9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026

*American Diabetes Association Professional Practice Committee for Diabetes**

Diabetes Care 2026;49(Suppl. 1):S183–S215 | https://doi.org/10.2337/dc26-S009

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee for Diabetes, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

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 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 depending on the person's or caregiver's needs or preferences. 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**

9.4 Insulin treatment plans and insulin-taking behaviors should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted to incorporate specific factors that affect 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, 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

**A complete list of members of the American Diabetes Association Professional Practice Committee for Diabetes can be found at https://doi.org/10.2337/dc26-SINT.*

Duality of interest information for each contributor is available at https://doi.org/10.2337/dc26-SDIS.

Suggested citation: American Diabetes Association Professional Practice Committee for Diabetes. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2026. Diabetes Care 2026;49(Suppl. 1):S183–S215

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 (7.3%) led to ∼50% reductions in microvascular complications compared with 9.1% mean A1C in the conventional treatment arm 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

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

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. Cost symbols are reflective of general costs, which may vary for individuals based on various circumstances: insurance coverage, discounts, rebates, and other price adjustments involved in prescription sales. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, injectable ultra-rapid-acting insulin analog or inhaled insulin. 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, including conventional CSII, sensor-augmented pump, low-glucose suspend; AID systems such as hybrid closed 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 > sensor-augmented open-loop > conventional CSII.	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.

Continued on p. S186

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; CSII, continuous subcutaneous insulin infusion; 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).

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. Reassessment of insulin-taking behavior and adjustment of treatment plans to account for specific factors, including cost, that affect 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 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 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).

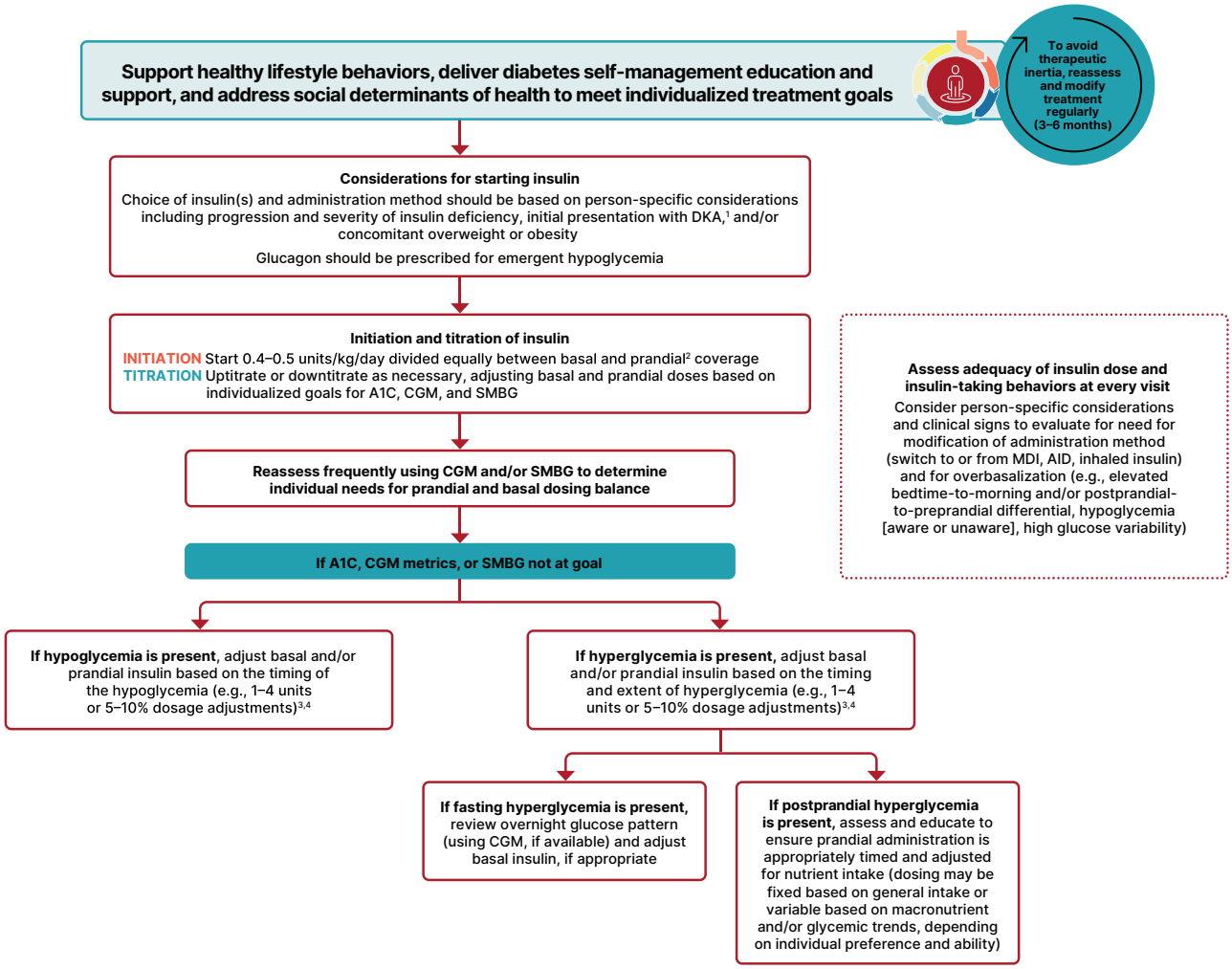
Integration of continuous glucose monitoring (CGM) into the treatment plan soon after diagnosis improves glycemic outcomes, decreases hypoglycemic events, and improves quality of life for individuals with type 1 diabetes (18–21). Its use is now considered standard of care for most people with type 1 diabetes (4) (see section 7, "Diabetes Technology"). Although nocturnal hypoglycemia is reduced in individuals with type 1 diabetes using sensor-augmented pump therapy with low-glucose suspend and predictive low-glucose suspend (22,23), evidence suggests that automated insulin delivery (AID) systems are superior for increasing percentage of time in range and reducing hypoglycemia (24–26). AID systems, which integrate CSII via an insulin pump, a CGM, and a control algorithm to adjust insulin delivery in real time based on glucose levels, are safe and effective for people with type 1 diabetes. Randomized controlled trials (RCTs) and real-world studies have demonstrated the ability of commercially available systems to improve achievement of glycemic goals while reducing the risk of hypoglycemia (27–32). Data are emerging on the safety and effectiveness of open-source AID systems (33,34). Intensive insulin management with CSII and CGM should be considered in individuals with type 1 diabetes whenever feasible. AID systems are preferred for individuals with type 1 diabetes who can use them safely (independently or with caregiver support), as they consistently improve time in range, lower A1C, and reduce hypoglycemia (26,28–31,35–38). 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 (39). This proportion depends on several factors, including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage (4,40–43). 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, the late luteal phase (premenstrual) in menstruating individuals, and 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 (44). In adults newly diagnosed with type 1 diabetes, insulin requirements at initiation typically range from 0.2 to 0.6 units/kg/day, with lower doses often sufficient in those with continued endogenous insulin production (during the partial remission phase or "honeymoon" period, or in people presenting outside of ketoacidosis) (44). This guideline provides an algorithm for insulin use for individuals with type 1 diabetes using insulin injections (**Fig. 9.2**) and 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 (45).

Typical multidose insulin treatment plans for adults with type 1 diabetes combine premeal prandial insulin with a longer-acting basal insulin. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best managed by an appropriately timed injection or inhalation of prandial insulin. Prandial insulin should ideally be administered before meals, although the optimal timing depends on the pharmacokinetics of the formulation (regular, rapid-acting analog, or inhaled), the premeal blood glucose level, and the anticipated carbohydrate intake. Dosing recommendations should therefore be individualized. Because physiologic insulin secretion varies with glycemia, meal size and composition, and tissue demand, 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 (46–51). Education regarding adjustment of prandial insulin dose for glycemic trends should be provided to individuals who are using CGM alone or an AID system (52–55). 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 (48). With some AID systems, use of a simplified meal announcement method may be an alternative for prandial insulin dosing (31,56). Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (57,58) (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). An individual's treatment plan and insulin-taking behaviors should be frequently reassessed to attain individualized treatment goals and assess risk or progression of complications and comorbidities. The timing of reassessment may vary based on time since diagnosis, ability to attain/maintain treatment goals, health status, comorbidities, and individual needs (4,45,59).

Initiation and adjustment of insulin using multiple daily dosing in individuals with type 1 diabetes



1. Refer to section 16, "Diabetes Care in the Hospital," for information on care during hospitalizations.
2. Prandial insulin options include: injectable rapid-acting and ultra-rapid-acting analog insulins, injectable short-acting human insulin, and inhaled human insulin.
3. Amount of dosage adjustment may vary between individuals depending on their severity of insulin deficiency and/or insulin resistance. Some individuals may require adjustments of 10–20%.
4. Adjustment may be done by their diabetes care team or by individuals, with guidance provided by their diabetes care team, as frequently as once to twice weekly using the lowest levels or average of the previous 3–4 days.

Figure 9.2—Insulin initiation and adjustment for people with type 1 diabetes using multiple daily dosing. AID, automated insulin delivery; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose.

Insulin Administration Technique

Ensuring that individuals and/or caregivers understand correct insulin administration technique is important to optimize glycemic management and insulin use safety. Advanced insulin injection technique and education with FITTER Forward expert recommendations have been published elsewhere outlining best practices for insulin administration (60). Proper insulin administration technique includes the following: injection, insertion of patch (for bolus patch or fixed-rate patch pump) or infusion set (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. Size 4-mm pen needles should be used to reduce inadvertent IM insulin delivery across ages and body types. IM risk is higher in younger, leaner individuals, with injections into limbs rather than truncal

sites (abdomen, buttocks), and with longer needles. Short needles (e.g., 4-mm) are effective and well tolerated compared with longer needles, including in adults with obesity (61).

Injection or infusion site rotation is 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 (60). 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 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 (~1–2 kg) with pramlintide (62). Similar results have been reported for several agents currently approved 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 (63,64). 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 (65,66). Higher rates of DKA and gastrointestinal side effects have limited their use in type 1 diabetes. 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 on preservation of β-cell function, but with liraglutide discontinuation there was worsening of C-peptide loss compared with placebo (67). Small retrospective case series and pilot studies have revealed potential benefits on body weight and glycemic metrics with addition of semaglutide or tirzepatide for individuals with type 1 diabetes and obesity (68–72). Prospective studies on use of incretin medications (i.e., GLP-1 RAs or a dual glucose-dependent insulinotropic polypeptide [GIP] and GLP-1 RA) for individuals with type 1 diabetes are ongoing and include evaluation of cardiovascular and kidney outcomes and other aspects of care (73–76).

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 (77); however, SGLT2 inhibitor use in type 1 diabetes was associated with an increased rate of DKA (78). 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 (79); however, sotagliflozin use was associated with an eightfold increase in DKA compared with placebo (80). The studies that led to the approved indication for heart failure (HF) excluded individuals with type 1 diabetes or a history of DKA (81,82). Sotagliflozin is therefore approved for HF and chronic kidney disease (CKD) but contraindicated in type 1 diabetes due to DKA risk. 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 (83).

There are currently no approved therapies for preservation of C-peptide or prolongation of the partial remission (honeymoon) phase in individuals with established stage 3 type 1 diabetes. Teplizumab was approved by the U.S. Food and Drug Administration. (FDA) in 2022 for delay of the progression from stage 2 to stage 3 type 1 diabetes (for additional guidance for use in early stage type 1 diabetes, refer to section 3, "Prevention or Delay of Diabetes and Associated Comorbidities"), but it is not indicated for those with established stage 3 type 1 diabetes (84). 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 (86).

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 (87). 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 (88). 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. 9.3**) (4).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.5 A person-centered shared decision-making approach should guide the

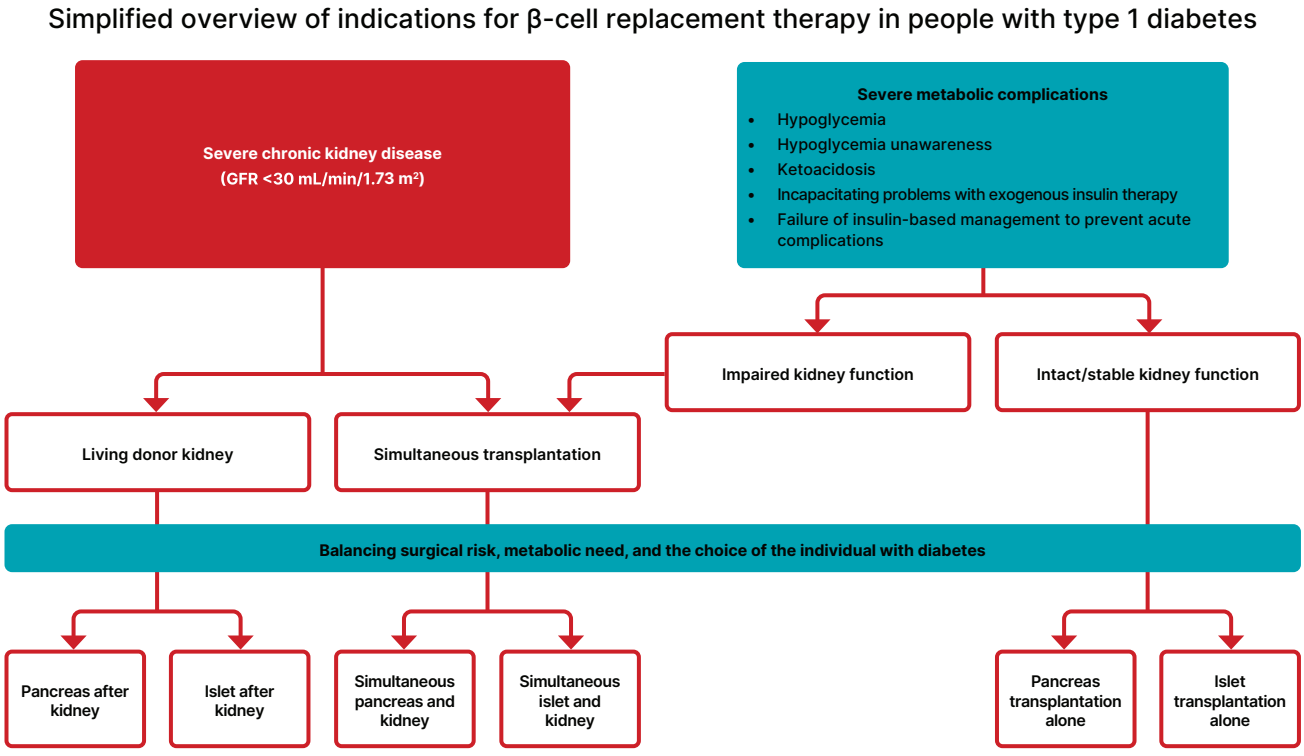


Figure 9.3—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation and islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has kidney failure, 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).

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. 9.4** and **Table 9.2**). **E**

9.6 Consider combination therapy in adults with type 2 diabetes for initial treatment to shorten time to attainment of individualized glycemic goals. **A**

9.7 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. 9.4** and **Table 9.2**). **A**

9.8 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. 9.4**). **A**

9.9a In adults with type 2 diabetes, obesity, and symptomatic heart failure with preserved ejection fraction (HFpEF), the glucose-lowering treatment plan should include a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA with demonstrated benefits for HF-related symptoms and reduction in HF events (irrespective of A1C). **A**

9.9b In adults with type 2 diabetes, obesity, and symptomatic HFpEF, the glucose-lowering treatment plan should include a GLP-1 RA with demonstrated benefits for HF-related symptoms **A** and/or reduction in HF events (irrespective of A1C). **B**

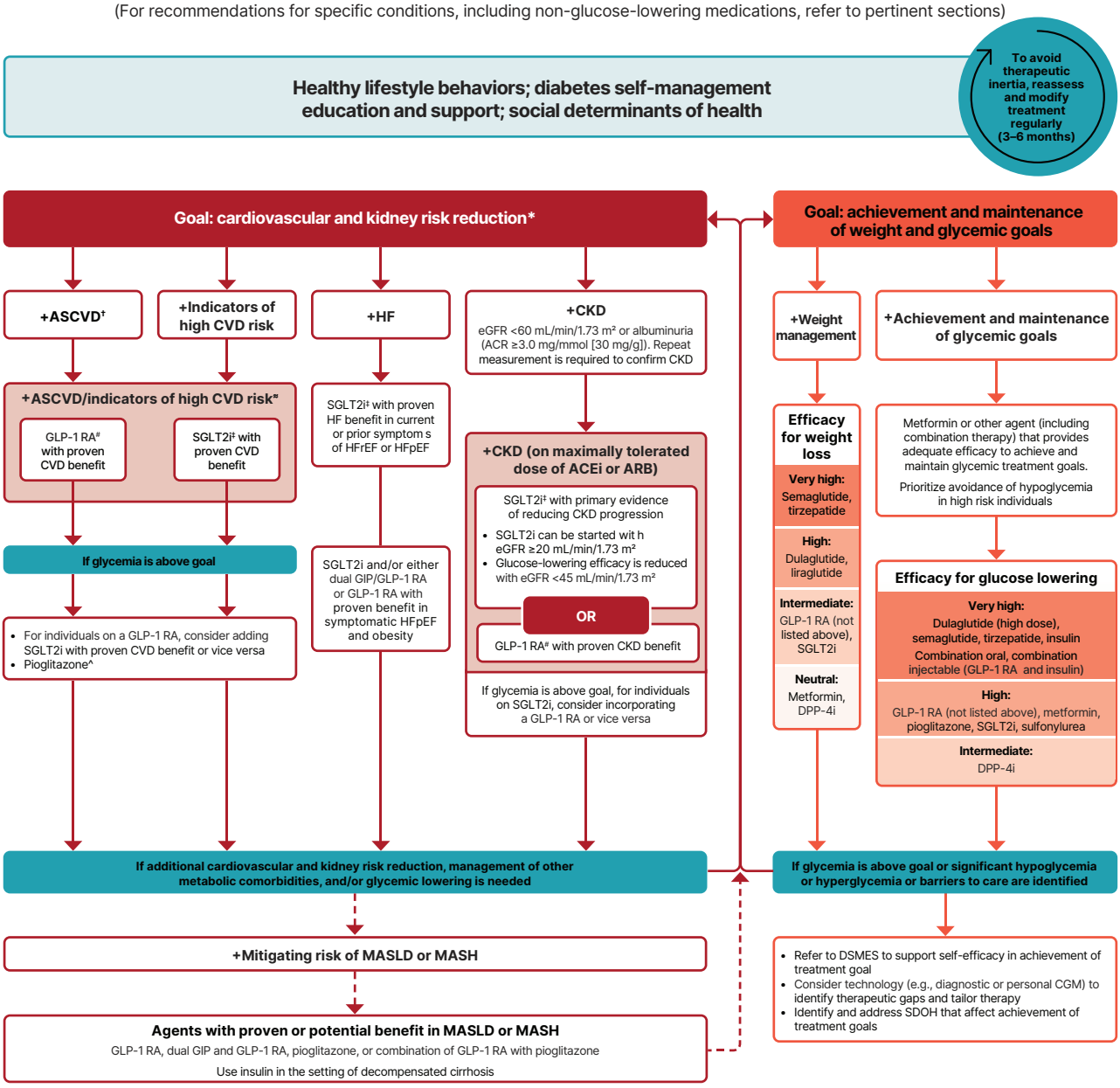
9.10 In adults with type 2 diabetes who have chronic kidney disease (CKD) (with confirmed estimated glomerular filtration rate [eGFR] 20–60 mL/min/1.73 m^2 and/or albuminuria), an SGLT2 inhibitor or GLP-1 RA with demonstrated benefit in this population should be used for both glycemic management and for slowing progression of CKD and reduction in cardiovascular events (irrespective of A1C) (**Fig. 9.4**). The glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min/1.73 m^2. **A**

9.11 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** Individuals on dialysis can be safely initiated or continued on GLP-1–based therapy (that is not dependent on kidney clearance) to reduce cardiovascular risk and mortality. **C**

9.12 In adults with type 2 diabetes, metabolic dysfunction–associated steatotic liver disease (MASLD), and overweight or obesity, consider using a GLP-1 RA with demonstrated benefits in metabolic dysfunction–associated steatohepatitis (MASH) **A** or a dual

Use of glucose-lowering medications in the management of type 2 diabetes

(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)



* 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 attainment of glycemic goal.

† 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 9.4—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, angiotensinconverting 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. (90).

GIP and GLP-1 RA with potential benefits in MASH **B** for glycemic management and as an adjunctive therapy to interventions for weight loss.

9.13a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), a GLP-1 RA is preferred for glycemic management due to beneficial effects on MASH. **A** Pioglitazone or a dual GIP and GLP-1 RA **B** can be considered for glycemic management due to potential beneficial effects on MASH. **B**

9.13b 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**

9.14 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 affect choice of treatment and ensure achievement of individualized glycemic goals (**Fig. 4.1** and **Table 9.2**). **E**

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

9.16 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**

9.17 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**

9.18 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–based therapy. **B**

9.19 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**

9.20 In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease duration 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**

9.21 In adults with type 2 diabetes without severe hyperglycemia or hyperglycemic crisis, GLP-1–based therapy is preferred to insulin for initial or add-on glucose-lowering therapy (**Fig. 9.4**). **A**

9.22 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**

9.23 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, Hypoglycemia, and Hyperglycemic Crises"), individualized weight goals (see section 8, "Obesity and Weight Management for the Prevention and Treatment of 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), 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%) (89). 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 effects 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 CKD, the

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, empagliflozin, dapagliflozin	• 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 or start for cardiovascular and kidney benefit if eGFR >20 mL/min/1.73 m^2. May continue 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 • Urosepsis and pyelonephritis: evaluate individuals for signs and symptoms of urinary tract infections and treat promptly • Necrotizing fasciitis in 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

Continued on p. S194

Table 9.2—Continued

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*		
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 and oral) Neutral: exenatide once weekly, lixisenatide	Benefit: semaglutide (SQ)	Benefit for kidney 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	Benefit: semaglutide (SQ)	• Thyroid C-cell tumors identified in rodents; human relevance not determined • Provide guidance on discontinuation prior to surgical procedures to mitigate potential for pulmonary aspiration with general anesthesia or deep sedation • 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 • Ileus: reported, but risk level is not well established • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]) • Nonarteritic anterior ischemic optic neuropathy (NAION) reported (rare incidence); monitor for NAION during eye examinations • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including 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
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Benefit: tirzepatide	Potential benefit	• 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	

Continued on p. S195

Table 9.2—Continued

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*		
									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
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) reversible upon discontinuation
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 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; association observed with higher cumulative exposure (e.g., longer duration, higher doses)
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

Continued on p. S196

Table 9.2—Continued

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*		
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 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. (107). [2]Tsapas et al. (317). Adapted from Davies et al. (90).

treatment plan should include agents that reduce cardiovascular and kidney disease risk (**Fig. 9.4** 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 Diabetes"), mitigation of metabolic dysfunction–associated steatotic 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 (90–92). 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 (93,94). Metformin is effective and safe, is inexpensive and widely available, and reduces risks of microvascular complications, cardiovascular events, and death (93,95,96). 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 (97). Metformin is also more effective than dipeptidyl peptidase 4 (DPP-4) inhibitors in lowering A1C and weight when used as monotherapy (98).

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 ≥30 mL/min/1.73 m^2 (99). Very high circulating levels (e.g., as a result of overdose or acute kidney injury) have been associated with lactic acidosis (100). However, the occurrence of this complication is very rare (101) and primarily occurs when the estimated glomerular filtration rate (eGFR) is <30 mL/min/1.73 m^2 (102). 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 ≤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 (103,104), 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 (105–107). 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**).

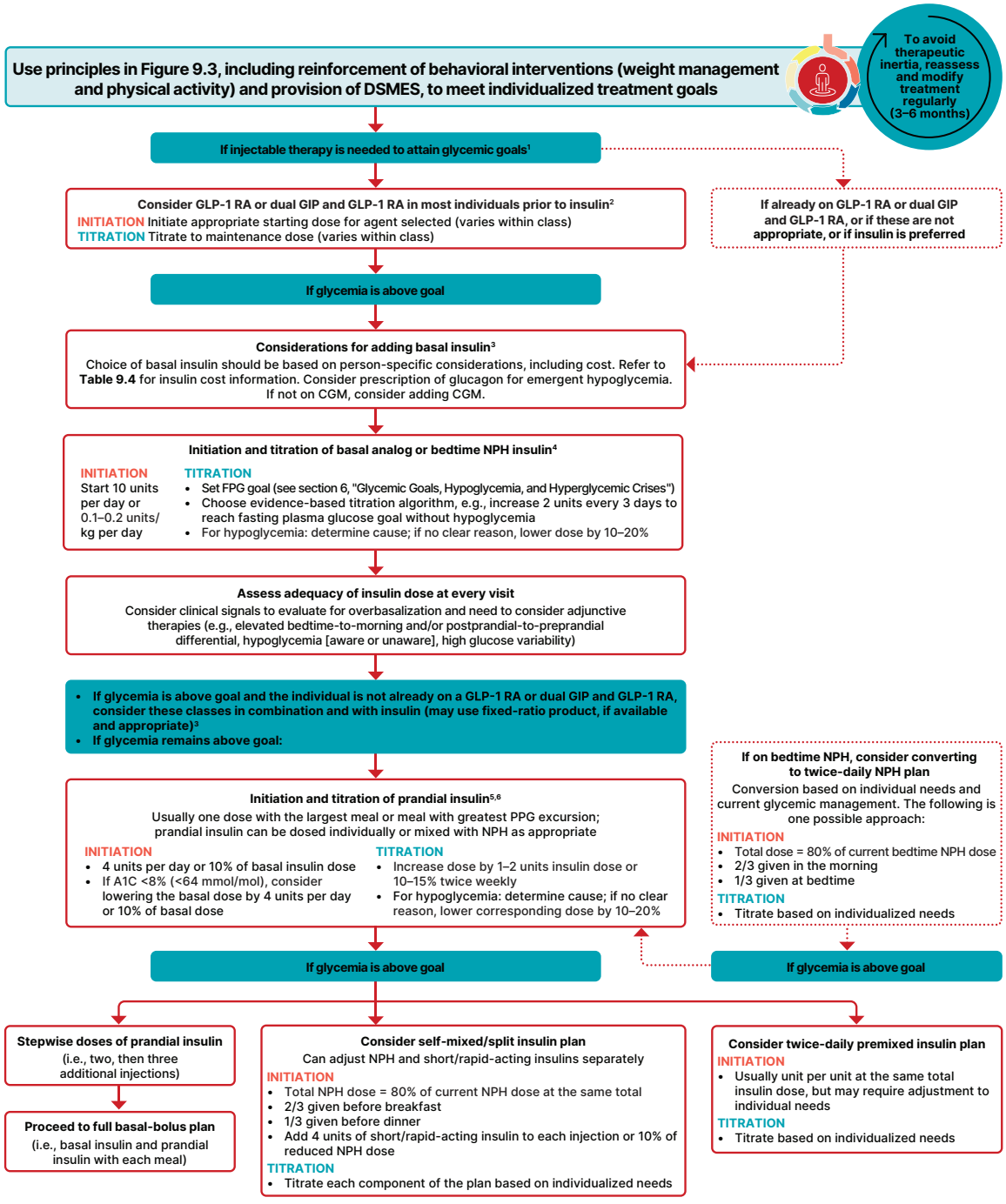
When A1C is ≥1.5% above the individualized glycemic goal (see section 6, "Glycemic Goals, Hypoglycemia, and Hyperglycemic Crises," for appropriate goals), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their goal A1C level (90) (**Fig. 9.4** 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 ≥300 mg/dL (≥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. 9.5**). 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 a dual GIP and GLP-1 RA, though evidence is scarce for individuals with baseline A1C above 10–12% (105,109–111). 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 with A1C levels 1.5–2.0% above their individualized goal or in those at high risk for cardiovascular disease (CVD) or with established CVD irrespective of A1C levels (GLP-1 RA and SGLT2 inhibitor combination therapy) (see section 10, "Cardiovascular Disease and Risk Management"). The incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (e.g., GLP-1 RAs, a 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. 9.4**).

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 (105,117,118) (**Fig. 9.4** and **Table 9.2**). Use of GLP-1 RAs (or the dual GIP and GLP-1 RA) together with a DPP-4 inhibitor is not recommended, 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



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, glycemic 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 9.5—Intensifying to injectable therapies in type 2 diabetes. CGM, continuous glucose monitoring; 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. (318).

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. 9.5**).

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 (90,131). 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. 9.4**). GLP-1 RAs or a dual GIP and GLP-1 RA with demonstrated benefits are recommended for people with type 2 diabetes, obesity, and symptomatic HF with preserved ejection fraction (132–135) (**Table 9.2** and **Fig. 9.4**). 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 (136).

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 without established CVD) with respect to achieving and maintaining A1C below 7%, found that individuals treated with liraglutide had a lower risk of cardiovascular events than individuals receiving the other three treatments (hazard ratio 0.7 [95% CI 0.6–0.9]), although no significant differences were found between individual treatment groups for major adverse cardiovascular events, hospitalization for HF, or cardiovascular death (137). 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 (138). 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 (139).

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 affect CKD progression, CVD risk, and hypoglycemia (140). 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 (141,142). 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, although post hoc analyses of clinical trials in people with type 2 diabetes have shown that tirzepatide slowed the rate of eGFR decline and reduced albuminuria (143,144). The GLP-1 RAs lixisenatide and exenatide, which require the kidneys for elimination, should be avoided in individuals with eGFR $\leq$30 mL/min/1.73 m^2 or with creatinine clearance $\leq$30 mL/min, respectively (145–147).

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 (148–150). However, their ability to lower glucose levels declines when the eGFR falls below 45 mL/min/1.73 m^2 (151–153). Metformin is also a therapeutic agent for those with CKD due to its well-documented efficacy and safety profile for 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 (99). 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 (154).

Individuals with CKD, particularly advanced CKD and kidney failure, are at high risk for hypoglycemia (136). 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 (140). 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 RAs, and a dual GIP and GLP-1 RA have favorable outcomes 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 (155–160). 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 (161–163). It is important to note that these studies are based on phase 2 clinical trials and that only semaglutide has recently shown benefit in a phase 3 clinical trial with histological outcomes in MASH, including improvements in steatohepatitis and fibrosis (156); this subsequently led to its approval by the FDA for the treatment of MASH with moderate to advanced liver fibrosis, while the other therapies 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 (164–168). 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 (169). Further details regarding treatment of obesity can be found in section 8, "Obesity and Weight Management for the Prevention and Treatment of Diabetes."

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.5**). 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 (170). 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 (57,58). 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 time 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 (171,172). 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) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin (173). Longer-acting basal analogs (U-300 glargine or degludec) convey a lower nocturnal hypoglycemia risk than U-100 glargine (174,175). 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 human NPH insulin or U-300 glargine to another insulin (176). 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 postprandial-to-preprandial 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 over-basalization should prompt reevaluation of the glucose-lowering treatment plan to better address postprandial hyperglycemia (177).

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. 9.5**). 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 (131,178). 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 (131,178).

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 (179). 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. 9.5**). 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 (180). 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 (181). 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 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 and may limit its use.

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 (182,183). 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 (184–186). The U-200 formulations of insulin degludec, insulin lispro, and insulin lispro-aabc have pharmacokinetics similar to those of their U-100 counterparts (187–189). 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 specific 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 faster than those of RAA (190). 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 (190–192). 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

9.24 Include healthy behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health as essential components of the glucose-lowering management of diabetes. **A**

9.25 Use of continuous glucose monitoring (CGM) is recommended at diabetes onset and anytime thereafter for adults with diabetes who are on insulin therapy, **A** on noninsulin therapies that can cause hypoglycemia, **B** and on any diabetes treatment where CGM aids in management. **B** The choice of CGM device and method for use should be made based on the individual's circumstances, preferences, and needs.

9.26 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**

9.27 Automated insulin delivery systems should be offered to all adults with type 1 and 2 diabetes on insulin depending on the person's or caregiver's needs and preferences. **A**

9.28 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. **A** 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 essential components for the glucose-lowering management plan that are relevant to people with all types of diabetes include encouraging healthy behaviors and diabetes self-management education and support (see section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"), considering social determinants of health (see section 1, "Improving Care and Promoting Health in Populations"), avoiding and preventing therapeutic inertia, and prescribing glucagon and affordable diabetes treatments.

Diabetes Technology and Glycemic Management

The use of continuous glucose monitoring (CGM) in adults with diabetes improves glycemic outcomes (e.g., A1C, time in range) and reduces episodes of hypoglycemia in adults with diabetes who are on insulin therapy or other noninsulin therapies that can induce hypoglycemia (193–209). In addition, the use of AID systems should be offered to adults with type 1 or type 2 diabetes who are on insulin therapy to improve glycemic management and glycemic outcomes (26,28–32,35–37,210–215). The decision of which CGM and/or AID system to use should be based on the preference of the individual with diabetes and their caregivers, availability of resources to provide the needed training and education, and available support. As the diabetes technology landscape is rapidly evolving and individuals require a tailored approach, health care teams may encounter challenges with determining the best technology for people with diabetes. An ADA resource, which can be found at diabetes.org/living-with-diabetes/treatment-care/diabetes-technology-guide, can provide helpful information for health care professionals and individuals with diabetes in making decisions regarding technology. For more information on diabetes technology, see section 7, "Diabetes Technology."

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 (216,217). Clinicians should routinely review the individual's access to glucagon, as appropriate glucagon prescribing is low (218–220). See section 6, "Glycemic Goals, Hypoglycemia, and Hyperglycemic Crises," 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 (221). **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) (222) and National Average Drug Acquisition Costs (NADAC) (223); these estimates allow for a comparison of drug prices but do not represent the actual costs to

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 (IR)	2,000 mg	$85 ($3, $216)	$2
		500 mg (ER)	2,000 mg	$89 ($5, $6,719)	$3
		850 mg (IR)	2,550 mg	$108 ($3, $189)	$2
		1,000 mg (IR)	2,000 mg	$87 ($2, $144)	$1
		1,000 mg (ER)	2,000 mg	$1,884 ($242, $7,214)	$26 ($24, $28)
		500 mg (Sol)	2,000 mg	$810 ($810, $1,478)	$417
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	8 mg	$73 ($71, $198)	$2
	• Glipizide	10 mg (IR)	40 mg	$72 ($67, $91)	$6
		10 mg (XL/ER)	20 mg	$48	$9
	• Glyburide	6 mg (micronized)	12 mg	$54 ($48, $71)	$13
		5 mg	20 mg	$88 ($63, $432)	$7
Thiazolidinedione	• Pioglitazone	45 mg	45 mg	$348 ($7, $349)	$4
α-Glucosidase inhibitors	• Acarbose	100 mg	300 mg	$106 ($104, $378)	$22
	• Miglitol	100 mg	300 mg	$294 ($241, $346)	$183
Meglitinides	• Nateglinide	120 mg	360 mg	$104	$16
	• Repaglinide	2 mg	16 mg	$878 ($799, $1,728)	$28
DPP-4 inhibitors	• Alogliptin	25 mg	25 mg	$234	$143
	• Linagliptin	5 mg	5 mg	$630	$504
	• Saxagliptin	5 mg	5 mg	$524 ($523, $524)	$179
	• Sitagliptin	100 mg	100 mg	$341	$303
		25 mg/mL	100 mg	$354	NA
SGLT2 inhibitors	• Bexagliflozin	20 mg	20 mg	$47	NA
	• Canagliflozin	300 mg	300 mg	$718	$575
	• Dapagliflozin	10 mg	10 mg	$664	$345
	• Empagliflozin	25 mg	25 mg	$629	$604
	• Ertugliflozin	15 mg	15 mg	$428	$343
GLP-1 RAs	• Dulaglutide	4.5 mg pen	4.5 mg‡	$1,185	$953
	• Liraglutide	18 mg/3 mL pen	1.8 mg	$929 ($845, $929)	$577
	• Semaglutide	2 mg pen	2 mg‡	$1,197	$966
		14 mg (tablet)	14 mg	$1,197	$965
Dual GIP and GLP-1 RA	• Tirzepatide	15 mg pen	15 mg‡	$1,296	$1,041
Bile acid sequestrant	• Colesevelam	625 mg tabs	3.75 g	$692 ($674, $712)	$56
		3.75 g suspension	3.75 g	$674 ($673, $675)	$93
Dopamine-2 agonist	• Bromocriptine	0.8 mg	4.8 mg	$1,188	$957

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; Sol, solution. AWP and NADAC prices as of 15 July 2025. *Calculated for 30-day supply (AWP [222] or NADAC [223] 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.

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 (224); cost-reducing strategies may improve medication-taking behavior in some cases (225).

Caps on out-of-pocket costs for insulin have been implemented for individuals with Medicare insurance (to $35 per insulin prescription per month) and individuals with state-regulated commercial insurance plans who live in 26 states and the District of Columbia that implemented such legislation (to either $35 per insulin prescription per month or $100 per total monthly insulin payment) (226–228). Additionally, insulin manufacturers have introduced cost reductions and copayment assistance programs; however, these do not cover all insulins, and the copayment assistance programs have variable eligibility requirements and reduce out-of-pocket payments to variable degrees (229) (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 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

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/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 biosimilars#	U-100 vial	$83	NA
		U-100 prefilled pen	$107	NA
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$358
	• Glulisine	U-100 vial	$102	$82
		U-100 prefilled pen	$132	$105
	• Inhaled insulin	Inhalation cartridges	$1,578	$1,265
	• 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	$110
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$56 ($54, $58)‡	$44 ($43, $46)‡
		U-100 prefilled pen	$73	$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	$143
		U-500 prefilled pen	$230	$183
Long-acting	• Degludec	U-100 vial	$142†	$114†
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$142†	$114†
	• Glargine	U-100 vial	$77	$62
		U-100 prefilled pen	$77	$62
		U-300 prefilled pen	$152	$122†
	• Glargine biosimilar/follow-on products	U-100 vial	$76†	$61†
		U-100 prefilled pen	$74 ($74,† $261)	$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	$56 ($54, $58)	$45 ($43, $46)
		U-100 prefilled pen	$93 ($73, $113)‡	$74 ($58, $90)‡
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 mg prefilled pen	$1,073	$859
	• Glargine/lixisenatide	100/33 mg prefilled pen	$713	$571

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (222) and NADAC (223) prices as of 15 July 2025. *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. #Pricing for aspart-xjhz not available on 15 July 2025.

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 (230).

SPECIAL CIRCUMSTANCES AND POPULATIONS

Recommendations

9.31a Use of compounded products that are not approved by the U.S. Food and Drug Administration (FDA) is not recommended due to uncertainty about their content and resulting concerns about safety, quality, and effectiveness. **C**

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 of childbearing potential with diabetes 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 of childbearing potential with diabetes. **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 Individuals who develop hyperglycemia during treatment with immunotherapy (including anti-PD-1 or anti-PD-L1 therapy, e.g., nivolumab, pembrolizumab, or avelumab) should be assessed for the immediate need for initiation of insulin therapy due to the potential risk of diabetic ketoacidosis while additional testing is completed to determine if the hyperglycemia is related to immunotherapy-associated diabetes. Close monitoring, education, and dose adjustment are needed if insulin is started. **C**

9.34 Consider metformin as the first-line treatment of hyperglycemia due to mTOR inhibitors. **E**

9.35a Consider metformin as the first-line treatment of hyperglycemia due to phosphoinositide 3-kinase (PI3K) inhibitors that affect the α isoform (e.g., alpelisib and inavolisib). **E**

9.35b Use of insulin should be reserved for severe hyperglycemia and hyperglycemic crises due to its potential impact on the efficacy of PI3K inhibitors. **E**

9.36 Adjust or initiate additional glucose-lowering therapies to maintain individualized glycemic goals based on the specific glucocorticoid treatment plan, with frequent reassessment of glucose levels and glucocorticoid treatment plans. **C**

9.37 In adults with posttransplantation diabetes mellitus (PTDM) or preexisting type 2 diabetes, insulin is preferred for the management of hyperglycemia in the postoperative setting. **A** A DPP-4 inhibitor can be considered for mild hyperglycemia. **A**

9.38a In adults with PTDM or preexisting type 2 diabetes, noninsulin pharmacotherapy can be used for long-term glycemic management, **C** and medication selection may differ depending on the transplanted organ(s). **E**

9.38b In adults with PTDM or preexisting type 2 diabetes, a GLP-1 RA can be considered for long-term glycemic management due to additional cardiometabolic benefits (e.g., cardiovascular, kidney, weight, and liver benefits). **C**

9.38c If long-term individualized glycemic goals cannot be achieved or maintained with noninsulin pharmacotherapy in adults with PTDM or preexisting type 2 diabetes, consider adding insulin. **C**

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

Therapeutic Strategies With Medication Unavailability

Health care professionals and people with diabetes struggle when medication supplies are insufficient to meet the demand. 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 (231). 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 (232). A significant number of concerning reports regarding safety and efficacy of compounded incretin products have emerged, 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 (233–236). Due to safety, quality, and effectiveness concerns, use of non-FDA-approved compounded products is not recommended (237). Instead, consider switching to a different FDA-approved medication as clinically appropriate (238). 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 affect 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 (239). Tirzepatide, the

dual GIP and GLP-1 RA, was shown to affect the levels of oral contraception during the time of its highest impact on gastric emptying; the GLP-1 RAs may affect the levels of oral contraception as well but to a lesser extent than tirzepatide (240,241). 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 (242).

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. Individuals planning pregnancy should be counseled that a period of several months is usually needed and adjustment of therapy approved for use in pregnancy to achieve preconception glycemic goals 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 diabetes. Immune checkpoint inhibitors (ICIs) impair regulatory components of the immune system, allowing for immunogenic response against cancer cells, which can result in autoimmune toxicities, including an autoimmune form of diabetes that results in β-cell destruction (incidence approximately ≤1%) (243–246). This form of diabetes is most common after exposure to ICIs that target programmed cell death protein 1 (PD-1) (i.e., nivolumab and pembrolizumab) and those that target programmed cell death protein ligand 1 (PD-L1) (i.e., durvalumab and avelumab). ICIs that target cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) (i.e., ipilimumab) have also been implicated in this process, but much less commonly (247).

Hyperglycemia as a result of ICIs can occur at any time after the initiation of therapy—as quickly as 1 week after the first dose to up to 12 months after. Insulin therapy is the cornerstone of management, as individuals typically present with rapid-onset, severe hyperglycemia or DKA (248). Early initiation of therapy can prevent these drastic presentations, and the initiation of basal insulin should be considered in individuals with blood glucose >250 mg/dL while further evaluation takes place. Prandial insulin is often required as well, if insulinopenia is confirmed. ICI treatment should not be discontinued in the event of severe hyperglycemia, as the β-cell destruction associated with this process is irreversible. Lifelong insulin therapy is generally required (249).

Phosphatidylinositol 3-kinase (PI3K) inhibitors are small molecules that inhibit intracellular signaling, interfering with cancer cell proliferation and survival. Four isoforms have been identified as therapeutic targets, with both pan-PI3K inhibitors and isoform-specific inhibitors in clinical use. The α isoform of this enzyme (PI3Kα) is also involved in insulin signaling, and the inhibition of this pathway by either pan-PI3K inhibitors (i.e., copanlisib and duvelisib) or specific PI3Kα inhibitors (i.e., alpelisib and inavolisib) can lead to hyperglycemia (250). Hyperglycemia typically occurs within the first 2 weeks of therapy, with an incidence of approximately 60% (251–254). Risk factors include preexisting dysglycemia, BMI >25 kg/m^2, and age >65 years. Adequate management is crucial, as uncontrolled hyperglycemia can lead to discontinuation and/or reduction in medication dose, which can negatively affect the efficacy of the therapy (254–256).

Metformin is the first-line oral agent to treat PI3K inhibitor–induced hyperglycemia, with uptitration of the dose as tolerated (256). Pioglitazone is also an option as monotherapy or in combination with metformin, but its slow onset of action can limit its effectiveness (257). SGLT2 inhibitors have also shown efficacy, but close monitoring is needed, as ketoacidosis has been reported (258). Insulin and sulfonylureas should be considered only as a last resort, as increased insulin levels may reactivate the PI3K pathway, counteracting the antitumor effects of PI3K inhibition (256,259). There is no direct evidence for the use of GLP-1 RAs for PI3K inhibitor–induced hyperglycemia. They should not be considered for treatment in this circumstance at this time due to their uncertain effect on PI3K inhibitor efficacy (based on their increase in insulin secretion) and the potential to cause nausea and vomiting.

mTOR kinase inhibitors, including everolimus, 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 because of its efficacy and safety profile. Due to its ability to reduce insulin resistance, pioglitazone may be considered as a second-line treatment, depending on the risks of its adverse effects to the individual. There is no direct evidence regarding the efficacy of GLP-1 RAs or SGLT2 inhibitors for mTOR inhibitor–induced hyperglycemia; however, there is also no evidence that they impair the efficacy of the mTOR inhibitor. Thus, evaluation of their use as second- or third-line treatments for this circumstance should be made based on their overall benefits and risks. Insulin is typically reserved for cases of refractory hyperglycemia after noninsulin treatments are used, in the presence of intolerance or contraindications to noninsulin treatments, or for severe hyperglycemia (260–262).

Glucocorticoids (including prednisone and dexamethasone), which are often used as part of acute, adjunctive, and chronic treatment of cancer and inflammatory conditions (e.g., rheumatoid arthritis and inflammatory bowel disease) as well as posttransplantation, cause hyperglycemia primarily by increased insulin resistance and hepatic glucose production. Other contributing effects include increased appetite, decreased production/secretion of insulin, and enhanced effects of counterregulatory hormones (such as epinephrine) (263–266). The timing and extent of hyperglycemia vary based on the dose, duration, route of administration (i.e., intravenous, oral, or intraarticular) and the specific glucocorticoid used (265–271). For example, with morning administration of prednisone (with the first meal of the day), glucose starts rising after the first meal, with peak effects in the afternoon and evening, and declines to baseline by the next morning; in contrast, with a single dose of dexamethasone, glucose elevations may last more than 24 h with some decline overnight. The extent of the elevation is dependent on the dose, so as the glucocorticoid is tapered, the extent of hyperglycemia will

decline. Monitoring glucose levels solely in the morning may miss the extent of the hyperglycemia experienced due to glucocorticoid use and prevent appropriate management (263,265–267,272). Thus, glucose-lowering medication adjustments or additions should match the timing and extent of hyperglycemia and allow for rapid adjustment as the dose of the glucocorticoid dose changes to minimize the likelihood of hyperglycemia and hypoglycemia. Insulin is the most frequently used glucose-lowering medication to manage hyperglycemia secondary to glucocorticoid use. The selection of insulin type and dose depends on the dose and duration of the glucocorticoid (265,266,269, 272–275). Additions or dose adjustments of sulfonylureas, including meglitinides, have also been used for those with type 2 diabetes or no previous diagnosis of diabetes. Due to lack of direct evidence and the time needed to achieve the glucose-lowering effect, additions or dose adjustments of other glucose-lowering medications are reserved for when stable doses of glucocorticoids are chronically administered and are not for acute management (265,266,269,272, 275,276).

Pancreatic Diabetes and Cystic Fibrosis–Related Diabetes

Individuals with pancreatic 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, a dual 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 AID systems, should be considered when appropriate (277).

Posttransplantation Diabetes Mellitus

The diagnosis of posttransplantation diabetes mellitus (PTDM) relies on the same glycemic characteristics as other forms of diabetes. However, due to the unique effects of immunosuppressant drugs, an oral glucose tolerance test (OGTT) is the preferred and most accurate method for diagnosis (compared with A1C or fasting plasma glucose) (278). In 2024, an update from the 3rd International PTDM Consensus Meeting recommended screening for diabetes risk factors with a pretransplant OGTT while the individual is on the waitlist, followed by early OGTT at 3 months posttransplantation to diagnose PTDM and a late OGTT at 1 year and onward as appropriate (279).

As with all strategies in metabolic management, lifestyle modifications remain a mainstay of long-term management. The Comparing Glycaemic Benefits of Active Versus Passive Lifestyle Intervention in Kidney Allograft Recipients (CAVIAR) study compared active and passive lifestyles after kidney transplantation using behavior therapy and found a statistically significant reduction in fat mass and weight loss with active lifestyle. However, there were no changes in the primary outcomes of glucose metabolism (i.e., insulin secretion, insulin sensitivity, or disposition index). The rate of PTDM was halved in the active group, but this finding was not statistically significant (280).

In early postoperative periods, insulin is the preferred drug for glycemic management due to its lack of interactions with other transplant medications, immediate efficacy, and added potential to prevent PTDM, albeit with the expected risk of hypoglycemia (281–283). Sulfonylureas may also be used for individuals with stable kidney function with similar precautions of hypoglycemia, but they may not confer any added metabolic benefits outside of glucose management (284).

Although still limited, data are increasing to inform the optimal pharmacologic management of PTDM and preexisting type 2 diabetes at the time of transplant (285,286) (for diagnosis and classification of PTDM, see section 2, "Diagnosis and Classification of Diabetes"). While many individuals require insulin therapy immediately posttransplantation, 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 solid organ transplantation have demonstrated effectiveness and safety but are limited by small sample sizes, short follow-up, and risk of bias due to retrospective, single-center, or single-arm prospective designs (287). The majority of studies are in individuals who have undergone kidney transplantation, but studies in liver and heart transplantation are available to a lesser degree as well. Selection of pharmacotherapeutic classes should take into account organ-specific physiology, immunosuppressant plan, and general metabolic and cardiovascular circumstances.

Metformin can be used but with caution; it should not be initiated if eGFR is <45 mL/min/1.73 m^2, and it should be discontinued with eGFR <30 mL/min/1.73 m^2. Limitations in metformin use include the risk of lactic acidosis with fluctuating kidney function, either with graft dysfunction or rejection in kidney transplantation or acute kidney injury in other solid organ transplantation. Metformin use may be associated with lower risks of cardiac allograft vasculopathy after heart transplantation (288) and all-cause, malignancy-related, and infection-related mortality after kidney transplantation (289).

DPP-4 inhibitors have been shown to be safe and effective posttransplantation in RCTs, even in the immediate posttransplant period for mild hyperglycemia or impaired glucose tolerance, and have the potential to decrease progression to PTDM (290).

GLP-1 RA therapy may be preferred for many individuals, as shown by increasing evidence from large retrospective studies on the benefits of GLP-1 RAs on cardiovascular, kidney, weight loss, and glucose lowering outcomes. Studies have not found any concern for negative interaction with immunosuppressants, which would necessitate changes in in dosing (291–303). However, caution should be used when gastrointestinal side effects occur, particularly if individuals have this additive effect to the side effects of the immunosuppressants. Additionally, in lung transplant recipients, gastroparesis and gastroesophageal reflux are of particular concern, as these conditions may induce allograft lung damage and are frequent side effects of GLP-1 RAs. A gastric emptying study may be useful in identifying ideal candidates before initiation.

SGLT2 inhibitors may be similarly preferred for individuals with ASCVD, HF, and CKD and appear to be safe and effective in PTDM (304–309). However, there is increased risk of genitourinary tract infection, which is of particular concern in immunosuppressed individuals. Of note, kidney transplant recipients have an innate anatomical increased risk of urinary tract infections (UTIs), particularly immediately posttransplant when the ureteral stent is still in place. Prior history of UTIs and individual risk of UTIs should be considered when using this class after kidney transplant.

It is essential that diabetes management posttransplantation is implemented in the setting of an interprofessional team. The transplant physicians and the endocrinologists should work collaboratively to monitor for medication toxicity and deleterious side effects that may affect allograft function and to optimize cardiovascular and metabolic outcomes.

Maturity-Onset Diabetes of the Young

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 (310) (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 (311). 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 (310).

SGLT Inhibition and Risk of Ketosis

Individuals with type 1 diabetes (83,312) and insulin-deficient type 2 diabetes are at increased risk for DKA with SGLT inhibitor therapy (SGLT2 inhibitors or the SGLT1/2 inhibitor). 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 type 1 diabetes not treated with SGLT inhibitors (313). 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 (314). Risk factors for DKA in individuals with either type 1 or type 2 diabetes treated with SGLT inhibitors include very-low-carbohydrate eating patterns, prolonged fasting, dehydration, excessive alcohol intake, and other common precipitating factors (83,312). Up to a third of people treated with SGLT2 inhibitors who developed DKA present with glucose levels <200 mg/dL (<11.1 mmol/L) (315), and in one study 71% presented with glucose levels ≤250 mg/dL (≤13.9 mmol/L) (316); 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, Hypoglycemia, and Hyperglycemic Crises."

References

1. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383
2. Lachin JM, Bebu I, Nathan DM; DCCT/EDIC Research Group. The beneficial effects of earlier versus later implementation of intensive therapy in type 1 diabetes. Diabetes Care 2021;44:2225–2230
3. Lachin JM, Nathan DM; DCCT/EDIC Research Group. Understanding metabolic memory: the prolonged influence of glycemia during the Diabetes Control and Complications Trial (DCCT) on future risks of complications during the study of the Epidemiology of Diabetes Interventions and Complications (EDIC). Diabetes Care 2021;44:2216–2224
4. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625
5. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ 2014;349:g5459
6. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442–449
7. Little S, Shaw J, Home P. Hypoglycemia rates with basal insulin analogs. Diabetes Technol Ther 2011;13(Suppl. 1):S53–S64
8. Aronson R, Biester T, Leohr J, et al. Ultra rapid lispro showed greater reduction in postprandial glucose versus Humalog in children, adolescents and adults with type 1 diabetes mellitus. Diabetes Obes Metab 2023;25:1964–1972
9. Heise T, Pieber TR, Danne T, Erichsen L, Haahr H. A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. Clin Pharmacokinet 2017;56:551–559
10. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled Technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 2015;38:2266–2273
11. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care 2017;40:943–950
12. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. Diabetes Obes Metab 2020;22:1799–1807
13. Lane W, Bailey TS, Gerety G, et al.; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA 2017;318:33–44
14. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care 2015;38:2217–2225
15. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336–347
16. Speight J, Choudhary P, Wilmot EG, et al. Impact of glycaemic technologies on quality of life and related outcomes in adults with type 1 diabetes: a narrative review. Diabet Med 2023;40:e14944
17. Tzivian L, Sokolovska J, Grike AE, et al. Quantitative and qualitative analysis of the quality of life of type 1 diabetes patients using insulin pumps and of those receiving multiple daily insulin injections. Health Qual Life Outcomes 2022;20:120
18. Mulinacci G, Alonso GT, Snell-Bergeon JK, Shah VN. Glycemic outcomes with early initiation of continuous glucose monitoring system in recently diagnosed patients with type 1 diabetes. Diabetes Technol Ther 2019;21:6–10
19. Elbalshy M, Haszard J, Smith H, et al. Effect of divergent continuous glucose monitoring technologies on glycaemic control in type 1 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials. Diabet Med 2022;39:e14854
20. Champakanath A, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Continuous glucose monitoring initiation within first year of type 1 diabetes diagnosis is associated with improved glycemic outcomes: 7-year follow-up study. Diabetes Care 2022;45:750–753
21. Polonsky WH, Hessler D, Ruedy KJ, Beck RW; DIAMOND Study Group. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. Diabetes Care 2017;40:736–741
22. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
23. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care 2018;41:2155–2161
24. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
25. Collyns OJ, Meier RA, Betts ZL, et al. Improved glycemic outcomes with Medtronic

MiniMed advanced hybrid closed-loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. Diabetes Care 2021;44:969–975
26. Breton MD, Kovatchev BP. One year real-world use of the control-IQ advanced hybrid closed-loop technology. Diabetes Technol Ther 2021;23:601–608
27. Peacock S, Frizelle I, Hussain S. A systematic review of commercial hybrid closed-loop automated insulin delivery systems. Diabetes Ther 2023;14: 839–855
28. Choudhary P, Kolassa R, Keuthage W, et al.; ADAPT study Group. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. Lancet Diabetes Endocrinol 2022;10:720–731
29. Arunachalum S, Velado K, Vigersky RA, Cordero TL. Glycemic outcomes during real-world hybrid closed-loop system use by individuals with type 1 diabetes in the United States. J Diabetes Sci Technol 2023;17:951–958
30. Garg SK, Grunberger G, Weinstock R, et al.; Adult and Pediatric MiniMed HCL Outcomes 6-month RCT: HCL versus CSII Control Study Group. Improved glycemia with hybrid closed-loop versus continuous subcutaneous insulin infusion therapy: results from a randomized controlled trial. Diabetes Technol Ther 2023;25:1–12
31. Russell SJ, Beck RW, Damiano ER, et al.; Bionic Pancreas Research Group. Multicenter, randomized trial of a bionic pancreas in type 1 diabetes. N Engl J Med 2022;387:1161–1172
32. Stahl-Pehe A, Shokri-Mashhadi N, Wirth M, et al. Efficacy of automated insulin delivery systems in people with type 1 diabetes: a systematic review and network meta-analysis of outpatient randomised controlled trials. EClinicalMedicine 2025;82:103190
33. Burnside MJ, Lewis DM, Crocket HR, et al. Open-source automated insulin delivery in type 1 diabetes. N Engl J Med 2022;387:869–881
34. Burnside MJ, Lewis DM, Crocket HR, et al. Extended use of an open-source automated insulin delivery system in children and adults with type 1 diabetes: the 24-week continuation phase following the CREATE randomized controlled trial. Diabetes Technol Ther 2023;25:250–259
35. Lepore G, Rossini A, Bellante R, et al. Switching to the Minimed 780G system achieves clinical targets for CGM in adults with type 1 diabetes regardless of previous insulin strategy and baseline glucose control. Acta Diabetol 2022;59:1309–1315
36. Matejko B, Juza A, Kieć-Wilk B, et al. Transitioning of people with type 1 diabetes from multiple daily injections and self-monitoring of blood glucose directly to MiniMed 780G advanced hybrid closed-loop system: a two-center, randomized, controlled study. Diabetes Care 2022;45:2628–2635
37. Isganaitis E, Raghinaru D, Ambler-Osborn L, et al.; iDCL Trial Research Group. Closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the international diabetes closed-loop trial. Diabetes Technol Ther 2021;23:342–349
38. Forlenza GP, Carlson AL, Galindo RJ, et al. Real-world evidence supporting tandem control-IQ hybrid closed-loop success in the Medicare and Medicaid type 1 and type 2 diabetes populations. Diabetes Technol Ther 2022;24:814–823
39. Lal RA, Maahs DM. Optimizing basal insulin dosing. J Pediatr 2019;215:7–8
40. Mitsui Y, Kuroda A, Ishizu M, et al. Basal insulin requirement in patients with type 1 diabetes depends on the age and body mass index. J Diabetes Investig 2022;13:292–298
41. Castellano E, Attanasio R, Giagulli VA, et al.; Associazione Medici Endocrinologi (AME). The basal to total insulin ratio in outpatients with diabetes on basal-bolus regimen. J Diabetes Metab Disord 2018; 17:393–399
42. Matejko B, Kukułka A, Kieć-Wilk B, Stąpór A, Klupa T, Malecki MT. Basal insulin dose in adults with type 1 diabetes mellitus on insulin pumps in real-life clinical practice: a single-center experience. Adv Med 2018;2018:1473160
43. King AB. Mean basal insulin dose is 0.2 U/kg/d at near normal glycaemia for type 1 or 2 diabetes on continuous subcutaneous insulin infusion or once-nightly basal insulin. Diabetes Obesity Metabolism 2021;23:866–869
44. Peters Al, Lafell L. *The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook*. American Diabetes Association, 2013
45. Chiang JL, Kirkman MS, Laffel LMB, Peters AL, Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014; 37:2034–2054
46. Sämann A, Mühlhauser I, Bender R, Hunger-Dathe W, Kloos C, Müller UA. Flexible intensive insulin therapy in adults with type 1 diabetes and high risk for severe hypoglycemia and diabetic ketoacidosis. Diabetes Care 2006;29:2196–2199
47. Builes-Montaño CE, Ortiz-Cano NA, Ramirez-Rincón A, Rojas-Henao NA. Efficacy and safety of carbohydrate counting versus other forms of dietary advice in patients with type 1 diabetes mellitus: a systematic review and meta-analysis of randomised clinical trials. J Hum Nutr Diet 2022;35:1030–1042
48. Al Balwi R, Al Madani W, Al Ghamdi A. Efficacy of insulin dosing algorithms for high-fat high-protein mixed meals to control postprandial glycemic excursions in people living with type 1 diabetes: a systematic review and meta-analysis. Pediatr Diabetes 2022;23:1635–1646
49. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose Adjustment For Normal Eating (DAFNE) randomised controlled trial. BMJ 2002;325:746
50. Hopkins D, Lawrence I, Mansell P, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012;35:1638–1642
51. Speight J, Amiel SA, Bradley C, et al. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled type 1 diabetes. Diabetes Res Clin Pract 2010;89:22–29
52. Bruttomesso D, Boscari F, Lepore G, et al. A "slide rule" to adjust insulin dose using trend arrows in adults with type 1 diabetes: test in silico and in real life. Diabetes Ther 2021;12:1313–1324
53. Aleppo G, Laffel LM, Ahmann AJ, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system for the management of adults with diabetes. J Endocr Soc 2017;1:1445–1460
54. Buckingham B, Xing D, Weinzimer S, et al.; Diabetes Research In Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr Diabetes 2008;9:142–147
55. Parise M, Di Molfetta S, Graziano RT, et al. A head-to-head comparison of two algorithms for adjusting mealtime insulin doses based on CGM trend arrows in adult patients with type 1 diabetes: results from an exploratory study. Int J Environ Res Public Health 2023;20:3945
56. Petrovski G, Campbell J, Pasha M, et al. Simplified meal announcement versus precise carbohydrate counting in adolescents with type 1 diabetes using the MiniMed 780G advanced hybrid closed loop system: a randomized controlled trial comparing glucose control. Diabetes Care 2023; 46:544–550
57. Turrin KB, Trujillo JM. Effects of diabetes numeracy on glycemic control and diabetes self-management behaviors in patients on insulin pump therapy. Diabetes Ther 2019;10:1337–1346
58. White RO, Wolff K, Cavanaugh KL, Rothman R. Addressing health literacy and numeracy to improve diabetes education and care. Diabetes Spectr 2010;23:238–243
59. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2023;46:e151–e199
60. Klonoff DC, Berard L, Franco DR, et al. Advance insulin injection technique and education with FITTER forward expert recommendations. Mayo Clin Proc 2025;100:682–699
61. Bergenstal RM, Strock ES, Peremislov D, Gibney MA, Parvu V, Hirsch LJ. Safety and efficacy of insulin therapy delivered via a 4mm pen needle in obese patients with diabetes. Mayo Clin Proc 2015; 90:329–338
62. Qiao Y-C, Ling W, Pan Y-H, et al. Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. Oncotarget 2017;8:66504–66515
63. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2018;34:e2983
64. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5: 597–609
65. Mathieu C, Zinman B, Hemmingsson JU, et al.; ADJUNCT ONE Investigators. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care 2016;39:1702–1710
66. Ahrén B, Hirsch IB, Pieber TR, et al.; ADJUNCT TWO Investigators. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care 2016;39:1693–1701
67. von Herrath M, Bain SC, Bode B, et al.; Anti-IL-21–liraglutide Study Group investigators and contributors. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:212–224
68. Garg SK, Kaur G, Haider Z, Rodriquez E, Beatson C, Snell-Bergeon J. Efficacy of semaglutide in over-

weight and obese patients with type 1 diabetes. Diabetes Technol Ther 2024;26:184–189
69. Garg SK, Akturk HK, Kaur G, Beatson C, Snell-Bergeon J. Efficacy and safety of tirzepatide in overweight and obese adult patients with type 1 diabetes. Diabetes Technol Ther 2024;26:367–374
70. Pasqua M-R, Tsoukas MA, Kobayati A, Aboznadah W, Jafar A, Haidar A. Subcutaneous weekly semaglutide with automated insulin delivery in type 1 diabetes: a double-blind, randomized, crossover trial. Nat Med 2025;31:1239–1245
71. Akturk HK, Dong F, Snell-Bergeon JK, Karakus KE, Shah VN. Efficacy and safety of tirzepatide in adults with type 1 diabetes: a proof of concept observational study. J Diabetes Sci Technol 2025;19:292–296
72. Shah VN, Akturk HK, Kruger D, et al. Semaglutide in adults with type 1 diabetes and obesity. NEJM Evid 2025;4:EVIDoa2500173
73. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. Type 1 Diabetes Impacts of Semaglutide on Cardiovascular Outcomes (T1-DISCO) (NCT05819138). Accessed 23 August 2025. Available from https://clinicaltrials.gov/study/NCT05819138?tab=results
74. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. Trial of Semaglutide for Diabetic Kidney Disease in Type 1 Diabetes (RT1D) (NCT05822609). Accessed 20 August 2025. Available from https://www.clinicaltrials.gov/study/NCT05822609
75. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. Alleviating Carbohydrate Counting for Patients with Type-1 Diabetes Using a Closed Loop System with Weekly Subcutaneous Semaglutide (SEMA SMA) (NCT06387199). Accessed 20 August 2025. Available from https://clinicaltrials.gov/study/NCT06387199
76. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. Obesity Complicating Type 1 Diabetes: GLP-1 Analogue Anti-obesity Treatment (NCT06411210). Accessed 20 August 2025. Available from https://clinicaltrials.gov/study/NCT06411210
77. Rao L, Ren C, Luo S, Huang C, Li X. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: meta-analysis of randomized controlled trials. Acta Diabetol 2021;58:869–880
78. Li M, Liu Z, Yang X, et al. The effect of sodium-glucose cotransporter 2 inhibitors as an adjunct to insulin in patients with type 1 diabetes assessed by continuous glucose monitoring: a systematic review and meta-analysis. J Diabetes Complications 2023;37:108632
79. Chen M-B, Xu R-J, Zheng Q-H, Zheng X-W, Wang H. Efficacy and safety of sotagliflozin adjuvant therapy for type 1 diabetes mellitus: a systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e20875
80. U.S. Food and Drug Administration. FDA Introductory Remarks: January 17, 2019: Endocrinologic and Metabolic Drugs Advisory Committee Meeting. 2019. Accessed 25 August 2025. Available from https://wayback.archive-it.org/7993/20190207212714/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629782.pdf
81. Bhatt DL, Szarek M, Steg PG, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117–128
82. Bhatt DL, Szarek M, Pitt B, et al.; SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021;384:129–139
83. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care 2019;42:1147–1154
84. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–613
85. Lachin JM, McGee P, Palmer JP; DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes 2014;63:739–748
86. Kosheleva L, Koshelev D, Lagunas-Rangel FA, Levit S, Rabinovitch A, Schiöth HB. Disease-modifying pharmacological treatments of type 1 diabetes: molecular mechanisms, target checkpoints, and possible combinatorial treatments. Pharmacol Rev 2025;77:100044
87. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. BMJ 2017;357:j1321
88. U.S. Food & Drug Administration. Lantidra. Accessed 25 August 2025. Available from https://www.fda.gov/vaccines-blood-biologics/lantidra
89. Geta ET, Terefa DR, Hailu WB, et al. Effectiveness of shared decision-making for glycaemic control among type 2 diabetes mellitus adult patients: a systematic review and meta-analysis. PLoS One 2024;19:e0306296
90. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786
91. Lingvay I, Sumithran P, Cohen RV, Le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet 2022;399:394–405
92. Wing RR, Lang W, Wadden TA, et al.; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481–1486
93. Adler AI, Coleman RL, Leal J, Whiteley WN, Clarke P, Holman RR. Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). Lancet 2024;404:145–155
94. Kunutsor SK, Balasubramanian VG, Zaccardi F, et al. Glycaemic control and macrovascular and microvascular outcomes: a systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes. Diabetes Obes Metab 2024;26:2069–2081
95. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
96. Bahardoust M, Mousavi S, Yariali M, et al. Effect of metformin (vs. placebo or sulfonylurea) on all-cause and cardiovascular mortality and incident cardiovascular events in patients with diabetes: an umbrella review of systematic reviews with meta-analysis. J Diabetes Metab Disord 2024;23:27–38
97. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751
98. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369
99. U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Accessed 25 August 2025. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain
100. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med 2003;163:2594–2602
101. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;2010:CD002967
102. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–1437
103. Out M, Kooy A, Lehert P, Schalkwijk CA, Stehouwer CDA. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3year trial. J Diabetes Complications 2018;32:171–178
104. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101:1754–1761
105. Frías JP, Davies MJ, Rosenstock J, et al.; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 2021;385:503–515
106. Sorli C, Harashima S-I, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017;5:251–260
107. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med 2020;173:278–286
108. Nathan DM, Lachin JM, Balasubramanyam A, et al.; GRADE Study Research Group. Glycemia reduction in type 2 diabetes - glycemic outcomes. N Engl J Med 2022;387:1063–1074
109. Babu A, Mehta A, Guerrero P, et al. Safe and simple emergency department discharge therapy for patients with type 2 diabetes mellitus and severe hyperglycemia. Endocr Pract 2009;15:696–704
110. Buse JB, Peters A, Russell-Jones D, et al. Is insulin the most effective injectable antihyperglycaemic therapy? Diabetes Obes Metab 2015;17:145–151
111. D'Alessio D, Häring H-U, Charbonnel B, et al.; EAGLE Investigators. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes Obes Metab 2015;17:170–178

112. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care 2016;39(Suppl. 2):S137–S145
113. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab 2015;17:268–275
114. Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and safety of initial combination therapy in treatment-naïve type 2 diabetes patients: a systematic review and meta-analysis. Diabetes Ther 2018;9:1995–2014
115. Aroda VR, González-Galvez G, Grøn R, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:596–605
116. Khunti K, Davies MJ. Clinical inertia-time to reappraise the terminology? Prim Care Diabetes 2017;11:105–106
117. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613
118. Maloney A, Rosenstock J, Fonseca V. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. Clin Pharmacol Ther 2019;105:1213–1223
119. Lajthia E, Bucheit JD, Nadpara PA, et al. Combination therapy with once-weekly glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a case series. Pharm Pract (Granada) 2019;17:1588
120. Violante R, Oliveira JHA, Yoon K-H, et al. A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin. Diabet Med 2012;29:e417–e424
121. Nauck MA, Kahle M, Baranov O, Deacon CF, Holst JJ. Addition of a dipeptidyl peptidase-4 inhibitor, sitagliptin, to ongoing therapy with the glucagon-like peptide-1 receptor agonist liraglutide: a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab 2017;19:200–207
122. Pratley R, Amod A, Hoff ST, et al.; PIONEER 4 investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:39–50
123. Del Prato S, Kahn SE, Pavo I, et al.; SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet 2021;398:1811–1824
124. Singh S, Wright EE, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2017;19:228–238
125. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. Diabetes Metab Syndr Obes 2017;10:123–139
126. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. Diabetes Obes Metab 2017;19:216–227
127. Giorgino F, Benroubi M, Sun J-H, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care 2015;38:2241–2249
128. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355–366
129. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir. Diabetes Care 2013;36:1368–1376
130. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 2010;375:2234–2243
131. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA 2022;327:534–545
132. Packer M, Zile MR, Kramer CM, et al.; SUMMIT Trial Study Group. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med 2025;392:427–437
133. Kosiborod MN, Petrie MC, Borlaug BA, et al.; STEP-HFpEF DM Trial Committees and Investigators. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med 2024;390:1394–1407
134. Pratley RE, Tuttle KR, Rossing P, et al.; FLOW Trial Committees and Investigators. Effects of semaglutide on heart failure outcomes in diabetes and chronic kidney disease in the FLOW trial. J Am Coll Cardiol 2024;84:1615–1628
135. Kosiborod MN, Deanfield J, Pratley R, et al.; SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM Trial Committees and Investigators. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet 2024;404:949–961
136. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Association of cumulative multimorbidity, glycemic control, and medication use with hypoglycemia-related emergency department visits and hospitalizations among adults with diabetes. JAMA Netw Open 2020;3:e1919099
137. Nathan DM, Lachin JM, Bebu I, et al.; GRADE Study Research Group. Glycemia reduction in type 2 diabetes - microvascular and cardiovascular outcomes. N Engl J Med 2022;387:1075–1088
138. McCoy RG, Herrin J, Swarna KS, et al. Effectiveness of glucose-lowering medications on cardiovascular outcomes in patients with type 2 diabetes at moderate cardiovascular risk. Nat Cardiovasc Res 2024;3:431–440
139. Berg DD, Wiviott SD, Scirica BM, et al. Heart failure risk stratification and efficacy of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes mellitus. Circulation 2019;140:1569–1577
140. Kidney Disease: improving Global Outcomes Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102:S1–S127
141. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776–785
142. Perkovic V, Tuttle KR, Rossing P, et al.; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024;391:109–121
143. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol 2022;10:774–785
144. Heerspink HJL, Friedman AN, Bjornstad P, et al. Kidney parameters with tirzepatide in obesity with or without type 2 diabetes. J Am Soc Nephrol 2025;36:2190–2200
145. U.S. Food & Drug Administration. Exenatide extended-release prescribing information. Accessed 20 September 2025. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022200s026lbl.pdf
146. U.S. Food & Drug Administration. Lixisenatide prescribing information. Accessed 20 September 2025. Available from https://products.sanofi.us/soliqua100-33/soliqua100-33.pdf
147. Scheen AJ. Pharmacokinetics and clinical use of incretin-based therapies in patients with chronic kidney disease and type 2 diabetes. Clin Pharmacokinet 2015;54:1–21
148. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–158
149. Reyes-Farias CI, Reategui-Diaz M, Romani-Romani F, Prokop L. The effect of sodium-glucose cotransporter 2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes mellitus on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS One 2023;18:e0295059
150. Herrington WG, Staplin N, Wanner C, et al.; The Empa-Kidney Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117–127
151. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
152. Dagogo-Jack S, Pratley RE, Cherney DZI, et al. Glycemic efficacy and safety of the SGLT2 inhibitor ertugliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease: an analysis from the VERTIS CV randomized trial. BMJ Open Diabetes Res Care 2021;9:e002484
153. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int 2018;93:231–244
154. Wexler DJ, de Boer IH, Ghosh A, et al.; GRADE Research Group. Comparative effects of glucose-lowering medications on kidney outcomes in

type 2 diabetes: the GRADE randomized clinical trial. JAMA Intern Med 2023;183:705–714
155. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307
156. Sanyal AJ, Newsome PN, Kliers I, et al.; ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med 2025;392:2089–2099
157. Newsome PN, Buchholtz K, Cusi K, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113–1124
158. Loomba R, Hartman ML, Lawitz EJ, et al.; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299–310
159. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 2022;10:393–406
160. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–690
161. Sathyanarayana P, Jogi M, Muthupillai R, Krishnamurthy R, Samson SL, Bajaj M. Effects of combined exenatide and pioglitazone therapy on hepatic fat content in type 2 diabetes. Obesity (Silver Spring) 2011;19:2310–2315
162. Abdul-Ghani M, Migahid O, Megahed A, DeFronzo RA, Al-Ozairi E, Jayyousi A. Combination therapy with pioglitazone/exenatide improves beta-cell function and produces superior glycaemic control compared with basal/bolus insulin in poorly controlled type 2 diabetes: a 3-year follow-up of the Qatar study. Diabetes Obes Metab 2020;22:2287–2294
163. Lavynenko O, Abdul-Ghani M, Alatrach M, et al. Combination therapy with pioglitazone/exenatide/metformin reduces the prevalence of hepatic fibrosis and steatosis: the efficacy and durability of initial combination therapy for type 2 diabetes (EDICT). Diabetes Obes Metab 2022;24:899–907
164. Garvey WT, Frias JP, Jastreboff AM, et al.; SURMOUNT-2 investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2023;402:613–626
165. Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971–984
166. Bonora E, Frias JP, Tinahones FJ, et al. Effect of dulaglutide 3.0 and 4.5 mg on weight in patients with type 2 diabetes: exploratory analyses of AWARD-11. Diabetes Obes Metab 2021;23:2242–2250
167. Davies MJ, Bergenstal R, Bode B, et al.; NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687–699
168. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide er in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care 2018;41:258–266
169. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376:641–651
170. Blonde L, Merilainen M, Karwe V, Raskin P, TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. Diabetes Obes Metab 2009;11:623–631
171. Lucidi P, Candeloro P, Cioli P, et al. Pharmacokinetic and pharmacodynamic head-to-head comparison of clinical, equivalent doses of insulin glargine 300 units · mL^{1} and insulin degludec 100 units·mL^{1} in type 1 diabetes. Diabetes Care 2021;44:125–132
172. Wang Z, Hedrington MS, Gogitidze Joy N, et al. Dose-response effects of insulin glargine in type 2 diabetes. Diabetes Care 2010;33:1555–1560
173. Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2020;11:CD005613
174. Mannucci E, Caiulo C, Naletto L, Madama G, Monami M. Efficacy and safety of different basal and prandial insulin analogues for the treatment of type 2 diabetes: a network meta-analysis of randomized controlled trials. Endocrine 2021;74:508–517
175. Russell-Jones D, Gall M-A, Niemeyer M, Diamant M, Del Prato S. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: a meta-analysis of seven clinical trials. Nutr Metab Cardiovasc Dis 2015;25:898–905
176. Mehta R, Goldenberg R, Katselnik D, Kuritzky L. Practical guidance on the initiation, titration, and switching of basal insulins: a narrative review for primary care. Ann Med 2021;53:998–1009
177. Cowart K. Overbasalization: addressing hesitancy in treatment intensification beyond basal insulin. Clin Diabetes 2020;38:304–310
178. Maiorino MI, Chiodini P, Bellastella G, et al. The good companions: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2019;154:101–115
179. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2:30–37
180. McCall AL. Insulin therapy and hypoglycemia. Endocrinol Metab Clin North Am 2012;41:57–87
181. Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. Cochrane Database Syst Rev 2018;12:CD013228
182. de la Peña A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. Diabetes Care 2011;34:2496–2501
183. Hood RC, Borra S, Fan L, Pollom RD, Huang A, Chen J. Treatment patterns and outcomes, before and after humulin R U-500 initiation, among high-dose type 2 diabetes mellitus patients in the United States. Endocr Pract 2021;27:798–806
184. Becker RHA, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 units · mL^{1} provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units · mL^{1}. Diabetes Care 2015;38:637–643
185. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab 2015;17:835–842
186. Yki-Järvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care 2014;37:3235–3243
187. Korsatko S, Deller S, Koehler G, et al. A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. Clin Drug Investig 2013;33:515–521
188. de la Peña A, Seger M, Soon D, et al. Bioequivalence and comparative pharmacodynamics of insulin lispro 200 U/mL relative to insulin lispro (Humalog) 100 U/mL. Clin Pharmacol Drug Dev 2016;5:69–75
189. Gentile S, Fusco A, Colarusso S, et al. A randomized, open-label, comparative, crossover trial on preference, efficacy, and safety profiles of lispro insulin u-100 versus concentrated lispro insulin u-200 in patients with type 2 diabetes mellitus: a possible contribution to greater treatment adherence. Expert Opin Drug Saf 2018;17:445–450
190. Grant M, Heise T, Baughman R. Comparison of pharmacokinetics and pharmacodynamics of inhaled technosphere insulin and subcutaneous insulin lispro in the treatment of type 1 diabetes mellitus. Clin Pharmacokinet 2022;61:413–422
191. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. Diabetes Technol Ther 2018;20:639–647
192. Hoogwerf BJ, Pantalone KM, Basina M, Jones MC, Grant M, Kendall DM. Results of a 24-week trial of Technosphere insulin versus insulin aspart in type 2 diabetes. Endocr Pract 2021;27:38–43
193. Price DA, Deng Q, Kipnes M, Beck SE. Episodic real-time CGM use in adults with type 2 diabetes: results of a pilot randomized controlled trial. Diabetes Ther 2021;12:2089–2099
194. Chesser H, Srinivasan S, Puckett C, Gitelman SE, Wong JC. Real-time continuous glucose monitoring in adolescents and young adults with type 2 diabetes can improve quality of life. J Diabetes Sci Technol 2024;18:911–919
195. Martens TW, Willis HJ, Bergenstal RM, Kruger DF, Karslioglu-French E, Steenkamp DW. A randomized controlled trial using continuous glucose monitoring to guide food choices and diabetes

self-care in people with type 2 diabetes not taking insulin. Diabetes Technol Ther 2025;27:261–270
196. Battelino T, Lalic N, Hussain S, et al. The use of continuous glucose monitoring in people living with obesity, intermediate hyperglycemia or type 2 diabetes. Diabetes Res Clin Pract 2025;223:112111
197. Aronson R, Brown RE, Chu L, et al. Impact of flash glucose monitoring in people with type 2 diabetes inadequately controlled with non-insulin antihyperglycaemic therapy (IMMEDIATE): a randomized controlled trial. Diabetes Obes Metab 2023;25:1024–1031
198. Moon SJ, Kim K-S, Lee WJ, Lee MY, Vigersky R, Park C-Y. Efficacy of intermittent short-term use of a real-time continuous glucose monitoring system in non-insulin-treated patients with type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab 2023;25:110–120
199. Martens T, Beck RW, Bailey R, et al.; MOBILE Study Group. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. JAMA 2021;325:2262–2272
200. Agarwal S, Varghese RT, Savian R, Low Wang CC, Galindo RJ. Moving beyond glycated hemoglobin to glucose patterns: newer indications for continuous glucose monitor use. Endocr Pract 2025;31:1046–1053
201. van Dijk P, Bouma A, Landman GW, et al. Hypoglycemia in frail elderly patients with type 2 diabetes mellitus treated with sulfonylurea. J Diabetes Sci Technol 2017;11:438–439
202. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476
203. Hansen KW, Bibby BM. The frequency of intermittently scanned glucose and diurnal variation of glycemic metrics. J Diabetes Sci Technol 2022;16:1461–1465
204. Urakami T, Yoshida K, Kuwabara R, et al. Frequent scanning using flash glucose monitoring contributes to better glycemic control in children and adolescents with type 1 diabetes. J Diabetes Investig 2022;13:185–190
205. Laffel LM, Kanapka LG, Beck RW, et al.; CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. JAMA 2020;323:2388–2396
206. New JP, Ajjan R, Pfeiffer AFH, Freckmann G. Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). Diabet Med 2015;32:609–617
207. Gubitosi-Klug RA, Braffett BH, Bebu I, et al. Continuous glucose monitoring in adults with type 1 diabetes with 35 years duration from the DCCT/EDIC study. Diabetes Care 2022;45:659–665
208. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. Diabetologia 2022;65:604–619
209. Seidu S, Kunutsor SK, Ajjan RA, Choudhary P. Efficacy and safety of continuous glucose monitoring and intermittently scanned continuous glucose monitoring in patients with type 2 diabetes: a systematic review and meta-analysis of interventional evidence. Diabetes Care 2024;47:169-179
210. Phillip M, Nimri R, Bergenstal RM, et al. Consensus recommendations for the use of automated insulin delivery technologies in clinical practice. Endocr Rev 2023;44:254–280
211. Brown SA, Beck RW, Raghinaru D, et al.; iDCL Trial Research Group. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. Diabetes Care 2020;43:1822–1828
212. Pasquel FJ, Davis GM, Huffman DM, et al.; Omnipod 5 SECURE-T2D Consortium. Automated insulin delivery in adults with type 2 diabetes: a nonrandomized clinical trial. JAMA Netw Open 2025;8:e2459348
213. Bhargava A, Bergenstal RM, Warren ML, et al.; IMPACT2D Study Group. Safety and effectiveness of MiniMedTM 780G advanced hybrid closed-loop insulin intensification in adults with insulin-requiring type 2 diabetes. Diabetes Technol Ther 2025;27:366–375
214. Davis GM, Peters AL, Bode BW, et al. Safety and efficacy of the Omnipod 5 automated insulin delivery system in adults with type 2 diabetes: from injections to hybrid closed-loop therapy. Diabetes Care 2023;46:742–750
215. Kudva YC, Raghinaru D, Lum JW, et al.; 2IQP Study Group. A randomized trial of automated insulin delivery in type 2 diabetes. N Engl J Med 2025;392:1801–1812
216. Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. Diabetes Technol Ther 2019;21:522–530
217. Settles JA, Gerety GF, Spaepen E, Suico JG, Child CJ. Nasal glucagon delivery is more successful than injectable delivery: a simulated severe hypoglycemia rescue. Endocr Pract 2020;26:407–415
218. Herges JR, Galindo RJ, Neumiller JJ, Heien HC, Umpierrez GE, McCoy RG. Glucagon prescribing and costs among U.S. adults with diabetes, 2011-2021. Diabetes Care 2023;46:620–627
219. Kahn PA, Liu S, McCoy R, Gabbay RA, Lipska K. Glucagon use by U.S. adults with type 1 and type 2 diabetes. J Diabetes Complications 2021;35:107882
220. Benning TJ, Heien HC, Herges JR, Creo AL, Al Nofal A, McCoy RG. Glucagon fill rates and cost among children and adolescents with type 1 diabetes in the United States, 2011–2021. Diabetes Res Clin Pract 2023;206:111026
221. Riddle MC, Herman WH. The cost of diabetes care-an elephant in the room. Diabetes Care 2018;41:929–932
222. Merative. Redbook (electronic version). Accessed 15 July 2025. Available from https://www.micromedexsolutions.com
223. Data.Medicaid.gov. NADAC (National Average Drug Acquisition Cost). Accessed 15 July 2025. Available from https://healthdata.gov/dataset/NADAC-National-Average-Drug-Acquisition-Cost-2024/3tha-57c6/about_data
224. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. Diabetes Res Clin Pract 2018;143:24–33
225. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. Med Care 2016;54:796–803
226. Centers for Medicare & Medicaid Services. Part D Senior Savings Model. Accessed 25 August 2025. Available from https://www.cms.gov/priorities/innovation/innovation-models/part-d-savings-model
227. Baig KA, Fry CE, Buntin MB, Powers AC, Dusetzina SB. Insulin out-of-pocket spending caps and employer-sponsored insurance: changes in out-of-pocket and total costs for insulin and healthcare. Health Serv Res 2025:e14656
228. American Diabetes Association. State Insulin Copay Caps. Accessed 25 August 2025. Available from https://diabetes.org/tools-resources/affordable-insulin/state-insulin-copay-caps
229. Suran M. All 3 major insulin manufacturers are cutting their prices-here's what the news means for patients with diabetes. JAMA 2023;329:1337–1339
230. Herges JR, Neumiller JJ, McCoy RG. Easing the financial burden of diabetes management: a guide for patients and primary care clinicians. Clin Diabetes 2021;39:427–436
231. U.S. Food & Drug Administration. FDA Drug Shortages. Accessed 17 August 2025. Available from https://dps.fda.gov/drugshortages
232. U.S. Food & Drug Administration. Drug Compounding and Drug Shortages. Accessed 25 August 2025. Available from https://www.fda.gov/drugs/human-drug-compounding/drug-compounding-and-drug-shortages
233. Ashraf AR, Mackey TK, Schmidt J, et al. Safety and risk assessment of no-prescription online semaglutide purchases. JAMA Netw Open 2024;7:e2428280
234. U.S. Food & Drug Administration. FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products. Accessed 25 August 2025. Available from https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded
235. Lambson JE, Flegal SC, Johnson AR. Administration errors of compounded semaglutide reported to a poison control center-case series. J Am Pharm Assoc (2003) 2023;63:1643–1645
236. U.S. Food & Drug Administration. FDA warns consumers not to use counterfeit Ozempic (semaglutide) found in U.S. drug supply chain. Accessed 25 August 2025. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain
237. Neumiller JJ, Bajaj M, Bannuru RR, et al. Compounded GLP-1 and dual GIP/GLP-1 receptor agonists: a statement from the American Diabetes Association. Diabetes Care 2025;48:177–181
238. Whitley HP, Trujillo JM, Neumiller JJ. Special report: potential strategies for addressing GLP-1 and dual GLP-1/GIP Receptor agonist shortages. Clin Diabetes 2023;41:467–473
239. Urva S, Coskun T, Loghin C, et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists. Diabetes Obes Metab 2020;22:1886–1891
240. Skelley JW, Swearengin K, York AL, Glover LH. The impact of tirzepatide and glucagon-like peptide 1 receptor agonists on oral hormonal contraception. J Am Pharm Assoc (2003) 2024;64:204–211.e4 e204

241. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. A Study of the Effect of Tirzepatide on How the Body Handles Birth Control Pills in Healthy Female Participants (NCT04172987). Accessed 12 June 2024. Available from https://clinicaltrials.gov/study/NCT04172987
242. U.S. Food & Drug Administration. Tirzepatide prescribing information. Accessed 25 August 2025. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf
243. Chang L-S, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev 2019;40:17–65
244. Zhou L, Yang S, Li Y, Xue C, Wan R. A comprehensive review of immune checkpoint inhibitor-related diabetes mellitus: incidence, clinical features, management, and prognosis. Front Immunol 2024;15:1448728
245. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018;4:173–182
246. Liu J, Zhou H, Zhang Y, et al. Reporting of immune checkpoint inhibitor therapy-associated diabetes, 2015–2019. Diabetes Care 2020;43:e79–e80
247. Mulla K, Farag S, Moore B, et al. Hyperglycaemia following immune checkpoint inhibitor therapy-Incidence, aetiology and assessment. Diabet Med 2023;40:e15053
248. Byun DJ, Braunstein R, Flynn J, et al. Immune checkpoint inhibitor-associated diabetes: a single-institution experience. Diabetes Care 2020;43:3106–3109
249. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021;39:4073–4126
250. Goncalves MD, Hopkins BD, Cantley LC. phosphatidylinositol 3-kinase, growth disorders, and cancer. N Engl J Med 2018;379:2052–2062
251. André F, Ciruelos E, Rubovszky G, et al.; SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929–1940
252. André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021;32:208–217
253. Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. Ann Oncol 2020;31:1001–1010
254. Jhaveri KL, Im S-A, Saura C, et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. N Engl J Med 2025;393:151–161
255. Liu D, Weintraub MA, Garcia C, et al. Characterization, management, and risk factors of hyperglycemia during PI3K or AKT inhibitor treatment. Cancer Med 2022;11:1796–1804
256. Gallagher EJ, Moore H, Lacouture ME, et al. Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. NPJ Breast Cancer 2024;10:12
257. Ihle NT, Lemos R, Schwartz D, et al. Peroxisome proliferator-activated receptor gamma agonist pioglitazone prevents the hyperglycemia caused by phosphatidylinositol 3-kinase pathway inhibition by PX-866 without affecting antitumor activity. Mol Cancer Ther 2009;8:94–100
258. Borrego MR, Lu Y-S, Reyes-Cosmelli F, et al. SGLT2 inhibition improves PI3Kα inhibitor-induced hyperglycemia: findings from preclinical animal models and from patients in the BYLieve and SOLAR-1 trials. Breast Cancer Res Treat 2024;208:111–121
259. Goncalves MD, Farooki A. Management of phosphatidylinositol-3-kinase inhibitor-associated hyperglycemia. Integr Cancer Ther 2022;21:15347354211073163
260. Cheung Y-MM, McDonnell M, Hamnvik O-PR. A targeted approach to phosphoinositide-3-kinase/Akt/mammalian target of rapamycin-induced hyperglycemia. Curr Probl Cancer 2022;46:100776
261. Khan KH, Wong M, Rihawi K, et al. Hyperglycemia and phosphatidylinositol 3-kinase/protein kinase b/mammalian target of rapamycin (PI3K/AKT/mTOR) inhibitors in phase I trials: incidence, predictive factors, and management. Oncologist 2016;21:855–860
262. Busaidy NL, Farooki A, Dowlati A, et al. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. J Clin Oncol 2012;30:2919–2928
263. Nowak KM, Rdzanek-Pikus M, Romanowska-Próchnicka K, Nowakowska-Płaza A, Papierska L. High prevalence of steroid-induced glucose intolerance with normal fasting glycaemia during low-dose glucocorticoid therapy: an oral glucose tolerance test screening study. Rheumatology (Oxford) 2021;60:2842–2851
264. Kulkarni S, Durham H, Glover L, et al. Metabolic adverse events associated with systemic corticosteroid therapy-a systematic review and meta-analysis. BMJ Open 2022;12:e061476
265. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Miñambres I, Gomez-Huelgas R. Glucocorticoid-induced hyperglycemia. J Diabetes 2014;6:9–20
266. Elena C, Chiara M, Angelica B, et al. Hyperglycemia and diabetes induced by glucocorticoids in nondiabetic and diabetic patients: revision of literature and personal considerations. Curr Pharm Biotechnol 2018;19:1210–1220
267. Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. J Clin Endocrinol Metab 2011;96:1789–1796
268. Zhang F, Karam JG. Glycemic profile of intravenous dexamethasone-induced hyperglycemia using continuous glucose monitoring. Am J Case Rep 2021;22:e930733
269. Wallace MD, Metzger NL. Optimizing the treatment of steroid-induced hyperglycemia. Ann Pharmacother 2018;52:86–90
270. Limbachia V, Nunney I, Page DJ, et al. The effect of different types of oral or intravenous corticosteroids on capillary blood glucose levels in hospitalized inpatients with and without diabetes. Clin Ther 2024;46:e59–e63
271. Limbachia V, Nunney I, Page DJ, et al. Differential effects of oral versus intravenous hydrocortisone and dexamethasone on capillary blood glucose levels in adult inpatients - a single centre study. Clin Med (Lond) 2024;24:100249
272. Roberts A, James J, Dhatariya K, Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med 2018;35:1011–1017
273. Gerards MC, de Maar JS, Steenbruggen TG, Hoekstra JBL, Vriesendorp TM, Gerdes VEA. Add-on treatment with intermediate-acting insulin versus sliding-scale insulin for patients with type 2 diabetes or insulin resistance during cyclic glucocorticoid-containing antineoplastic chemotherapy: a randomized crossover study. Diabetes Obes Metab 2016;18:1041–1044
274. Burt MG, Drake SM, Aguilar-Loza NR, Esterman A, Stranks SN, Roberts GW. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. Intern Med J 2015;45:261–266
275. Joharatnam-Hogan N, Chambers P, Dhatariya K, Board R; Joint British Diabetes Society for Inpatient Care (JBDS), UK Chemotherapy Board (UKCB). A guideline for the outpatient management of glycaemic control in people with cancer. Diabet Med 2022;39:e14636
276. Türk T, Pietruck F, Dolff S, et al. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. Am J Transplant 2006;6:842–846
277. Ode KL, Ballman M, Battezzati A, et al. ISPAD clinical practice consensus guidelines 2022: management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2022;23:1212–1228
278. Kurnikowski A, Nordheim E, Schwaiger E, et al. Criteria for prediabetes and posttransplant diabetes mellitus after kidney transplantation: a 2-year diagnostic accuracy study of participants from a randomized controlled trial. Am J Transplant 2022;22:2880–2891
279. Sharif A, Chakkera H, de Vries APJ, et al. International consensus on post-transplantation diabetes mellitus. Nephrol Dial Transplant 2024;39:531–549
280. Kuningas K, Driscoll J, Mair R, et al. Comparing glycaemic benefits of active versus passive lifestyle intervention in kidney allograft recipients: a randomized controlled trial. Transplantation 2020;104:1491–1499
281. Hecking M, Haidinger M, Döller D, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. J Am Soc Nephrol 2012;23:739–749
282. Schwaiger E, Krenn S, Kurnikowski A, et al. Early postoperative basal insulin therapy versus standard of care for the prevention of diabetes mellitus after kidney transplantation: a multicenter randomized trial. J Am Soc Nephrol 2021;32:2083–2098
283. Chandra A, Rao N, Pooniya V, Singh A. Hypoglycemia with insulin in post-transplant diabetes mellitus. Transpl Immunol 2023;78:101833
284. Tuerk TR, Bandur S, Nuernberger J, et al. Gliquidone therapy of new-onset diabetes mellitus after kidney transplantation. Clin Nephrol 2008;70:26–32
285. Lo C, Toyama T, Oshima M, et al. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. Cochrane Database Syst Rev 2020;8:CD009966
286. Lawrence SE, Chandran MM, Park JM, et al. Sweet and simple as syrup: a review and guidance for use of novel antihyperglycemic agents for

post-transplant diabetes mellitus and type 2 diabetes mellitus after kidney transplantation. Clin Transplant 2023;37:e14922
287. Munoz Pena JM, Cusi K. Posttransplant diabetes mellitus: recent developments in pharmacological management of hyperglycemia. J Clin Endocrinol Metab 2023;109:e1–e11
288. Ram E, Lavee J, Tenenbaum A, et al. Metformin therapy in patients with diabetes mellitus is associated with a reduced risk of vasculopathy and cardiovascular mortality after heart transplantation. Cardiovasc Diabetol 2019;18:118
289. Vest LS, Koraishy FM, Zhang Z, et al. Metformin use in the first year after kidney transplant, correlates, and associated outcomes in diabetic transplant recipients: a retrospective analysis of integrated registry and pharmacy claims data. Clin Transplant 2018;32:e13302
290. Abdelaziz TS, Ali AY, Fatthy M. Efficacy and safety of dipeptidyl peptidase-4 inhibitors in kidney transplant recipients with post-transplant diabetes mellitus (PTDM)- a systematic review and meta-analysis. Curr Diabetes Rev 2020;16:580–585
291. Thangavelu T, Lyden E, Shivaswamy V. A retrospective study of glucagon-like peptide 1 receptor agonists for the management of diabetes after transplantation. Diabetes Ther 2020;11:987–994
292. Kukla A, Hill J, Merzkani M, et al. The use of GLP1R agonists for the treatment of type 2 diabetes in kidney transplant recipients. Transplant Direct 2020;6:e524
293. Singh P, Pesavento TE, Washburn K, Walsh D, Meng S. Largest single-centre experience of dulaglutide for management of diabetes mellitus in solid organ transplant recipients. Diabetes Obes Metab 2019;21:1061–1065
294. Liou J-H, Liu Y-M, Chen C-H. Management of diabetes mellitus with glucagonlike peptide-1 agonist liraglutide in renal transplant recipients: a retrospective study. Transplant Proc 2018;50:2502–2505
295. Vigara LA, Villanego F, Orellana C, et al. Effectiveness and safety of glucagon-like peptide-1 receptor agonist in a cohort of kidney transplant recipients. Clin Transplant 2022;36:e14633
296. Sweiss H, Hall R, Zeilmann D, et al. Single-center evaluation of safety & efficacy of glucagon-like peptide-1 receptor agonists in solid organ transplantation. Prog Transplant 2022;32:357–362
297. Zelada H, Campana M, Kawai K, et al. Efficacy, tolerability, and safety of glucagon-like peptide 1 receptor agonists (GLP1-RA) in kidney transplant recipients with diabetes. Clin Transplant 2025;39:e70144
298. Kim HS, Lee J, Jung CH, Park J-Y, Lee WJ. Dulaglutide as an effective replacement for prandial insulin in kidney transplant recipients with type 2 diabetes mellitus: a retrospective review. Diabetes Metab J 2021;45:948–953
299. Orandi BJ, Chen Y, Li Y, et al. GLP-1 receptor agonists in kidney transplant recipients with pre-existing diabetes: a retrospective cohort study. Lancet Diabetes Endocrinol 2025;13:374–383
300. Lin L-C, Chen J-Y, Huang TT-M, Wu V-C. Association of glucagon-like peptide-1 receptor agonists with cardiovascular and kidney outcomes in type 2 diabetic kidney transplant recipients. Cardiovasc Diabetol 2025;24:87
301. Diker Cohen T, Rudman Y, Turjeman A, et al. Glucagon-like peptide 1 receptor agonists and renal outcomes in kidney transplant recipients with diabetes mellitus. Diabetes Metab 2025;51:101624
302. Dotan I, Rudman Y, Turjeman A, et al. Glucagon-like peptide 1 receptor agonists and cardiovascular outcomes in solid organ transplant recipients with diabetes mellitus. Transplantation 2024;108:e121–e128
303. Sammour Y, Nassif M, Magwire M, et al. Effects of GLP-1 receptor agonists and SGLT-2 inhibitors in heart transplant patients with type 2 diabetes: initial report from a cardiometabolic center of excellence. J Heart Lung Transplant 2021;40:426–429
304. Lim J-H, Kwon S, Jeon Y, et al. The efficacy and safety of SGLT2 inhibitor in diabetic kidney transplant recipients. Transplantation 2022;106:e404–e412
305. Schwaiger E, Burghart L, Signorini L, et al. Empagliflozin in posttransplantation diabetes mellitus: a prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. Am J Transplant 2019;19:907–919
306. Halden TAS, Kvitne KE, Midtvedt K, et al. Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. Diabetes Care 2019;42:1067–1074
307. Mahling M, Schork A, Nadalin S, Fritsche A, Heyne N, Guthoff M. Sodium-glucose cotransporter 2 (SGLT2) inhibition in kidney transplant recipients with diabetes mellitus. Kidney Blood Press Res 2019;44:984–992
308. Shah M, Virani Z, Rajput P, Shah B. Efficacy and safety of canagliflozin in kidney transplant patients. Indian J Nephrol 2019;29:278–281
309. Sánchez Fructuoso AI, Bedia Raba A, Banegas Deras E, et al. Sodium-glucose cotransporter-2 inhibitor therapy in kidney transplant patients with type 2 or post-transplant diabetes: an observational multicentre study. Clin Kidney J 2023;16:1022–1034
310. Greeley SAW, Polak M, Njølstad PR, et al. ISPAD clinical practice consensus guidelines 2022: the diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2022;23:1188–1211
311. Christensen AS, Hædersdal S, Støy J, et al. Efficacy and safety of glimepiride with or without linagliptin treatment in patients with HNF1A diabetes (maturity-onset diabetes of the young type 3): a randomized, double-blinded, placebo-controlled, crossover trial (GLIMLINA). Diabetes Care 2020;43:2025–2033
312. Umpierrez GE, Davis GM, ElSayed NA, et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024;47:1257–1275
313. Wolfsdorf JI, Ratner RE. SGLT inhibitors for type 1 diabetes: proceed with extreme caution. Diabetes Care 2019;42:991–993
314. Colacci M, Fralick J, Odutayo A, Fralick M. Sodium-glucose cotransporter-2 inhibitors and risk of diabetic ketoacidosis among adults with type 2 diabetes: a systematic review and meta-analysis. Can J Diabetes 2022;46:10–15.e2
315. Bonora BM, Avogaro A, Fadini GP. Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: an updated review of the literature. Diabetes Obes Metab 2018;20:25–33
316. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. Diabetes Metab Res Rev 2017;33:10.1002/dmrr.2924
317. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Obes Metab 2021;23:2116–2124
318. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701