9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 Treat most adults with type 1 diabetes with continuous subcutaneous insulin infusion or multiple daily doses of prandial (injected or inhaled) and basal insulin. **A**

9.2 For most adults with type 1 diabetes, insulin analogs (or inhaled insulin) are preferred over injectable human insulins to minimize hypoglycemia risk. **A**

9.3 Early use of continuous glucose monitoring is recommended for adults with type 1 diabetes to improve glycemic outcomes and quality of life and to minimize hypoglycemia. **B**

9.4 Automated insulin delivery systems should be offered to all adults with type 1 diabetes. **A**

9.5 To improve glycemic outcomes and quality of life and to minimize hypoglycemia risk, most adults with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake and fat and protein intake. They should also be taught how to modify the insulin dose (correction dose) based on concurrent glycemia, glycemic trends (if available), sick-day management, and anticipated physical activity. **B**

9.6 Insulin treatment plan and insulin-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted to incorporate specific factors that impact choice of treatment and ensure achievement of individualized glycemic goals. **E**

Insulin Therapy

Insulin treatment is essential for individuals with type 1 diabetes because the hallmark of type 1 diabetes is absent or near-absent β-cell function. In addition to hyperglycemia,

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insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily insulin injections for the six or seven decades after the discovery of insulin. Over the past four decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3). The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive management (7%) led to ∼50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 person-years of therapy) (1). Follow-up of participants from the DCCT demonstrated fewer macrovascular and microvascular complications in the group that received intensive treatment. Achieving intensive glycemic goals during the active treatment period of the study had a persistent beneficial impact over the 20 years after the active treatment component of the study ended (1–3).

Insulin replacement plans typically consist of basal insulin, mealtime insulin, and correction insulin (**Fig. 9.1**) (4). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant and consistent plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain and lower A1C compared with injectable human insulins (5–7). Two injectable ultra-rapid-acting analog (URAA) insulin formulations are available that contain excipients that accelerate absorption and provide more activity in the first portion of their profile compared with the other RAA (8,9). Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA (10) (see also subsection ALTERNATIVE INSULIN ROUTES IN PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES). These newer formulations may cause less hypoglycemia while improving postprandial glucose excursions and administration flexibility (in relation to prandial intake) compared with RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14).

Despite the advantages of insulin analogs in individuals with type 1 diabetes, the expense and/or complexity of treatment required for their use may be prohibitive (**Table 9.1**). There are multiple approaches to insulin treatment. The central precept in the management of type 1 diabetes is that some form of insulin be given in a defined treatment plan tailored to the individual to prevent diabetic ketoacidosis (DKA) and minimize clinically relevant hypoglycemia while achieving the individual's glycemic goals. The impact of the introduction of interchangeable biosimilars and unbranded versions of some analog products as well as current and upcoming price reductions on insulin access need to be evaluated. Reassessment of insulin-taking behavior and adjustment of treatment plans to account for specific factors, including cost, that impact choice of treatment is recommended at regular intervals (every 3–6 months).

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. A systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (15). Use of CSII is associated with improvement in quality of life, particularly in areas related to fear of hypoglycemia and diabetes distress, compared with multiple

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes

Injected insulin plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	$$$
Less-preferred, alternative injected insulin plans			
MDI with NPH + RAA or URAA	++	++	$$
MDI with NPH + short-acting (regular) insulin	++	+	$
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	$

Continuous insulin infusion plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
Automated insulin delivery systems	+++++	+++++	$$$$$
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	$$$$$
Insulin pump therapy without automation	+++	+++	$$$$

Figure 9.1—Choices of insulin plans in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. The number of plus or dollar signs is an estimate of relative association of the plan with greater flexibility, lower risk of hypoglycemia, and higher costs between the different plans. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Adapted from Holt et al. (4).

Table 9.1—Examples of subcutaneous insulin treatment plans

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Plans that more closely mimic normal insulin secretion				
Insulin pump therapy (also including AID systems: hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 30–50% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with premeal insulin ∼15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise, and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for AID systems. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive plan. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus. AID systems: carbohydrate ratio, insulin on board, targets, and/or ISF may be adjusted, depending on the system. Make sure to review and adjust manual mode settings, if available.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 30–50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI plans with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ∼20% of TDD. Pre-lunch: RAA ∼10% of TDD. Pre-dinner: RAA ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

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Table 9.1—Continued

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ∼20% of TDD. Pre-lunch: R ∼10% of TDD. Pre-dinner: R ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Plans with fewer daily injections				
Three injections daily: N + R or N + RAA	Pre-breakfast: N ∼40% TDD + R or RAA ∼15% TDD. Pre-dinner: R or RAA ∼15% TDD. Bedtime: N ∼30% TDD.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N + R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily "split-mixed": N + R or N + RAA	Pre-breakfast: N ∼40% TDD + R or RAA ∼15% TDD. Pre-dinner: N ∼30% TDD + R or RAA ∼15% TDD.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N + R) or less (N + RAA) expensive insulins vs. analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

AID, automated insulin delivery; BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TBR, time below range; TDD, total daily insulin dose; TIR, time in range; URAA, ultra-rapid-acting analog (inhaled insulin may be considered if appropriate). Adapted from Holt et al. (4).

daily injections of insulin (16,17). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (4). Integration of continuous glucose monitoring (CGM) into the treatment plan soon after diagnosis improves glycemic outcomes, decreases hypoglycemic events, and improves quality of life for individuals with type 1 diabetes (18–23). Its use is now considered standard of care for most people with type 1 diabetes (4) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level, with further improvements when using devices with predictive low-glucose insulin delivery suspension (24,25).

Automated insulin delivery (AID) systems are safe and effective for people with type 1 diabetes. Randomized controlled trials and real-world studies have demonstrated the ability of commercially available systems to improve achievement of glycemic goals while reducing the risk of hypoglycemia (26–31). Data are emerging on the safety and effectiveness of do-it-yourself systems (32,33). Evidence suggests that an AID hybrid closed-loop system is superior to AID sensor-augmented pump therapy for increased percentage of time in range and reduction of hypoglycemia (34,35).

Intensive insulin management using a version of CSII and CGM should be considered in individuals with type 1 diabetes whenever feasible. AID systems are preferred and should be considered for individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) to improve time in range and reduce A1C and hypoglycemia (26,28–31,36–42). When choosing among insulin delivery systems, individual preferences, cost, insulin type, dosing plan, and self-management capabilities should be considered. See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require approximately 30–50% of their daily insulin as basal and the remainder as prandial (43). This proportion depends on several factors, including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage (4,44–48). Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1 unit/kg/day. Higher amounts may be required during puberty, menses, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in adults with type 1 diabetes who are metabolically stable, with approximately one-half administered as prandial insulin given to manage blood glucose after meals and the remaining portion as basal insulin to manage glycemia in the periods between meal absorption (49). Starting doses and those soon after diagnosis may be higher, if an individual presents with ketoacidosis, or lower (0.2–0.6 units/kg), particularly in young children and those with continued endogenous insulin production (during the partial remission phase or "honeymoon period," or in people who present with type 1 diabetes in adulthood) (49–51). This guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (52).

Typical multidose treatment plans for individuals with type 1 diabetes combine premeal use of prandial insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best managed by a well-timed injection or inhalation of prandial insulin. Prandial insulin should ideally be administered prior to meal consumption; however, the optimal time to administer varies based on the pharmacokinetics of the formulation (regular, RAA, or inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demand for glucose. To address this variability in people treated with insulin, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to adjust prandial insulin to account for nutritional intake and the correction dose based on premeal glucose levels, anticipated activity, and sick-day management can be effective and should be offered to most individuals (53–58). Education regarding adjustment of prandial insulin dose for glycemic trends should be provided to individuals who are using CGM alone or an AID system (59–62). Further adjustment of prandial insulin doses for nutritional intake of protein and fat, in addition to carbohydrates, is recommended but may be more feasible for individuals using CSII than for those using multiple daily injections (55). With some AID systems, use of a simplified meal announcement method may be an alternative for prandial insulin dosing (31,63). Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (64,65) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," and Section 7, "Diabetes Technology").

The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin plans and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (4).

Insulin Administration Technique

Ensuring that individuals and/or caregivers understand correct insulin administration technique is important to optimize glycemic management and insulin use safety. Recommendations have been published elsewhere outlining best practices for insulin administration (66). Proper insulin administration technique includes the following: injection, insertion of patch or infusion (for CSII or AID systems) into appropriate body areas, or oral inhalation (inhaled human insulin); injection or infusion site rotation; appropriate care of injection or infusion sites to avoid infection or other complications; avoidance of intramuscular (IM) insulin delivery; and filling of the reservoir (for bolus patch, CSII, or AID systems) or inhaler (for inhaled human insulin) depending on the method of administration. Selection of method of administration (vial and syringe, insulin pen, insulin patch, inhaled insulin, connected insulin pens/devices, or insulin pumps) will depend on a variety of individual-specific factors and needs, cost and coverage, and individual preferences. Reassessment of the appropriate administration technique should be completed during routine follow-up.

Exogenously delivered insulin should be injected or infused into subcutaneous tissue, not intramuscularly. Recommended sites for insulin administration include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated compared with longer needles, including a study performed in adults with obesity (67).

Injection or infusion site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection or infusion site rotation and how to recognize and avoid injecting in areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin administration sites for the presence of lipohypertrophy, as well as assessment of administration device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection, infusion, or inhalation technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral noninsulin glucose-lowering medications have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (∼1 kg) with pramlintide (68). Similar results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes was associated with small reductions in body weight, insulin dose, and lipid levels but did not sustainably improve A1C (69,70). The largest clinical trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, and results showed modest A1C reductions (∼0.4%), decreases in weight (∼5 kg), and reductions in insulin doses (71,72). Liraglutide was also assessed for impact on C-peptide in individuals with type 1 diabetes and residual β-cell function. During treatment there was no impact, and with liraglutide discontinuation there was worsening of C-peptide loss compared with placebo (73). Retrospective case series have revealed potential benefits on body weight and glycemic metrics with addition of semaglutide or tirzepatide for individuals with type 1 diabetes and obesity (74,75). Prospective studies using semaglutide are ongoing (76,77).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C, reduced body weight, and improved blood pressure (78); however, SGLT2 inhibitor use in type 1 diabetes was associated with an increased rate of DKA (79). The SGLT1/2 inhibitor sotagliflozin has been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C and body weight (80); however, sotagliflozin use was associated with an eightfold increase in DKA compared with placebo (81). The studies that led to the approved indication for heart failure (HF) excluded individuals with type 1 diabetes or a history of DKA (82,83). See SGLT INHIBITION AND RISK OF KETOSIS, later in this section, and PREVENTION AND TREATMENT OF HEART FAILURE in Section 10, "Cardiovascular Disease and Risk Management," for information on risk mitigation with the use of SGLT inhibitors in those with type 1 diabetes. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on selection of candidates for treatment and precautions (84).

There are currently no approved therapies for preservation of C-peptide or delaying the progression of symptomatic type 1 diabetes. Higher C-peptide levels have been associated with better A1C, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia (85). Various therapies, including verapamil, menin inhibitors, Janus kinase inhibitors, antithymocyte globulin, several monoclonal antibodies including teplizumab, and cell therapies, are currently under active investigation.

SURGICAL TREATMENT OF TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous kidney transplantation, following kidney transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite optimized glycemic management (86). In much of the world, allogenic islet transplantation is regulated as an organ transplant. However, in the U.S., allogenic islet transplantation is regulated as a cell therapy, and the first such allogeneic islet cell therapy, donislecel-jujn, was approved in 2023. Donislecel is indicated for the treatment of adults with type 1 diabetes who are unable to reach their A1C goals because of repeated episodes of severe hypoglycemia despite intensive diabetes management and education (87). Alternative islet sources are currently under active investigation.

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes (**Fig. 9.2**) (4).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.7 Healthy behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health should

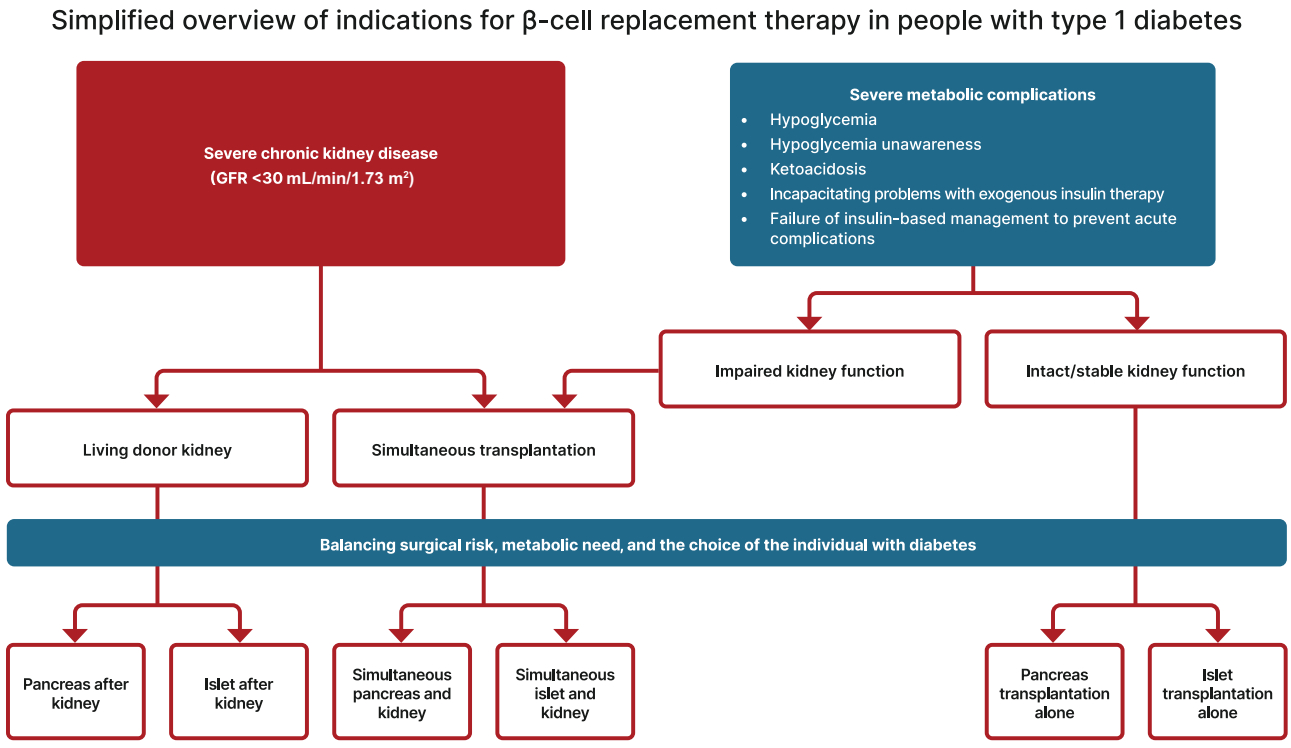


Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation and islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage kidney disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must consider the surgical risk, metabolic need, and the choices of the individual with diabetes. GFR, glomerular filtration rate. Adapted from Holt et al. (4).

be included in the glucose-lowering management of type 2 diabetes. **A**

9.8 A person-centered shared decision-making approach should guide the choice of glucose-lowering medications for adults with type 2 diabetes. Use medications that provide sufficient effectiveness to achieve and maintain intended treatment goals with consideration of the effects on cardiovascular, kidney, weight, and other relevant comorbidities; hypoglycemia risk; cost and access; risk for adverse reactions and tolerability; and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.9 Combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals. **A**

9.10 In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, the treatment plan should include medications with demonstrated benefits to reduce cardiovascular events (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] and/or sodium–glucose cotransporter 2 [SGLT2] inhibitor) for glycemic management and comprehensive cardiovascular risk reduction (irrespective of A1C) (**Fig. 9.3** and **Table 9.2**). **A**

9.11 In adults with type 2 diabetes who have heart failure (HF) (with either reduced or preserved ejection fraction), an SGLT2 inhibitor is recommended for both glycemic management and prevention of HF hospitalizations (irrespective of A1C) (**Fig. 9.3**). **A**

9.12 In adults with type 2 diabetes and symptomatic heart failure with preserved ejection fraction (HFpEF) and obesity, a GLP-1 RA with demonstrated benefits for both glycemic management and reduction of HF-related symptoms (irrespective of A1C) is recommended. **A**

9.13 In adults with type 2 diabetes who have CKD (with confirmed estimated glomerular filtration rate [eGFR] 20–60 mL/min/1.73 m^2 and/or albuminuria), an SGLT2 inhibitor or GLP-1 RA with demonstrated benefit in this population should be used for both glycemic management (irrespective of A1C) and for slowing progression of CKD and reduction in cardiovascular events (**Fig. 9.3**). The glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min/1.73 m^2. **A**

9.14 In adults with type 2 diabetes and advanced CKD (eGFR <30 mL/min/1.73 m^2), a GLP-1 RA is preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction. **B**

9.15 In adults with type 2 diabetes, metabolic dysfunction–associated steatotic liver disease (MASLD), and overweight or obesity, consider using a GLP-1 RA or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA with potential benefits in metabolic dysfunction–associated steatohepatitis (MASH) for glycemic management and as an adjunctive to healthy interventions for weight loss. **B**

9.16a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management due to potential beneficial effects on MASH. **B**

9.16b Combination therapy with pioglitazone plus a GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) due to potential beneficial effects on MASH. **B**

9.17 Medication plan and medication-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.2**). **E**

9.18 Treatment modification (intensification or deintensification) for adults not meeting individualized treatment goals should not be delayed. **A**

9.19 Choice of glucose-lowering therapy modification should take into consideration individualized glycemic and weight goals, presence of comorbidities (cardiovascular, kidney, liver, and other metabolic comorbidities), and the risk of hypoglycemia. **A**

9.20 When initiating a new glucose-lowering medication, reassess the need for and/or dose of medications with higher hypoglycemia risk (i.e., sulfonylureas, meglitinides, and insulin) to minimize the risk of hypoglycemia and treatment burden. **A**

9.21 Concurrent use of dipeptidyl peptidase 4 (DPP-4) inhibitors with a GLP-1 RA or a dual GIP and GLP-1 RA is not recommended due to lack of additional glucose lowering beyond that of a GLP-1 RA alone. **B**

9.22 In adults with type 2 diabetes who have not achieved their individualized weight goals, additional weight management interventions (e.g., intensification of lifestyle modifications, structured weight management programs, pharmacologic agents, or metabolic surgery, as appropriate) are recommended. **A**

9.23 In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if symptoms of hyperglycemia are present or when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]). **E**

9.24 In adults with type 2 diabetes and no evidence of insulin deficiency, a GLP-1 RA, including a dual GIP and GLP-1 RA, is preferred to insulin (**Fig. 9.4**). **A**

9.25 If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. **A**

9.26 In adults with type 2 diabetes who are initiating insulin therapy, continue glucose-lowering agents (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits). **A**

A holistic, multifaceted, person-centered approach that accounts for the complexity of managing type 2 diabetes and its complications across the life span is recommended. Person-specific factors that affect choice of treatment include individualized glycemic goals (see Section 6, "Glycemic Goals and Hypoglycemia"), individualized weight goals (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), the individual's risk for hypoglycemia, and the individual's history of or risk factors for cardiovascular, kidney, liver, and other comorbidities and complications of diabetes (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). In addition, treatment decisions must consider the tolerability and side effect profiles of medications, complexity of the medication plan and the individual's capacity to implement it given their specific situation and context, and the access, cost, and availability of medications. Lifestyle modifications and health behaviors that improve health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults," and Section 14, "Children and Adolescents," have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management," have recommendations for the use of glucose-lowering drugs in the management of cardiovascular disease and kidney disease, respectively.

Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management education and support (DSMES), avoidance of therapeutic inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities, considerations of adverse effects (including hypoglycemia) and treatment burden, and treatment goals and preferences. Shared decision-making can be facilitated during clinical encounters through use of decision aides and has been shown to improve A1C in adults with type 2 diabetes, though in clinical trials the benefits of shared decision-making were limited to face-to-face discussions (not online encounters) and to individuals with elevated A1C (>8%) (88). Pharmacotherapy should be started at the time type 2 diabetes is diagnosed, without delay, unless there are contraindications. Medication plans should have adequate efficacy to achieve and maintain individualized treatment goals with respect to glucose lowering, reduction of cardiovascular and kidney disease risks, weight management, and impacts on other health conditions and treatment burden. In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD), the treatment plan should include agents that reduce cardiovascular and kidney disease risk (**Fig. 9.3** and **Table 9.2**) (see also Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management").

In individuals without ASCVD, HF, or CKD, choice of therapy should be informed by considerations of weight management (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), mitigation of

metabolic dysfunction–associated liver disease (MASLD) or metabolic dysfunction–associated steatohepatitis (MASH) risk (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"), and achievement and maintenance of individualized glycemic goals. In general, higher-efficacy approaches, including combination therapy, have greater likelihood of achieving treatment goals. Weight management is a distinct treatment goal, along with glycemic management, as it has multifaceted benefits, including reduction of A1C, reduction in hepatic steatosis, and improvement in cardiovascular risk factors (89–91). For individuals with type 2 diabetes who require initiation or intensification of glucose-lowering therapy to achieve and/or maintain individualized glycemic goals and who do not have additional considerations informing choice of therapy beyond need for glucose lowering, metformin is a commonly used medication that historically has been the first-line treatment for type 2 diabetes (92,93). Metformin is effective and safe, is inexpensive and widely available, and reduces risks of microvascular complications, cardiovascular events, and death (92,94,95). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, is weight neutral, does not cause hypoglycemia, and reduces cardiovascular mortality (96). Metformin is also more effective than dipeptidyl peptidase 4 (DPP-4) inhibitors in lowering A1C and weight when used as monotherapy (97).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration and/or using extended-release formulation. The drug is cleared by kidney filtration, and metformin may be safely used in people with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (98). Very high circulating levels (e.g., as a result of overdose or acute kidney injury) have been associated with lactic acidosis (99). However, the occurrence of this complication is very rare (100) and primarily occurs when the estimated glomerular filtration rate (eGFR) is $<$30 mL/min/1.73 m^2 (101). For people with an eGFR of 30–45 mL/min/1.73 m^2, there is an increased risk for periodic decreases of eGFR to $\leq$30 mL/min/1.73 m^2 which heightens the risk of lactic acidosis. Metformin use is also associated with increased risk of vitamin B12 deficiency and worsening of symptoms of neuropathy (102,103), suggesting periodic testing of vitamin B12 levels (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities").

The comparative glucose-lowering efficacy of different pharmacologic agents has been examined primarily in network meta-analyses, as few prospective clinical trials have compared multiple drug classes head-to-head. In general, the largest reductions in A1C levels are achieved by treatment plans that include insulin, select GLP-1 RAs (particularly semaglutide), and tirzepatide, while DPP-4 inhibitors resulted in the smallest reductions in A1C (104–106). In A Diabetes Outcome Progression Trial (ADOPT), rosiglitazone monotherapy was more effective than metformin and glyburide monotherapies in achieving and maintaining fasting plasma glucose below 180 mg/dL (10 mmol/L) among recently diagnosed individuals with type 2 diabetes whose baseline fasting plasma glucose was 126–180 mg/dL (7–10 mmol/L), while glyburide was least effective (107). More recently, the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) trial compared use of insulin glargine U-100, liraglutide, sitagliptin, and glimepiride as add-on treatments to metformin monotherapy among individuals with type 2 diabetes and baseline A1C 6.8–8.5% (108). It found that at 5 years, all therapies decreased A1C levels but glargine and liraglutide were modestly more effective in achieving and maintaining A1C below 7%, while sitagliptin was least effective. Severe hypoglycemia was significantly more common in those prescribed glargine or glimepiride. An observational study that emulated many of GRADE's design features and included canagliflozin as a comparator arm, but did not include insulin glargine, found that liraglutide was more effective at achieving and maintaining A1C below 7% than sitagliptin, canagliflozin, or glimepiride, which all had comparable effectiveness (108).

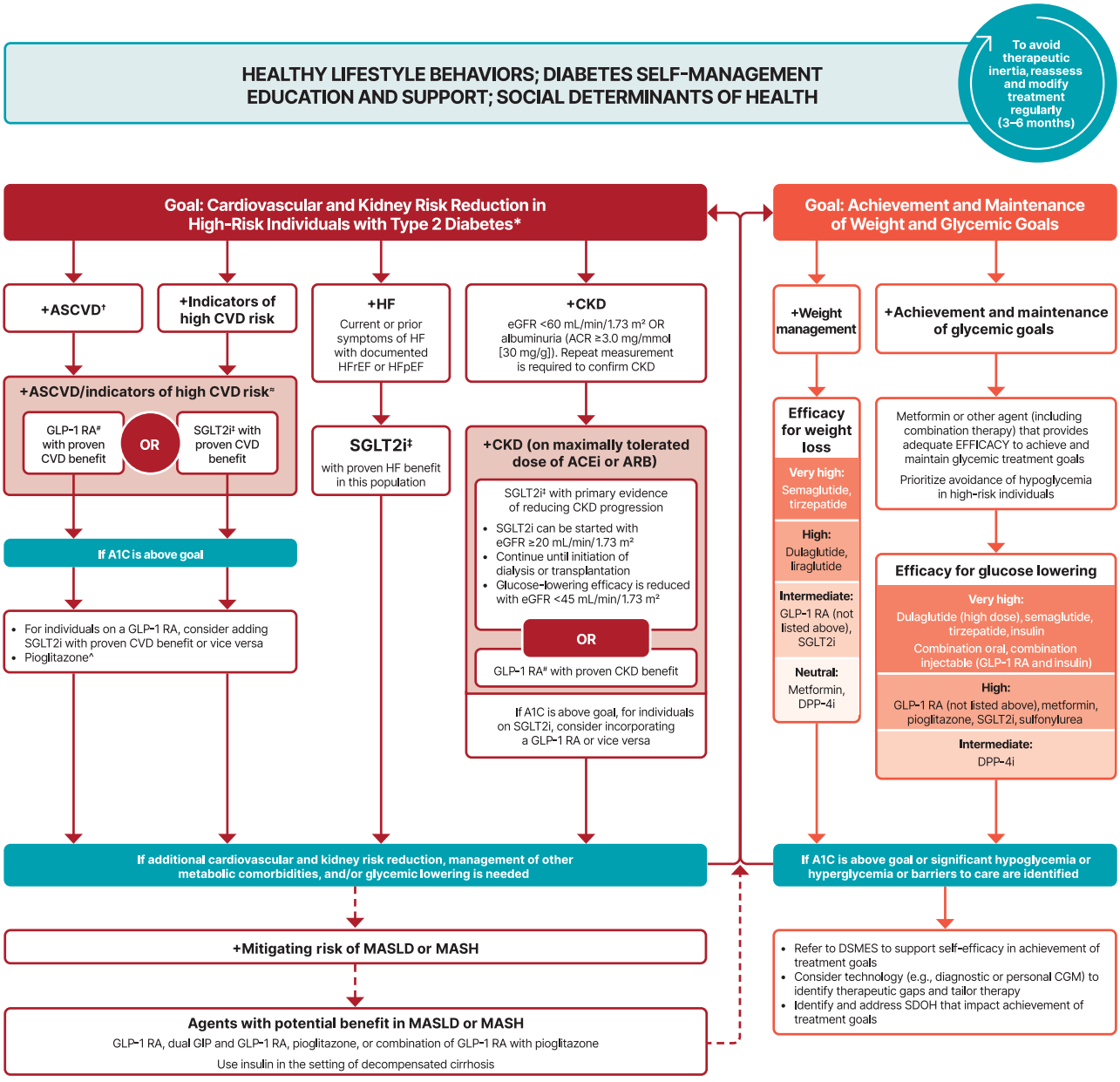
Thus, when choosing a glucose-lowering medication to achieve individualized glycemic goals, we recommend engaging in shared decision-making and considering factors such as glucose-lowering efficacy, the side effect profile, and medication accessibility and affordability (108). In all cases, treatment plans need to be continuously reviewed for efficacy, side effects, hypoglycemia, and treatment burden (**Table 9.2**).

When A1C is $\geq$1.5% above the individualized glycemic goal (see Section 6, "Glycemic Goals and Hypoglycemia," for appropriate goals), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their goal A1C level (89) (**Fig. 9.3** and **Table 9.2**). Insulin should be considered as part of any combination medication plan when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, and ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels $\geq$300 mg/dL ($\geq$16.7 mmol/L) or A1C $>$10% ($>$86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (unexpected weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the medication plan and/or changing to noninsulin agents is possible. Additionally, there is evidence that people with type 2 diabetes and severe hyperglycemia can also be effectively treated with a sulfonylurea, a GLP-1 RA, or dual GIP and GLP-1 RA, though evidence is scarce for individuals with baseline A1C above 10–12% (104,109–111). GLP-1 RAs and tirzepatide have additional benefits over insulin and sulfonylureas, specifically lower risks for hypoglycemia (both) and favorable weight (both), cardiovascular (GLP-1 RAs), kidney (GLP-1 RAs), and liver (both) end points.

Combination Therapy

Because type 2 diabetes is a progressive disease, maintenance of glycemic goals often requires combination therapy. Traditional recommendations have called for the use of stepwise addition of medications to metformin to maintain A1C goals. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (112). However, some data support initial combination therapy for more rapid attainment of glycemic goals (113,114) and later combination therapy for longer durability of glycemic effect (115). Initial combination therapy should be considered in people presenting

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

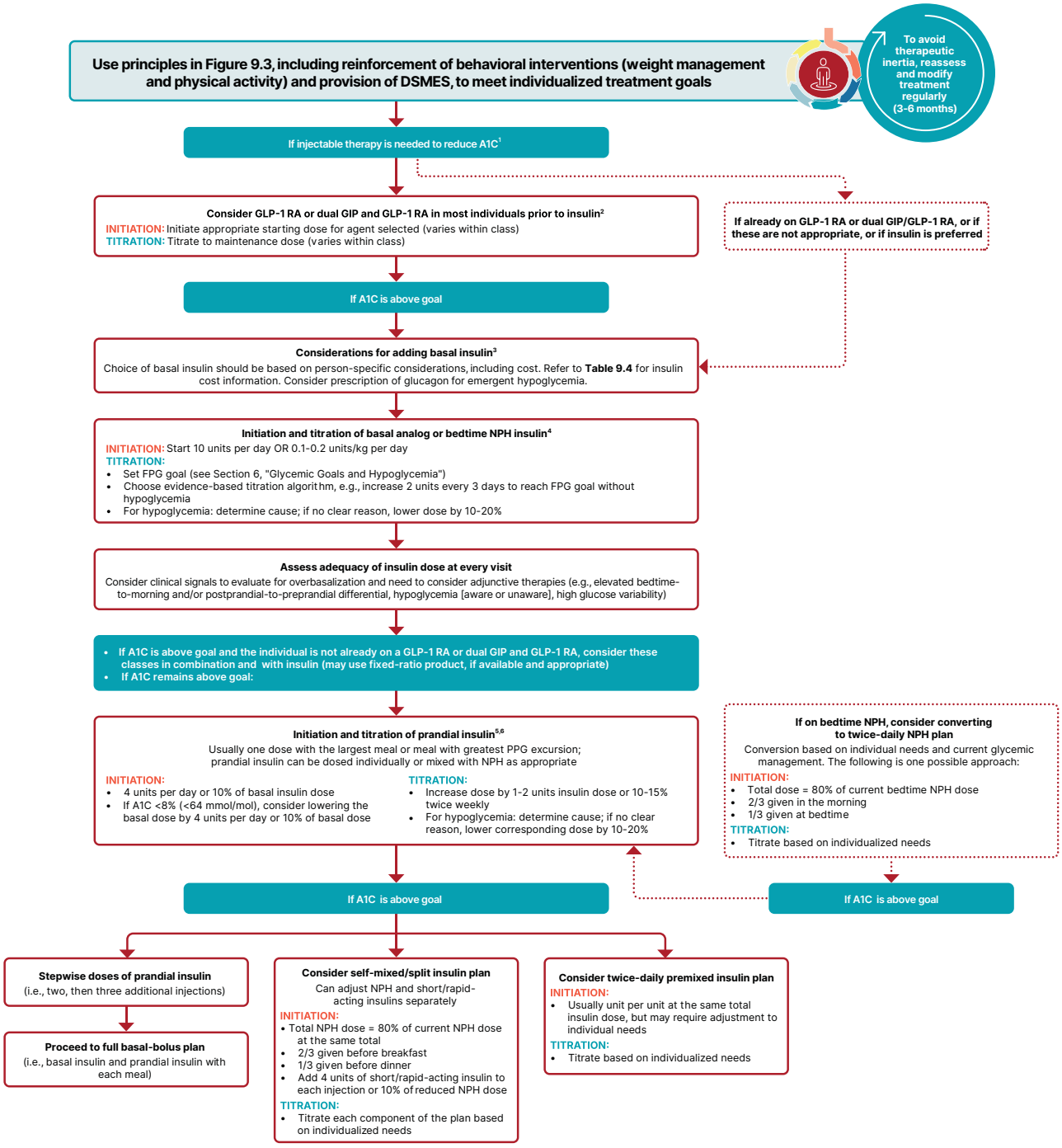
^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. The left side of the algorithm prioritizes mitigation of diabetes-related complications and end-organ effects, while the right side addresses weight and glucose management goals. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; DSMES, diabetes self-management education and support; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes. Adapted from Davies et al. (89).

Table 9.2—Features of medications for lowering glucose in type 2 diabetes

Medication (route of administration)	Glucose-lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Metformin (oral)	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m^2	Neutral	• GI side effects: mitigate with slow dose titration, extended-release formulations, and administration with food. • Potential for vitamin B12 deficiency: monitor and replete as appropriate.
SGLT2 inhibitors (oral)	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels of individual agents for dosage considerations for kidney function • Glucose-lowering effect is minimal at eGFR <45 mL/min/1.73 m^2 and lower; continue for cardiovascular and kidney benefit until dialysis or transplantation	Unknown	• DKA risk in individuals with insulin deficiency (rare in T2D): discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting. • Genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals. • Necrotizing fasciitis of the perineum (Fournier gangrene): rare; prompt treatment if suspected. • Intravascular volume depletion: attention to volume status and blood pressure, particularly when ill or fasting; adjust other volume-contracting agents as applicable; monitor kidney function upon initiation.
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment for dulaglutide, liraglutide, or semaglutide • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	• Thyroid C-cell tumors identified in rodents; human relevance not determined. • Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. • Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. • Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]). • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). • GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	
DPP-4 inhibitors (oral)	Intermediate	No	Neutral	Neutral	Neutral (potential risk: saxagliptin)	Neutral	• Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin) • No dose adjustment required for linagliptin	Unknown	• Pancreatitis has been reported, but causality has not been established. Discontinue if pancreatitis is suspected. • Postmarketing concerns about joint pain (consider discontinuing if debilitating and other treatment options are feasible) and bullous pemphigoid (discontinue if suspected).
Pioglitazone (oral)	High	No	Gain	Potential benefit	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in kidney impairment due to potential for fluid retention	Potential benefit	• Increased risk of HF and fluid retention. Do not use in the setting of HF. • Risk of bone fractures. • Bladder cancer: do not use in individuals with active bladder cancer, and use caution in those with prior history of bladder cancer.
Sulfonylureas (2nd generation) (oral)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in CKD • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Unknown	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text). • Use with caution in individuals at risk for hypoglycemia, particularly if in combination with insulin.
Insulin (human) (SQ; regular insulin also available as inhaled formulation) **Insulin (analogs)** (SQ)	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	Unknown	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs • Risk of hypoglycemia and duration of activity increases with the severity of impaired kidney function. • Refer to device-specific instructions for insulins compatible with different delivery systems (i.e., pumps, connected insulin pens, insulin patches).

CKD, chronic kidney disease; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (106). [2]Tsapas et al. (241). Adapted from Davies et al. (89).



1. Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, and frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit; oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal Insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal Insulin. Consider dosing NPH in the morning for steroid-induced hyperglycemia.
5. Prandial insulin options include injectable rapid- and ultra-rapid-acting analog insulins, injectable short-acting human insulin, or inhaled human insulin.
6. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; PPG, postprandial glucose. Adapted from Davies et al. (242).

with A1C levels 1.5–2.0% above their individualized goal. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (e.g., GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors) may reduce the need for agents that increase the risks of hypoglycemia and weight gain or are less well tolerated. Thus, treatment intensification requires purposeful selection of medications in alignment with multiple individualized person-centered treatment goals simultaneously (**Fig. 9.3**).

Treatment intensification, deintensification, or modification, as appropriate, for people not meeting individualized treatment goals should not be delayed (therapeutic inertia) (116). Results from comparative effectiveness meta-analyses suggest that each new class of oral noninsulin agents when added to metformin generally lowers A1C by approximately 0.7–1.0% (8–11 mmol/mol). Addition of GLP-1 RAs or the dual GIP and GLP-1 RA to metformin usually results in 1 to ≥2% lowering of A1C (104,117,118) (**Fig. 9.3** and **Table 9.2**). We do not recommend using GLP-1 RAs (or the dual GIP and GLP-1 RA) together with a DPP-4 inhibitor as there is no added glucose-lowering benefit beyond that of the GLP-1 RA alone (119–121).

When even greater potency of glucose reduction is needed, basal insulin, either human NPH or a long-acting insulin analog, should be initiated. However, if the individual is not already receiving GLP-1 RA or dual GIP and GLP-1 RA therapy, an agent from these classes should be started first, as it may be sufficient for achieving individualized A1C goals but with lower risk of hypoglycemia and with favorable weight, cardiovascular, kidney, and liver profiles. While most GLP-1 RAs are injectable medications, an oral formulation of semaglutide is commercially available (122). In trials analyzing the addition of an injectable GLP-1 RA, dual GIP and GLP-1 RA, or insulin in people needing further glucose lowering, glycemic efficacies of GLP-1 RAs and the dual GIP and GLP-1 RA were similar to or greater than that of basal insulin (123–130). GLP-1 RAs and dual GIP and GLP-1 RA in these trials also had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support high-potency GLP-1 RAs and dual GIP and GLP-1 RA as the preferred options for individuals requiring more intensive glucose management (**Fig. 9.4**).

In individuals who are intensified to insulin therapy, combination therapy with a GLP-1 RA or a dual GIP and GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effects, as well as weight and hypoglycemia benefits, than treatment intensification with insulin alone (89,131). However, cost, accessibility, and tolerability are important considerations for GLP-1 RA and dual GIP and GLP-1 RA use.

In all cases, treatment plans need to be continuously reviewed for efficacy, side effects (including hypoglycemia), and treatment burden (**Table 9.2**). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, hypoglycemia, intolerable side effects, new contraindications, expense, or a change in glycemic goals (e.g., in response to development of comorbidities). See below for cost considerations of glucose-lowering therapies (MEDICATION COSTS AND AFFORDABILITY). Section 13, "Older Adults," has a full discussion of treatment considerations in older adults. Treatment deintensification may also be needed in the setting of weight loss and/or optimization of lifestyle behaviors, when fewer pharmacologic agents are needed to maintain A1C goals. In this case, we recommend preferential deescalation of therapies that are most likely to cause side effects, hypoglycemia, and/or treatment burden and do not have cardiovascular, kidney, or metabolic benefits for continued use.

Glucose-Lowering Therapy for People With Cardiovascular Disease or Risk Factors for Cardiovascular Disease

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated cardiovascular benefit (**Table 9.2**) is recommended independent of A1C, with or without metformin use, and in consideration of person-specific factors (**Fig. 9.3**). Individuals with these comorbidities already achieving their individualized glycemic goals with other medications may benefit from switching to these preferred medications to reduce risk of ASCVD, HF, and/or CKD in addition to achieving glycemic goals (see Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). This is particularly important because SGLT2 inhibitors and GLP-1 RAs are associated with lower risk of hypoglycemia and individuals with ASCVD, HF, and CKD have higher hypoglycemia risk than individuals without these conditions (132).

Individuals at lower risk for ASCVD may still benefit from GLP-1 RA therapy to reduce their risk of future cardiovascular events. The GRADE trial, which was designed to examine the comparative effectiveness of insulin glargine U-100, glimepiride, liraglutide, and sitagliptin in individuals with relatively short duration of diabetes (and, due to study eligibility criteria, low ASCVD risk) with respect to achieving and maintaining A1C below 7%, found that individuals treated with liraglutide had a slightly lower risk of cardiovascular disease than individuals receiving the other three treatments (hazard ratio 0.7 [95% CI 0.6–0.9]), although no significant differences were found for major adverse cardiovascular events, hospitalization for HF, or cardiovascular death (133). Individuals with type 2 diabetes and moderate levels of CVD risk appear to derive cardiovascular and mortality benefits with preferential use of GLP-1 RA and SGLT2 inhibitors compared with sulfonylurea or DPP-4 inhibitors (134). Similarly, while greater reductions in HF hospitalization risk are observed with SGLT2 inhibitor therapy in individuals with higher baseline HF risk, some benefit is observed across the full range of HF risk (135).

Glucose-Lowering Therapy for People With Chronic Kidney Disease

For individuals with type 2 diabetes and CKD, considerations for selection of glucose-lowering medications include their effectiveness and safety when eGFR is reduced as well as the potential to impact CKD progression, CVD risk, and hypoglycemia (136). Preferred medications for glucose management in individuals with CKD are GLP-1 RAs and SGLT2 inhibitors (can be initiated if eGFR is above 20 mL/min/1.73 m^2). GLP-1 RAs are effective in lowering glucose levels, regardless of kidney function, with a low risk for hypoglycemia, and a recent clinical trial suggests that the GLP-1 RA semaglutide has a beneficial effect on CVD, mortality, and kidney outcomes among people with CKD,

leading to the recommendation that semaglutide can be used as another first-line agent for people with CKD (137,138). Other GLP-1 RAs (liraglutide and dulaglutide) may also have CKD benefits, but no other dedicated kidney trials have been published. Similarly, no dedicated kidney outcomes studies for the dual GIP and GLP-1 RA (tirzepatide) have been published. Dedicated kidney outcomes trials in people with CKD and type 2 diabetes have shown that the SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have beneficial effects on slowing progression of CKD and CV outcomes in this population (139–141). However, their ability to lower glucose levels declines when the eGFR falls below 45 mL/min/1.73 m^2 (142–144). Metformin is also a preferred agent for those with CKD due to its well-documented efficacy and safety profile for all people with type 2 diabetes. However, there is no documented direct kidney benefit. Importantly, metformin should not be started in those whose eGFR is $<$45 mL/min/1.73 m^2. For those already treated with metformin, the dose of metformin should be reduced once eGFR is $<$45 mL/min/1.73 m^2 and should be stopped once eGFR is $<$30 mL/min/1.73 m^2 (98). A secondary analysis of the GRADE trial found that insulin glargine, liraglutide, sitagliptin, and glimepiride did not prevent the development of CKD when added to metformin monotherapy in individuals without underlying CKD (145). Importantly, an SGLT2 inhibitor was not included in the GRADE trial.

Individuals with CKD, particularly advanced CKD and kidney failure, are at high risk for hypoglycemia (132). If treated with insulin and/or sulfonylureas, treatment needs to be closely monitored and adjusted as eGFR declines and individuals need to be educated about and closely monitored for hypoglycemia occurrence (136). See Section 11, "Chronic Kidney Disease and Risk Management," for more details about prevention and treatment of CKD in individuals with diabetes.

Glucose-Lowering Therapy for People With Metabolic Comorbidities

Many adults with diabetes, either type 2 diabetes or type 1 diabetes, with obesity are at high risk of developing MASLD or MASH as well as MASH cirrhosis. Hence, the presence of MASLD or MASH should be a consideration when choosing glucose-lowering therapies. Accruing randomized clinical trial data suggest that pioglitazone, GLP-1 RA, and a dual GIP and GLP-1 RA have potential benefits in terms of decreasing hepatic steatosis and in the resolution of MASH without worsening of fibrosis in individuals with biopsy-proven MASH or those at higher risk of clinically significant liver fibrosis identified with noninvasive tests (146–153). Combination therapy with pioglitazone plus GLP-1 RA should also be considered for treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at higher risk of clinically significant liver fibrosis identified with noninvasive tests, as such therapy is safe and effective and has been shown to reduce hepatic steatosis (154–156). It is important to note that these studies are based on phase 2 clinical trials and await further phase 3 confirmation of evidence. However, these plans are preferred as they offer potential benefit compared with lack of histological benefit (or clinical trial data) from other glucose-lowering therapies in MASLD. Further details regarding liver health in diabetes can be found in Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities."

Obesity is present in over 90% of people with type 2 diabetes, and in these individuals weight management is a key treatment goal, along with glucose lowering. In the setting of obesity, the choice of glucose-lowering medications should take into consideration their effects on weight. Insulins, sulfonylureas, and thiazolidinediones can promote weight gain and should be used judiciously and at the lowest possible dose. Glucose-lowering medications that promote weight loss should be prioritized. Of the currently available agents, tirzepatide and semaglutide have the highest efficacy in terms of glucose lowering as well as weight loss, followed by dulaglutide, liraglutide, and extended-release exenatide (157–161). Other glucose-lowering medications (metformin, SGLT2 inhibitors, DPP-4 inhibitors, dopamine agonists, bile acid sequestrants, and α-glucosidase inhibitors) are weight neutral or have a modest beneficial effect on weight. These medications can be used as add-on therapies in people with type 2 diabetes and obesity who require additional glucose lowering or if the more effective medications are not tolerated, are contraindicated, or are unavailable. Metabolic surgery, especially Roux-en-Y gastric bypass and sleeve gastrectomy, are very effective interventions to achieve both weight and glycemic goals and have additional health benefits beyond improving metabolism (162). Further details regarding treatment of obesity can be found in Section 8 ("Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See INSULIN ADMINISTRATION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to individuals with diabetes, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure. The utility and importance of insulin to achieve and maintain glycemic goals once progression of the disease overcomes the effect of other agents as well as for temporary use for acute situations (such as hospitalization, acute illness, or high-dose glucocorticoid therapy) should be emphasized. Educating and involving people with diabetes in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin on self-titration of insulin doses based on glucose monitoring improves glycemic management (163). Comprehensive education regarding glucose monitoring, nutrition, physical activity, contingency planning (for illness, fasting, or medication unavailability), and the prevention and appropriate treatment of hypoglycemia are critically important for all individuals using insulin. Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (64,65). See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for guidance on diabetes self-management education.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to noninsulin glucose-lowering medications. For individuals with type 2 diabetes, starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as

needed to achieve and maintain glycemic goals. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (164,165). Attainment of fasting glucose goals can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine and detemir) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin (166). Longer-acting basal analogs (U-300 glargine or degludec) convey a lower nocturnal hypoglycemia risk than U-100 glargine (167,168). It is important to understand how to convert individuals from one basal insulin to another, as switching insulins may be required due to the availability of more clinically appropriate insulin alternatives, removal of a product from the market (i.e., insulin detemir), or changes to insurance coverage. Often doses can be converted unit for unit and subsequently adjusted based on glucose monitoring; however, an initial dose reduction of 10–20% can be used for individuals in very tight management or at high risk for hypoglycemia and is typically needed when switching from insulin detemir or U-300 glargine to another insulin (169). Clinicians should also be aware of the potential for overbasalization with insulin therapy (i.e., use of higher than clinically necessary and appropriate dose of basal insulin, typically masking insufficient mealtime insulin). Clinical signals that should prompt evaluation for overbasalization include high bedtime-to-morning or preprandial-to-postprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL [≥2.8 mmol/L]), hypoglycemia (aware or unaware), and high glucose variability. Evidence of overbasalization should prompt reevaluation of the glucose-lowering treatment plan to better address postprandial hyperglycemia (170).

Combination Injectable Therapy and Prandial Insulin

If basal insulin has been titrated to an acceptable fasting blood glucose level and A1C remains above goal, if there is evidence of significant postprandial hyperglycemia, or if signs of overbasalization are present, advancement to combination injectable therapy is necessary (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of prandial insulin (131,171). If an individual is not already being treated with a GLP-1 RA or dual GIP and GLP-1 RA, a GLP-1 RA (either as an individual product or in a fixed-ratio combination with a basal insulin product) or dual GIP and GLP-1 RA should be considered prior to starting prandial insulin to address prandial management and to lower the risks of hypoglycemia and weight gain associated with insulin therapy (131,172).

Further intensification of insulin therapy entails adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a plan with multiple prandial doses if necessary (173). We suggest starting with a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion. The prandial insulin plan can then be intensified based on individual needs (**Fig. 9.4**). Alternatively, for an individual treated with basal insulin in whom additional prandial coverage is desired but administering insulin prior to one or more meals is not feasible, the medication plan can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial plans offer greater flexibility for individuals who eat on irregular schedules, have variable meal content, or otherwise benefit from greater individualization and flexibility in insulin administration. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (for example, 70/30) formulations, are often less costly alternatives to insulin analogs.

Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (174). Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported meaningful differences in A1C or hypoglycemia (175,176). Titration of prandial insulin can be based on home self-monitored blood glucose or CGM. When significant additions to the prandial insulin dose are made, particularly with the evening meal, consideration should be given to decreasing basal insulin to reduce risk of hypoglycemia. When initiating intensification of insulin therapy, metformin, SGLT2 inhibitors, and GLP-1 RAs (or a dual GIP and GLP-1 RA) should be maintained, unless adverse effects (including significant treatment burden) or contraindications are present. Use of sulfonylureas, meglitinides, and DPP-4 inhibitors should be limited or discontinued, as these medications do not have additional beneficial effects on cardiovascular, kidney, weight, or liver outcomes and (for sulfonylureas and meglitinides) increase risk of hypoglycemia and weight gain. Adjunctive use of pioglitazone may help to improve glycemia and reduce the amount of insulin needed, although potential side effects should be considered.

Once a basal-bolus insulin plan is initiated, dose titration is important, with adjustments made in both prandial and basal insulins based on blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). In some people with type 2 diabetes with significant clinical complexity, multimorbidity, and/or treatment burden, it may become necessary to simplify or deintensify complex insulin plans to decrease risk of hypoglycemia and improve quality of life (see Section 13, "Older Adults").

Concentrated Insulins

Concentrated preparations may be more convenient (fewer injections to achieve goal dose) and comfortable (less volume to inject the desired dose and/or less injection effort) for individuals and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin. Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-500 regular insulin has distinct pharmacokinetics with similar onset but a delayed, blunted, and prolonged peak effect and longer duration of action compared with U-100 regular insulin; thus, it has characteristics more like a premixed intermediate-acting (NPH) and regular insulin product and can be used as two or three daily injections (177,178). U-300 glargine and U-200 degludec are three and two times, respectively, as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action

than U-100 glargine but modestly lower efficacy per unit administered (179–181). The U-200 formulations of insulin degludec, insulin lispro, and insulin lispro-aabc have pharmacokinetics similar to those of their U-100 counterparts (182–184). While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors. If U-500 regular insulin vials are prescribed, the prescription should be accompanied by a prescription for U-500 syringes to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulin is primarily administered via subcutaneous injection or infusion. Administration devices provide some additional variation in the subcutaneous delivery beyond vial and syringe versus insulin pen. Those devices include continuous insulin pumps (programmable or automated basal and bolus settings and fixed basal and bolus settings) and bolus-only insulin patch pump. In addition, prandial or correction insulin doses may be administered using inhaled human insulin. Inhaled insulin is available as monomers of regular human insulin; studies in individuals with type 1 diabetes suggest that inhaled insulin has pharmacokinetics similar to those of RAA (185). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with the RAA insulin lispro as well as clinically meaningful A1C reductions and weight reductions compared with the RAA insulin aspart over 24 weeks (186–188). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 s [FEV_1]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV_1) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

ADDITIONAL RECOMMENDATIONS FOR ALL INDIVIDUALS WITH DIABETES

Recommendations

9.27 Monitor for signs of overbasalization during insulin therapy, such as significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability. When overbasalization is suspected, a thorough reevaluation should occur promptly to further tailor therapy to the individual's needs. **E**

9.28 Glucagon should be prescribed for all individuals requiring intensive insulin therapy or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not require reconstitution are preferred. **B**

9.29 Routinely assess all people with diabetes for financial obstacles that could impede their diabetes management. Clinicians, members of the diabetes care team, and social services professionals should work collaboratively, as appropriate and feasible, to support these individuals by implementing strategies to reduce costs, thereby improving their access to evidence-based care. **E**

9.30 In adults with diabetes and cost-related barriers, consider use of lower-cost medications for glycemic management (i.e., metformin, sulfonylureas, thiazolidinediones, and human insulin) within the context of their risks for hypoglycemia, weight gain, cardiovascular and kidney events, and other adverse effects. **E**

Several key aspects of insulin management that are relevant to all people with diabetes requiring insulin therapy, including available formulations, insulin plans and delivery systems, administration technique, and overbasalization, were discussed earlier in this section. Additional considerations for glucose-lowering therapy that may be relevant to people with all types of diabetes include glucagon coprescription and affordability of diabetes therapies.

Glucagon

Due to the risk of hypoglycemia with insulin treatment, all individuals treated with insulin or who are at high risk for hypoglycemia should be prescribed glucagon. Individuals with diabetes who are prescribed glucagon and those in close contact with them should be educated on the use and administration of the individual's prescribed glucagon product. The glucagon product available to individuals may differ based on coverage and cost; however, products that do not require reconstitution are preferred for ease of administration (189,190). Clinicians should routinely review the individual's access to glucagon, as appropriate glucagon prescribing is low (191–193). See Section 6, "Glycemic Goals and Hypoglycemia," for additional information on hypoglycemia and glucagon in individuals with diabetes.

Medication Costs and Affordability

Costs for noninsulin and insulin diabetes medications have increased dramatically over the past two decades, and an increasing proportion of cost is now passed on to people with diabetes and their families (194). **Table 9.3** provides cost information for currently approved noninsulin therapies, while **Table 9.4** provides these data for insulin. Of note, prices listed are average wholesale prices (AWP) (195) and National Average Drug Acquisition Costs (NADAC) (196); these estimates allow for a comparison of drug prices but do not represent the actual costs to people with diabetes because they do not account for various discounts, rebates, and other price adjustments often involved in prescription sales that affect the actual cost incurred by the individual. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (197); cost-reducing strategies may improve medication-taking behavior in some cases (198).

Although caps on out-of-pocket costs for insulin have been implemented for individuals with Medicare and for individuals on some commercial health plans, and three major insulin manufacturers have capped costs at $35 per month per insulin (199–202) (see Section 1, "Improving Care and Promoting Health in Populations"), individuals with high-deductible health plans and those without insurance coverage can incur very high out-of-pocket expenses for glucose-lowering therapies. Moreover, no such caps exist for diabetes durable medical equipment (i.e., equipment for glucose monitoring and insulin administration) or for

noninsulin medications. It is therefore essential to screen all people with diabetes for financial concerns and cost-related barriers to care and to engage members of the health care team, including pharmacists, certified diabetes care and education specialists, social workers, community health workers, community paramedics, and others, to identify cost-saving opportunities for medications, diabetes durable medical equipment, and glucagon (203).

SPECIAL CIRCUMSTANCES AND POPULATIONS

Recommendations

9.31a Use of compounded products that are not approved by the FDA is not recommended due to uncertainty about their content and resulting concerns about safety, quality, and effectiveness. **E**

9.31b If a glucose-lowering medication is unavailable (e.g., in shortage), it is recommended to switch to a different FDA-approved medication with similar efficacy, as clinically appropriate. **E**

9.31c Upon resolution of the unavailability (e.g., shortage), reassess the appropriateness of resuming the original FDA-approved medication. **E**

9.32a Individuals with diabetes of childbearing potential should be counseled on contraception options **A** and the impact of some glucose-lowering medications on contraception efficacy. **C**

9.32b A person-centered shared decision-making approach to preconception planning is essential for all individuals with diabetes and of childbearing potential. **A** Preconception planning should address attainment of glycemic goals, **A** the time frame for discontinuing noninsulin glucose-lowering medications, **E** and optimal glycemic management in preparation for pregnancy. **A**

9.33 Educate individuals with diabetes who are at risk for developing diabetic ketoacidosis and/or follow a ketogenic eating pattern and who are treated with SGLT inhibitors on the risks and signs of ketoacidosis and methods of risk mitigation management, and provide them with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate). **E**

Therapeutic Strategies With Medication Unavailability

Health care professionals and people with diabetes struggle when medication supplies are insufficient to meet the demand. Recent examples of such circumstances include recalls involving a number of metformin products and the marked increase in demand for agents from the GLP-1 RA and dual GIP and GLP-1 RA classes. The latter circumstance led to such a low level of availability that products were determined by the FDA to be in shortage (204). To assist with supply of medications during the time they are in shortage (as signaled by their inclusion on the FDA Drug Shortages Database), compounding pharmacies and outsourcing compounding facilities are allowed to make copies, or products that are essentially duplicates of the marketed FDA-approved product (205). A significant number of concerning reports regarding safety and efficacy of compounded incretin products have emerged, however, including using salt forms of the FDA-approved product's active ingredient that are not proven safe or effective for use in humans, incorporation of additional ingredients not clinically tested when mixed with incretin products (e.g., vitamin B12 and vitamin B6), products provided in nonstandard concentrations and doses and/or multidose vials and prefilled syringes not accompanied by education or labeling to mitigate administration errors, and the emergence of counterfeit products that pose significant risk to individuals taking these products (206–209). Due to safety, quality, and effectiveness concerns, use of non–FDA-approved compounded products is not recommended (210). Instead, consider switching to a different FDA-approved medication as clinically appropriate (211). Once the desired FDA-approved product becomes available, individuals should be reassessed to determine the appropriateness of resuming the product based on their current care needs, preferences, and priorities.

Care Considerations for Individuals of Childbearing Potential

The impact of glycemia during pregnancy is well understood; however, evidence for the safe use of noninsulin glucose-lowering medications is limited (see Section 15, "Management of Diabetes in Pregnancy"). Studies on the efficacy and safety of glucose-lowering medications exclude individuals who are pregnant and require individuals of childbearing potential to use one or two forms of contraception. It is recommended that individuals of childbearing potential use a form of contraception when also taking glucose-lowering medications with unknown risks, limited evidence on safety, or known risks during pregnancy, regardless of the individual's intention to become pregnant, as many pregnancies are unplanned. The options for contraception should be discussed with all individuals of childbearing potential with diabetes and should include information regarding the potential impact of glucose-lowering medications on the effectiveness of contraception. Medications that impact gastrointestinal emptying time (e.g., GLP-1 RAs or dual GIP and GLP-1 RA) may affect the absorption of orally administered medications, including oral contraception. The impact on gastric emptying with GLP-1 RAs and the dual GIP and GLP-1 RA is highest at initiation and with dosage increases and then diminishes with continued administration (212). Tirzepatide, the dual GIP and GLP-1 RA, was shown to impact the levels of oral contraception during the time of its highest impact on gastric emptying; the GLP-1 RAs may impact the levels of oral contraception as well but to a lesser extent than tirzepatide (213,214). Thus, individuals starting or increasing doses of tirzepatide who also take oral contraception should use a second form of contraception until the maintenance dose of tirzepatide is achieved and used for at least 4 weeks (215).

Preconception counseling should be part of the routine care of individuals with diabetes who have childbearing potential. Counseling should include the known benefits and risks of glucose-lowering medications as well as other medications (e.g., lipid-lowering and antihypertensive therapies) during pregnancy and recommendations for when changes in medications should occur prior to pregnancy (see Section 15, "Management of Diabetes in Pregnancy," for more information on preconception counseling and glucose-lowering treatment during pregnancy).

Therapeutic Strategies for Individuals Receiving Cancer Treatment

Hyperglycemia due to chemotherapy may either be transient (improving upon treatment cessation) or represent permanent

Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound	Dosage strength/ product (if applicable)	Maximum approved daily dose†	Median AWP (min, max)*	Median NADAC (min, max)*
Biguanides	• Metformin	500 mg (ER)	2,000 mg	$89 ($5, $6,719)	$3 ($3, $79)
		850 mg (IR)	2,550 mg	$108 ($4, $189)	$2
		1,000 mg (IR)	2,000 mg	$87 ($3, $146)	$1
		1,000 mg (ER)	2,000 mg	$1,884 ($242, $7,214)	$26 ($21, $31)
		500 mg (Sol)	2,000 mg	$1,144 ($810, $1478)	$427
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	8 mg	$73 ($71, $198)	$2
	• Glipizide	10 mg (IR)	40 mg	$72 ($67, $91)	$5
		10 mg (XL/ER)	20 mg	$48 ($46, $48)	$8
	• Glyburide	6 mg (micronized)	12 mg	$54 ($48, $71)	$13
		5 mg	20 mg	$82 ($63, $432)	$7
Thiazolidinedione	• Pioglitazone	45 mg	45 mg	$348 ($7, $349)	$3
α-Glucosidase inhibitors	• Acarbose	100 mg	300 mg	$106 ($104, $378)	$20
	• Miglitol	100 mg	300 mg	$294 ($241, $346)	$320
Meglitinides	• Nateglinide	120 mg	360 mg	$155	$23
	• Repaglinide	2 mg	16 mg	$878 ($799, $897)	$26
DPP-4 inhibitors	• Alogliptin	25 mg	25 mg	$234	$145
	• Linagliptin	5 mg	5 mg	$630	$503
	• Saxagliptin	5 mg	5 mg	$524 ($523, $524)	$165
	• Sitagliptin	100 mg	100 mg	$588	$550
SGLT2 inhibitors	• Bexagliflozin	20 mg	20 mg	$47	NA
	• Canagliflozin	300 mg	300 mg	$718	$574
	• Dapagliflozin	10 mg	10 mg	$664	$352
	• Empagliflozin	25 mg	25 mg	$733	$586
	• Ertugliflozin	15 mg	15 mg	$428	$343
GLP-1 RAs	• Dulaglutide	4.5 mg pen	4.5 mg‡	$1,173	$941
	• Exenatide	10 mg pen	20 mg	$1,020	$818
	• Exenatide (ER)	2 mg pen	2 mg‡	$993	$1,101
	• Liraglutide	18 mg/3 mL pen	1.8 mg	$929	$1,077
	• Semaglutide	2 mg pen	2 mg‡	$1,162	$933
		14 mg (tablet)	14 mg	$1,162	$933
Dual GIP and GLP-1 RA	• Tirzepatide	15 mg pen	15 mg‡	$1,283	$1,030
Bile acid sequestrant	• Colesevelam	625 mg tabs	3.75 g	$692 ($674, $712)	$47
		3.75 g suspension	3.75 g	$674 ($673, $675)	$115
Dopamine-2 agonist	• Bromocriptine	0.8 mg	4.8 mg	$1,220	$981
Amylin mimetic	• Pramlintide	120 μg pen	120 μg§	$2,952	NA

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. AWP (195) and NADAC (196) prices are as of 1 July 2024. *Calculated for 30-day supply (AWP or NADAC unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. †Used to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. ‡Administered once weekly. §AWP and NADAC calculated based on 120 μg three times daily.

diabetes. Immune checkpoint inhibitors (ICIs) (agents that block programmed cell death protein 1 [PD-1] and programmed cell death protein ligand 1 [PD-L1]) suppress physiologic blocks on immune responses, which can result in autoimmune toxicities, including autoimmune diabetes (incidence approximately ≤1%). ICI-diabetes is an insulin-deficient phenotype that presents as acute severe hyperglycemia or DKA and appears to occur more abruptly than type 1 diabetes (216–218).

Alpelisib, a phosphatidylinositol-3-kinase (PI3K) inhibitor, frequently results in hyperglycemia by inhibiting PI3Kα, which systemically blocks the intracellular action of insulin, resulting in a transient state of insulin resistance and hyperglycemia (219). Hyperglycemia occurs early during therapy (median time of onset of about 2 weeks from initiation of alpelisib) with an incidence of ∼60% overall and typically resolves upon treatment cessation (220–222). Metformin is the first-line oral agent to treat alpelsib-induced hyperglycemia, and prophylactic initiation of metformin has been recommended for people with prediabetes receiving alpelsib (223). SGLT2 inhibitors and pioglitazone are appropriate second- or third-line agents, depending on side effect and clinical profiles, and may be used in combination with or without metformin. Insulin and sulfonylureas should be considered last-line agents, as insulin can reactivate the PI3K pathway, negating the effects of alpelisib (223,224).

Table 9.4—Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage form or product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Aspart	U-100 vial	$87†	$70†
		U-100 cartridge	$107†	$86†
		U-100 prefilled pen	$112†	$90†
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Glulisine	U-100 vial	$102	$82
		U-100 prefilled pen	$132	$105
	• Inhaled insulin	Inhalation cartridges	$1,503	$1,298
	• Lispro	U-100 vial	$30†	$24†
		U-100 cartridge	$123	$98
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$263
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	$339
	• Lispro follow-on product	U-100 vial	$118	$94
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$58 ($54, $58)‡	$46 ($43, $58)‡
		U-100 prefilled pen	$73 ($54, $178)	$58
Intermediate-acting	• Human NPH	U-100 vial	$58 ($54, $58)‡	$45 ($43, $46)‡
		U-100 prefilled pen	$93 ($73, $113)	$74 ($58, $91)
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Degludec	U-100 vial	$142†	$114†
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$85†	$114†
	• Glargine	U-100 vial	$77	$109†
		U-100 prefilled pen	$77	$109†
		U-300 prefilled pen	$152†	$122†
	• Glargine biosimilar/follow-on products	U-100 vial	$118 ($76,† $323)	$61†
		U-100 prefilled pen	$118 ($74,† $323)	$59 ($59,† $209)
Premixed insulin products	• Aspart 70/30	U-100 vial	$87†‡	$69†‡
		U-100 prefilled pen	$112†‡	$90†‡
	• Lispro 50/50	U-100 vial	$102	NA
		U-100 prefilled pen	$127	$102
	• Lispro 75/25	U-100 vial	$102	$82
		U-100 prefilled pen	$127†	$102†
	• NPH/regular 70/30	U-100 vial	$58 ($54, $58)	$45 ($43, $46)
		U-100 prefilled pen	$73 ($73, $113)‡	$74 ($58, $90)‡
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 mg prefilled pen	$1,037	$791
	• Glargine/lixisenatide	100/33 mg prefilled pen	$713	$570

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (195) and NADAC (196) prices as of 1 July 2024. *AWP or NADAC calculated as in **Table 9.3**. †Unbranded product prices used when available. ‡AWP and NADAC data presented do not include human insulins (approximately $25/vial or $43/box of 5 pens) or select analog insulins (approximately $73/vial or $86/box of 5 pens) available at Walmart; median listed alone when only one product and/or price.

mTOR kinase inhibitors, including everilomus, cause hyperglycemia by interfering with insulin signaling, leading to impaired insulin secretion and increased insulin resistance. Metformin is the first-line treatment of hyperglycemia secondary to mTOR inhibitor treatment, with insulin and other noninsulin treatments added in a stepwise fashion dependent on glucose level (225).

Therapeutic Strategies for Individuals With Other Types of Diabetes

Individuals with pancreatogenic diabetes may require early insulin initiation to achieve and maintain glycemic goals. In

individuals with a history of pancreatitis, use of incretin medications (i.e., GLP-1 RAs, GIP and GLP-1 RA, and DPP-4 inhibitors) should be avoided (see Section 2, "Diagnosis and Classification of Diabetes"). Individuals with cystic fibrosis–related diabetes should be treated with insulin therapy; insulin pump therapy, including automated insulin delivery systems, should be considered when appropriate (226).

There are limited data to inform the optimal pharmacologic management of posttransplant diabetes (227) (see Section 2, "Diagnosis and Classification of Diabetes"). While immediately posttransplant many individuals require insulin therapy, noninsulin therapies can be used for long-term management. Studies of metformin, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 RAs, and pioglitazone in individuals who have undergone kidney, heart, or liver transplantation have demonstrated effectiveness and safety but are limited by small sample sizes, short follow-up, and risk of bias due to retrospective or single-arm prospective designs (228). Metformin should be used with caution; it should not be initiated if eGFR is $<$45 mL/min/1.73 m^2, it should be stopped with eGFR $\geq$30 mL/min/1.73 m^2, and it should not be used in the setting of clinical instability due to concerns for acute kidney injury and lactic acidosis. Metformin use may be associated with lower risks of cardiac allograph vasculopathy after heart transplantation (229) and all-cause, malignancy-related, and infection-related mortality after kidney transplantation (230). GLP-1 RA therapy may be preferred for many individuals due to the demonstrated benefit of GLP-1 RAs on cardiovascular, kidney, weight, and liver outcomes. Studies have not found evidence of drug interaction with immunosuppression, including finding no changes in dosing or toxicity (231–233). SGLT2 inhibitors may be similarly preferred for individuals with ASCVD, HF, and CKD and appear to be safe and effective in posttransplantation diabetes. However, there is increased risk of genitourinary tract infection, which is a concern in individuals receiving immunosuppression and in those who have undergone kidney transplantation.

Individuals with maturity-onset diabetes of the young due to *HNF1A* and *HNF4A* mutations can be treated with low-dose sulfonylurea therapy but may ultimately require insulin therapy (234) (see Section 2, "Diagnosis and Classification of Diabetes") (**Table 2.7**). For those with *HNF1A* mutations, addition of a DPP-4 inhibitor to the sulfonylurea may help improve glycemic variability and attainment of glycemic goals (235). Individuals with neonatal diabetes due to *KCNJ22* and *ABCC8* mutations can be treated with high-dose sulfonylureas, while those with *INS*, *GATA6*, *EIF2AK3*, and *FOXP3* mutations require insulin therapy (234).

SGLT Inhibition and Risk of Ketosis

Individuals with type 1 diabetes (84,236) and insulin-deficient type 2 diabetes are at increased risk for DKA with SGLT inhibitor therapy. SGLT inhibitor–associated DKA occurs in approximately 4% of people with type 1 diabetes; the risk can be 5–17 times higher than that in people with T1D not treated with SGLT inhibitors (237). It is important to note that SGLT2 inhibitors are not approved for use in people with type 1 diabetes. In contrast, DKA is uncommon in people with type 2 diabetes treated with SGLT inhibitors, with an estimated incidence of 0.6–4.9 events per 1,000 person-years (238). Risk factors for DKA in individuals with either type 1 or type 2 diabetes treated with SGLT inhibitors include very-low-carbohydrate diets, prolonged fasting, dehydration, excessive alcohol intake, and other common precipitating factors (84,236). Up to a third of people treated with SGLT2 inhibitors who developed DKA present with glucose levels $<$200 mg/dL (11.1 mmol/L) (239), and in one study 71% presented with glucose levels $\leq$250 mg/dL (13.9 mmol/L) (240); therefore, it is important to educate at-risk individuals about the signs and symptoms of DKA and DKA mitigation and management and to prescribe accurate tools for ketone measurement. Individuals who have experienced DKA should not be treated with SGLT inhibition. Additional guidance on DKA risk mitigation is available in Section 6, "Glycemic Goals and Hypoglycemia."

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