)
HARMONY	Albiglutide[b]	Age 40+ with ASCVD	9463	1.6 yr	HR 0.78 (0.68–0.90)
SGLT2i					
CANVAS	Canagliflozin[a]	Age 30+ with ASCVD; 50+ with 2+ CV risk factors	10,142	3.6 yr[c]	HR 0.86 (0.75–0.97)
EMPA-REG OUTCOME	Empagliflozin[d]	Age 18+ with ASCVD	7020	3.1 yr	HR 0.86 (0.74–0.99)
DECLARE-TIMI 58	Dapagliflozin	Age 40+ with ASCVD; men 55+ with 2+ CV risk factors; women 60+ with 1+ CV risk factor	17,160	4.2 yr	HR 0.93 (0.84–1.03)
VERTIS-CV	Ertugliflozin	Age 40+ with ASCVD	8237	N/A	Results expected 2020

[a]Labeled indication to reduce the risk of major adverse CV events in adults with type 2 diabetes and established CV disease.

[b]Removed from market in 2018 because of poor market penetration.

[c]Data expressed as mean.

[d]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.

Information from: Pfeffer MA, Claggett B, Diaz R. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57; Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22; Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228-39; Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44; Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind randomised placebo-controlled trial. Lancet 2019;394:121-30; Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519-29; Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57; Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28; Cannon CP, McGuire D, Pratley R, et al. Design and baseline characteristics of the evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial (VERTIS-CV). Am Heart J 2018;206:11-23; ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01986881).

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

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 m^2 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 m^2 and albuminuria (Perkovic 2019). The hypothesized nephroprotective 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 m^2. 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 m^2 for canagliflozin, dapagliflozin, and empagliflozin or less than 60 mL/minute/1.73 m^2 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 m^2 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 4. Product Characteristics of Newer Insulin Products

Generic Name	Brand Name	Supplied as Pen, Vial, or Both	Concentration (units/mL)	Units per Pen Device	Max Dose for Single Injection from Pen (units)	Shelf-life, Open and Unrefrigerated (days)
Degludec	Tresiba U-100	Both	100	300	80	56
	Tresiba U-200	Pen	200	600	160[a]	56
Glargine	Toujeo	Pen	300	450	80	56
	Toujeo Max	Pen	300	900	160[a]	56
	Lantus	Both	100	300	80	28
	Basaglar	Pen	100	300	80	28
Detemir	Levemir	Both	100	300	80	42
Lispro	Humalog U-100	Both	100	300	60	28
	Humalog U-100 Junior	Pen	100	300	30[b]	28
	Humalog U-200	Pen	200	600	60	28
	Admelog	Both	100	300	80	28
Aspart	NovoLog	Both	100	300	60	28
Glulisine	Apidra	Both	100	300	80	28
Fast-acting aspart	Fiasp	Both	100	300	80	28
Insulin human U-500	Humulin R U-500	Both	500	1500	300[c]	28

[a]Dosed in 2-unit increments.
[b]Dosed in 0.5-unit increments.
[c]Dosed in 5-unit increments.

0–2 minutes before a meal, and postmeal was 20 minutes after the start of the meal. Compared with traditional insulin aspart, postprandial plasma glucose at 1 and 2 hours after a meal was significantly lower with fast-acting insulin aspart administered at mealtime (-21.21 mg/dL and -12.01 mg/dL, 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

Table 5. Product Characteristics of Basal Insulin/GLP-1 RA Fixed-Ratio Combinations

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

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 at baseline (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.

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 m^2) compared with placebo, suggesting that metformin's role in T1DM is long-term weight management and renal benefits rather than glucose management (Petrie 2017).

GLP-1 RA Agents

In the ADJUNCT ONE treat-to-target trial comparing liraglutide 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 multicomponent 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/m^2, high insulin requirements, following up with an endocrinologist, and closely monitoring their glucoses 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 mealtime 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 understanding 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

Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care 2018;41:258-66.

Aroda VR, Rosenstock J, Terauchi Y, et al. Effect and safety of oral semaglutide monotherapy in type 2 diabetes – PIONEER 1 trial. Poster abstract presented at: American Diabetes Association Annual Meeting; June 2018; Orlando, FL.

Bays HE, Weinstein R, Law G, et al. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity 2014;22:1042-9.

Bettge K, Kahle M, Abd El Aziz MS, et al. Occurrence of nausea, vomiting and diarrhea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. Diabetes Obes Metab 2017;19:336-47.

Bhattacharyya A, Shetty R, Rajkumar C, et al. Switching from basal or basal-bolus insulin to biphasic insulin aspart 30: results from the Indian cohort of the A1Chieve study. Indian J Endocrinol Metab 2014;18:480-5.

Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab 2016;101:44-51.

Bowering K, Case C, Harvey J, et al. Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the ONSET 2 trial. Diabetes Care 2017;40:951-7.

Bzowyckyj AS. Embracing the insulin revolution in the ambulatory care setting. Diabetes Spectr 2016;29:140-5.

Centers for Disease Control and Prevention (CDC). 2017. National Diabetes Fact Sheet. Accessed January 10, 2019.

Cersosimo E, Solis-Herrera C, Triplitt C. Inhibition of renal glucose reabsorption as a novel treatment for diabetes patients. J Bras Nefrol 2014;36:80-92.

Dandona P, Mathieu C, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicenter, double-blind, phase 3, randomized controlled trial. Lancet Diabetes Endocrinol 2017;5:864-76.

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.

Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. Diabetes Care 2017;40:1790-9.

Ferrannini G, Hach T, Crowe S, et al. Energy balance after sodium-glucose cotransporter-2 inhibition. Diabetes Care 2015;38:1730-5.

Food and Drug Administration (FDA). 2017. FDA Confirms Increased Risk of Leg and Foot Amputations with the Diabetes Medicine Canagliflozin (Invokana, Invokamet, Invokamet XR). Accessed January 10, 2019.

Food and Drug Administration (FDA). 2019. FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; January 17, 2019. Accessed April 6, 2019.

Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the AACE and ACE on the comprehensive type 2 diabetes management algorithm – 2019 executive summary. Endocr Pract 2019;25:69-100.

Garg R, Schuman B, Hurwitz S, et al. Safety and efficacy of saxagliptin for glycemic control in non-critically ill hospitalized patients. BMJ Open Diabetes Res Care 2017a;5:e000394.

Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 2017b;377:2337-48.

Garg SK, Peters AL, Buse JB, et al. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. Diabetes Technol Ther 2018;20:571-5.

Hood RC, Arakaki RF, Wysham C, et al. Two treatment approaches for human regular U-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose U-100 insulin therapy with or without oral agents: a randomized, titration-to-target clinical trial. Endocr Pract 2015;21:782-93.

Htike ZZ, Zaccardi F, Papamargaritis D, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab 2017;19:524-36.

Klonoff DC, Evans ML, Lane W, et al. A randomized, multicenter trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (ONSET 5). Diabetes Obes Metab 2019;21:961-7.

Kumar S, Costello AJ, Colman PG. Fournier's gangrene in a man on empagliflozin for treatment of type 2 diabetes. Diabet Med 2017;34:1646-8.

Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA 2017;318:33-44.

Liu Y, Tian Q, Yang J, et al. No pancreatic safety concern following glucagon-like peptide-1 receptor agonist therapies: a pooled analysis of cardiovascular outcome trials. Diabetes Metab Res Rev 2018;34:e3061.

Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. Diabetologia 2018;61:2118-25.

Lyons SK, Hermann JM, Miller KM, et al. Use of adjuvant pharmacotherapy in type 1 diabetes: international comparison of 49,996 individuals in the Prospective Diabetes Follow-up and T1D Exchange registries. Diabetes Care 2017;40:e139-40.

Majewski C, Bakris GL. Blood pressure reduction: an added benefit of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes. Diabetes Care 2015;38:429-30.

Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.

Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care 2016;39:1702-10.

Mima A. Renal protection by sodium-glucose cotransporter-2 inhibitors and its underlying mechanisms in diabetic kidney disease. J Diabetes Complications 2018;32:720-5.

Monami M, Nreu B, Scatena A, et al. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): data from randomized controlled trials. Diabetes Obes Metab 2017;19:1233-41.

Mosley JF, Smith L, Everton E, et al. Sodium-glucose linked transporter-2 (SGLT2) inhibitors in the management of type-2 diabetes: a drug class overview. P T 2015;40:451-62.

National Center for Health Statistics (NCHS). 2017. Fact Sheet: National Health and Nutrition Examinations Survey. Access January 10, 2019.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

Orme ME, Nguyen H, Lu JY, et al. Comparative effectiveness of glycemic control in patients with type 2 diabetes treated with GLP-1 receptor agonists: a network meta-analysis of placebo-controlled and active-comparator trials. Diabetes Metab Syndr Obes 2017;10:111-22.

Palmer BF, Clegg DJ, Taylor SI, et al. Diabetic ketoacidosis, sodium glucose transporter-2 inhibitors and the kidney. J Diabetes Complications 2016;30:1162-6.

Pasquel FJ, Gianchandani R, Rubin DJ, et al. Efficacy of sitagliptin for the hospital management of general medicine and surgery patients with type 2 diabetes (Sita-Hospital): a multicenter, prospective, open-label, non-inferiority randomized trial. Lancet Diabetes Endocrinol 2017;5:125-33.

Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.

Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter-2 inhibition. Diabetes Care 2015;38:1687-93.

Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomized, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597-609.

Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomized, open-label, phase 3b trial. Lancet Diabetes Endocrinol 2018;6:275-86.

Rawla P, Vellipuram AR, Bandaru SS, et al. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. Endocrinol Diabetes Metab Case Rep 2017;2017.

Ribola FA, Cancado FB, Schoueri JHM, et al. Effects of SGLT2 inhibitors on weight loss in patients with type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci 2017;21:199-211.

Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care 2018;41:2560-9.

Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (ONSET 1). Diabetes Care 2017;40:943-50.

Saisho Y. Incretin-based therapy and pancreatitis: accumulating evidence and unresolved questions. Ann Transl Med 2018;6:131.

Schwartz SS, Epstein S, Corkey BE, et al. The time is right for a new classification system for diabetes: rationale and implications of the beta-cell-centric classification schema. Diabetes Care 2016;39:179-86.

Seidu S, Kunutsor SK, Cos X, et al. SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: a systematic review and meta-analysis. Prim Care Diabetes 2018;12:265-83.

Staite E, Zaremba N, Macdonald P, et al. "Diabulimia" through the lens of social media: a qualitative review and analysis of online blogs by people with type 1 diabetes mellitus and eating disorders. Diabet Med 2018;35:1329-36.

Steinberg WM, Buse JB, Ghorbani MLM, et al. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. Diabetes Care 2017;40:966-72.

Tang HL, Li DD, Zhang JJ, et al. Lack of evidence for a harmful effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. Diabetes Obes Metab 2016;18:1199-206.

Umpierrez GE, Korytkowski M. Is incretin-based therapy ready for the care of hospitalized patients with type 2 diabetes? Diabetes Care 2013;36:2112-7.

Wallace JP, Wallace JL, McFarland MS. Comparing dosing of basal insulin analogues detemir and glargine: is it really unit-per-unit and dose-per-dose? Ann Pharmacother 2014;48:361-8.

Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.

Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA 2017;318:45-56.

Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus: a systematic review and network meta-analysis. Diabetes Obes Metab 2016;18:783-94.

Zijlstra E, Demissie M, Graungaard T, et al. Investigation of pump compatibility of fast-acting insulin aspart in subjects with type 1 diabetes. J Diabetes Sci Technol 2018;12:145-51.

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

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 m^2, 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/m^2. His medical history is nonsignificant, 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/m^2). 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

week. Her C-peptide concentration is 0.4 ng/mL (normal range 0.5–3 ng/mL) with a corresponding glucose concentration of 182 mg/dL. The patient is requesting a modification to her diabetes regimen to help facilitate some weight loss. Which one of the following is best to recommend for this patient?

A. Initiate empagliflozin 10 mg daily, titrated to 25 mg daily.
B. Change insulin lispro to fast-acting insulin aspart 20 units three times daily with meals.
C. Change insulin glargine to glargine/lixisenatide 30 units/10 mcg daily.
D. Initiate semaglutide 0.25 mg weekly, titrated to 1 mg weekly.

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/m^2) 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