9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S158–S178 | https://doi.org/10.2337/dc24-S009

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PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

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

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

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

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

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

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

9.7 Insulin treatment plan and insulin-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted to incorporate specific

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

Suggested citation: American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. *Diabetes Care 2024;47 (Suppl. 1):S158–S178*

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factors that impact choice of treatment and ensure achievement of individualized glycemic goals. **E**

Insulin Therapy

Insulin treatment is essential for individuals with type 1 diabetes because the hallmark of type 1 diabetes is absent or near-absent β-cell function. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily 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 control (7%) led to ∼50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-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 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 (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 as well as lower A1C compared with injectable human insulins (5–7). More recently, two injectable ultra-rapid-acting analog (URAA) insulin formulations were developed to 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 intensity of treatment required for their use may be prohibitive. There are multiple approaches to insulin treatment. The central precept in the management of type 1 diabetes is that some form of insulin be given in a defined treatment plan tailored to the individual to prevent diabetic ketoacidosis (DKA) and minimize clinically relevant hypoglycemia while achieving the individual's glycemic goals. The impact of the introduction of interchangeable biosimilars and unbranded versions of some analog products as well as current and upcoming price reductions on insulin access need to be evaluated. Reassessment of insulin-taking behavior and adjustment of treatment plans to account for specific factors, including cost, that impact choice of treatment is recommended at regular intervals (every 3–6 months).

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. A systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (15). Use of CSII is associated with improvement in quality of life, particularly in areas related to fear of hypoglycemia and diabetes distress, compared with multiple daily injections of insulin (16,17). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (4). Integration of continuous glucose monitoring (CGM) into the treatment plan soon after diagnosis improves glycemic outcomes, decreases hypoglycemic events, and improves quality of life for individuals with type 1 diabetes (18–23). Its use is now considered standard of care for most people with type 1 diabetes (4) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level, with further improvements when using devices with predictive low glucose insulin delivery suspension (24,25).

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

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

In general, individuals with type 1 diabetes require approximately 30–50% of their daily insulin as basal and the remainder as prandial (43). This proportion is dependent on a number of factors,

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including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage (4,44–48). Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts may be required during puberty, menses, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in adults with type 1 diabetes who are metabolically stable, with approximately one-half administered as prandial insulin given to manage blood glucose after meals and the remaining portion as basal insulin to manage glycemia in the periods between meal absorption (49). Starting doses and those soon after diagnosis may be higher, if an individual presents with ketoacidosis, or lower (0.2–0.6 units/kg), particularly in young children and those with continued endogenous insulin production (during the partial remission phase or "honeymoon period," or in people who present with type 1 diabetes in adulthood) (49–52). This guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (53).

Typical multidose treatment plans for individuals with type 1 diabetes combine premeal use of prandial insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best managed by a well-timed injection or inhalation of prandial insulin. Prandial insulin should ideally be administered prior to meal consumption; however, the optimal time to administer varies based on the pharmacokinetics of the formulation (regular, RAA, or inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demands for glucose. To approach this variability in people using insulin treatment, 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 (54–59). Education regarding adjustment of prandial insulin dose for glycemic trends should be provided to individuals who are using CGM alone or an AID system (60–63). 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 (56). With some AID systems, use of a simplified meal announcement method may be an alternative for prandial insulin dosing (31,64) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," and Section 7, "Diabetes Technology").

Due to the risk of hypoglycemia with insulin treatment, all individuals with type 1 diabetes should be prescribed glucagon. Individuals with type 1 diabetes and/or those in close contact with individuals with type 1 diabetes 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 those that do not require reconstitution are preferred for ease of administration (65,66). Clinicians should routinely review the individual's access to glucagon, as appropriate glucagon prescribing is low (67,68). See Section 6, "Glycemic Goals and Hypoglycemia," for additional information on hypoglycemia and glucagon in individuals with diabetes. The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin plans and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (4).

Insulin Administration Technique

Ensuring that individuals and/or caregivers understand correct insulin administration technique is important to optimize glycemic management and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the correct way. Recommendations have been published elsewhere outlining best practices

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

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

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

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

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for insulin administration (69). Proper insulin administration technique includes injection or infusion (for CSII or AID systems) into appropriate body areas, injection or infusion site rotation, appropriate care of injection or infusion sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery. Selection of method of administration (vial and syringe, insulin pen, 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 via whichever method is used should be completed during routine follow-up.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin administration include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (70).

Injection or infusion site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection or infusion site rotation and how to recognize and avoid areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of administration device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection or infusion 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 glucose-lowering medications have been studied for their efficacy as adjunct to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (~1 kg) with pramlintide (71). Similar results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes was associated with small reductions in body weight, insulin dose, and lipid levels but did not sustainably improve A1C (72,73). The largest clinical trials of glucagon-like

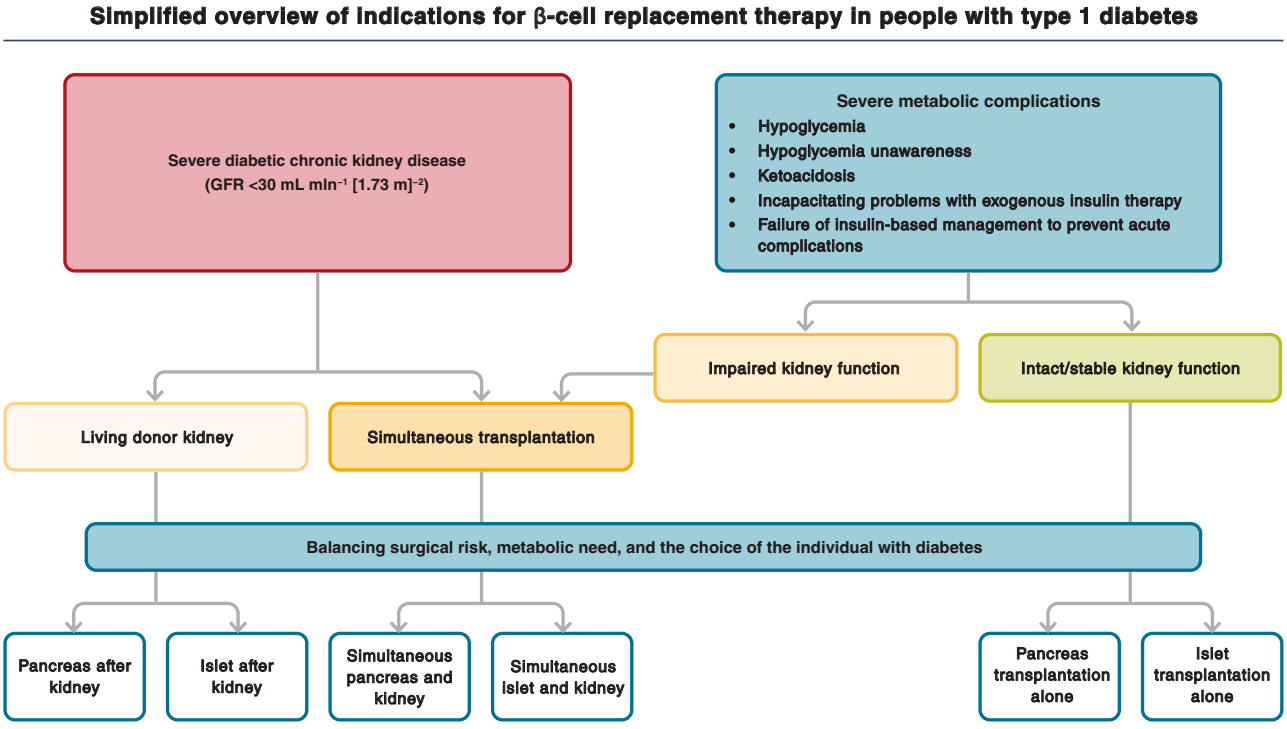

Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation or islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the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

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Table 9.1—Examples of subcutaneous insulin treatment plans

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

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Table 9.1—Continued

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

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

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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 (74,75). Similarly, 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 (76); however, SGLT2 inhibitor use in type 1 diabetes was associated with an increased rate of DKA. 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 (77); however, sotagliflozin use was associated with an eightfold increase in DKA compared with placebo (78). The studies that led to the approved indication for heart failure (HF) excluded individuals with type 1 diabetes or a history of DKA (79,80). See section PREVENTION AND TREATMENT OF HEART FAILURE within 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 patient selection and precautions (81).

There are currently no approved therapies for preservation of C-peptide or delaying the progression of clinical type 1 diabetes. Higher C-peptide levels have been associated with better A1C, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia (82). Several therapies, including verapamil and monoclonal antibodies, are currently under active investigation.

SURGICAL TREATMENT FOR 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 intensive glycemic management (83). 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 approach their A1C goal because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

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

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.8 Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. **A**

9.9 A person-centered shared decision-making approach should guide the choice of pharmacologic agents for adults with type 2 diabetes. Consider the effects on cardiovascular and renal comorbidities; effectiveness; hypoglycemia risk; impact on weight, cost and access; risk for adverse reactions and tolerability; and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.10 The glucose-lowering treatment plan should consider approaches that support weight management goals (**Fig. 9.3** and **Table 9.2**) for adults with type 2 diabetes. **A**

9.11 For adults with type 2 diabetes, use pharmacological strategies that provide sufficient effectiveness to achieve and maintain the intended treatment goals. **A**

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

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

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

9.15 In adults with type 2 diabetes without cardiovascular and/or kidney disease, pharmacologic agents should address both the individualized glycemic and weight goals (**Fig. 9.3**). **A**

9.16 In adults with type 2 diabetes who have not achieved their individualized glycemic goals, selection of subsequent glucose-lowering agents should take into consideration the individualized glycemic and weight goals as well as the presence of other metabolic comorbidities and the risk of hypoglycemia. **A**

9.17 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**

9.18 In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease (CKD), the treatment plan should include agent(s) that reduce cardiovascular and kidney disease risk (e.g., sodium–glucose cotransporter 2 inhibitor [SGLT2] and/or glucagon-like peptide 1 receptor agonist [GLP-1 RA]) (**Fig. 9.3**, **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) for glycemic management and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors (**Fig. 9.3**) (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.19 In adults with type 2 diabetes who have HF (with either reduced or preserved ejection fraction), an SGLT2 inhibitor is recommended, for glycemic management and prevention of HF hospitalizations (see Section 10,

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"Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.20 In adults with type 2 diabetes who have CKD (with confirmed estimated glomerular filtration rate [eGFR] of 20–60 mL/min per 1.73 m^2 and/or albuminuria), an SGLT2 inhibitor should be used for minimizing progression of CKD, reduction in cardiovascular events, and reduction in hospitalizations for HF (**Fig. 9.3**); however, the glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min per 1.73 m^2 (see Section 11, "Chronic Kidney Disease and Risk Management" for details on renal risk reduction recommendations). **A**

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

9.22 In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if there is evidence of ongoing catabolism (e.g., unexpected weight loss), 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**

9.23 In adults with type 2 diabetes, a GLP-1 RA, including a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, is preferred to insulin (**Fig. 9.4**). **A**

9.24 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**

9.25 In adults with type 2 diabetes, glucose-lowering agents may be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits). **A**

9.26 To minimize the risk of hypoglycemia and treatment burden when starting insulin therapy in adults with type 2 diabetes, reassess the need for and/or dose of glucose-lowering agents with higher hypoglycemia risk (i.e., sulfonylureas and meglitinides). **A**

9.27 Monitor for signs of overbasalization during insulin therapy, such as basal dose exceeding ~0.5 units/kg/day, significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability. When overbasalization is suspected, a thorough reevaluation should occur promptly to further tailor therapy to the individual's needs. **E**

9.28 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**

9.29 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**

The ADA/EASD consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2022" (84) recommends a holistic, multifaceted, person-centered approach accounting for the complexity of managing type 2 diabetes and its complications across the life span. Person-specific factors that affect choice of treatment include individualized glycemic goals (see Section 6, "Glycemic Goals and Hypoglycemia"), individualized weight goals, 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 medication. 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, avoidance of clinical 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 and treatment goals and preferences. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (84). In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD), the treatment plan should include agents that reduce cardiovascular and kidney disease risk (see **Fig. 9.3**, **Table 9.2**, Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA tirzepatide, insulin, combination

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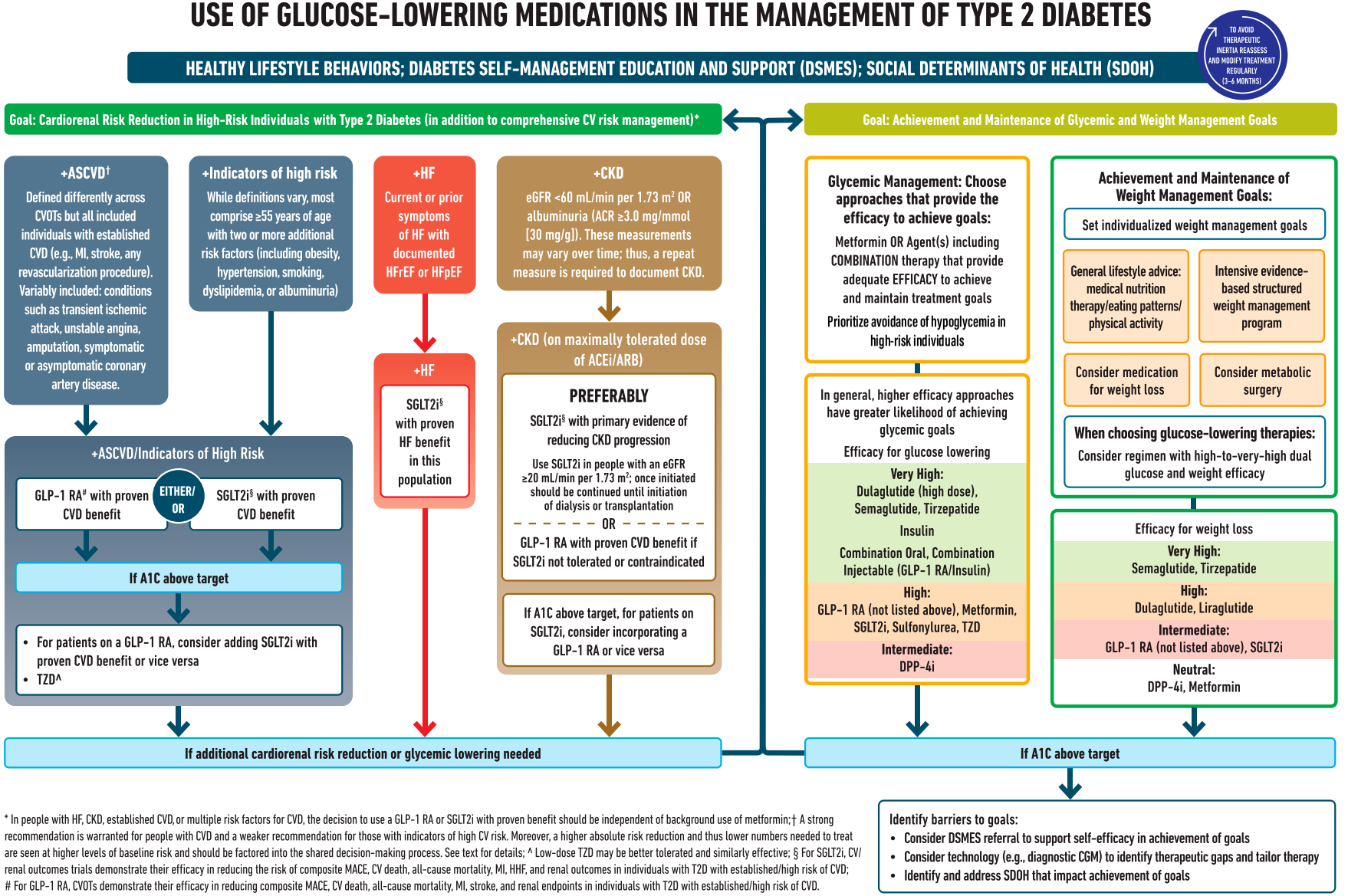
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. 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; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; 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; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

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Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*			
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Counsel patients about potential for ileus • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
Dual GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Not recommended for individuals with history of gastroparesis • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• 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 persons at risk for hypoglycemia
Insulin **Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Analogs								SQ	High	

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (104). [2]Tsapas et al. (152). Adapted from Davies et al. (84).

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oral therapy, and combination injectable therapy. Weight management is a distinct treatment goal, along with glycemic management, in individuals with type 2 diabetes, as it has multifaceted benefits, including improved glycemic management, reduction in hepatic steatosis, and improvement in cardiovascular risk factors (84–86). The glucose-lowering treatment plan should therefore consider approaches that support weight management goals, with semaglutide and tirzepatide currently having the highest weight loss efficacy among agents approved for glycemic management (**Fig. 9.3** and **Table 9.2**) (84,87,88). Additional weight management approaches, alone or in combination, should be used if needed to achieve individual goals (i.e., intensive behavioral management programs, weight loss pharmacotherapies, or metabolic surgery). See Section 8, "Obesity and Weight Management," for approaches to achieve weight management goals.

Metformin is effective and safe, is inexpensive and widely available, and may reduce risk of cardiovascular events and death (89). 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 (90).

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 renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be safely used in people with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (91). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (92). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 levels (93) (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities") in individuals treated with metformin for an extended period of time.

When A1C is $\geq$1.5% above the individualized glycemic goal (see Section 6, "Glycemic Goals and Hypoglycemia," for appropriate goals), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their goal A1C level (84,94) (**Fig. 9.3** and **Table 9.2**). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination medication plan when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels $\geq$300 mg/dL ($\geq$16.7 mmol/L) or A1C $>$10% ($>$86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (unexpected weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the medication plan and/or changing to noninsulin agents is often possible. However, there is evidence that people with poorly managed hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea, GLP-1 RA, or dual GIP and GLP-1 RA (87,88,95). GLP-1 RAs and tirzepatide have additional benefits over insulin and sulfonylureas, specifically lower risk for hypoglycemia (both) and favorable weight (both), cardiovascular (GLP-1 RAs), and kidney (GLP-1 RAs) end points.

Combination Therapy

Because type 2 diabetes is a progressive disease in many individuals, maintenance of glycemic goals often requires combination therapy. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain goal A1C. 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 (96). However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (97,98) and later combination therapy for longer durability of glycemic effect (99). The VERIFY (Vildagliptin Efficacy in combination with metformin For earlY treatment of type 2 diabetes) trial demonstrated that initial combination therapy—in this case of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin—is superior to sequential addition of medications for extending primary and secondary failure (100). Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above goal. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (e.g., GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors) may allow for weaning of the current medication plan, particularly of agents that may increase the risk of hypoglycemia and weight gain. Thus, treatment intensification may not necessarily follow a pure sequential addition of therapy but instead reflect a tailoring of the medication plan in alignment with person-centered treatment goals and pursuit of multifaceted treatment goals (**Fig. 9.3**).

Treatment intensification, deintensification, or modification—as appropriate—for people not meeting individualized treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment change. The choice of medication added to initial therapy is based on the clinical characteristics of the individual and their preferences and goals for care. Important clinical characteristics include the presence of overweight or obesity, established ASCVD or indicators of high ASCVD risk, HF, CKD, obesity, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, hypoglycemia, and risk for specific adverse drug effects, as well as safety, tolerability, accessibility, usability, and cost. Results from comparative effectiveness meta-analyses suggest that each new class of oral noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (8–11 mmol/mol); if a GLP-1 RA or the dual GIP and GLP-1 RA is added, a 1 to $\geq$2% lowering in A1C is expected (87,101,102) (**Fig. 9.3** and **Table 9.2**).

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 (see **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) is recommended as part of the glucose-lowering plan independent of A1C, independent of metformin use, and in consideration of person-specific factors (**Fig. 9.3**). Individuals with these comorbidities already achieving their individualized glycemic goals with other medications may benefit from switching to these preferred

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medications, if possible, 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 as SGLT2 inhibitors and GLP-1 RA are associated with lower risk of hypoglycemia and individuals with ASCVD, HF, and CKD experience heightened hypoglycemia risk.

For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences (103). A systematic review and network meta-analysis suggests that the greatest reductions in A1C level are with insulin plans, specific GLP-1 RAs (particularly semaglutide), and tirzepatide (87,88,104). In all cases, treatment plans need to be continuously reviewed for efficacy, side effects, and 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 or changes in treatment goals). Section 13, "Older Adults," has a full discussion of treatment considerations in older adults, in whom changes of glycemic goals and de-escalation of therapy are common.

The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent medication plans is a well-established approach that is effective for many individuals. In addition, evidence supports the utility of GLP-1 RAs in people not attaining their glycemic goals. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is commercially available (105). In trials comparing 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 injectable GLP-1 RA and dual GIP and GLP-1 RA were similar to or greater than that of basal insulin (106–113). GLP-1 RAs and dual GIP and GLP-1 RA in these trials 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 the potency of an injectable therapy for glucose management (**Fig. 9.4**). In individuals who are intensified to insulin therapy, combination therapy with a GLP-1 RA or a dual GIP and GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effect, as well as weight and hypoglycemia benefit, than treatment intensification with insulin alone (84,114). However, cost and tolerability issues are important considerations in GLP-1 RA and dual GIP and GLP-1 RA use.

Costs for diabetes medications have increased dramatically over the past two decades, and an increasing proportion is now passed on to people with diabetes and their families (115). **Table 9.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (116) and National Average Drug Acquisition Costs (NADAC) (117), separate measures to allow for a comparison of drug prices, but do not account for discounts, rebates, or 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 (118); cost-reducing strategies may improve medication-taking behavior in some cases (119). Although caps on costs are starting to occur for insulin products, no such caps exist for diabetes durable medical equipment or for noninsulin medications. It is therefore essential to screen all people with diabetes for financial concerns and cost-related barriers to care and to engage members of the health care team—including pharmacists, certified diabetes care and education specialists, social workers, community health workers, community paramedics, and others—to identify cost-saving opportunities for medications, diabetes durable medical equipment, and glucagon (120).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in adults with type 2 diabetes treated with an SGLT2 inhibitor or GLP-1 RA; see Section 10, "Cardiovascular Disease and Risk Management," for details. Participants enrolled in many of the cardiovascular outcomes trials had A1C ≥6.5% (≥48 mmol/mol), with more than 70% taking metformin at baseline, with analyses indicating benefit with or without metformin (84). Thus, a practical extension of these results to clinical practice is to use these medications preferentially in people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these individuals, incorporating one of the SGLT2 inhibitors and/or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (see **Fig. 9.3**, **Table 9.2**, and Section 10, "Cardiovascular Disease and Risk Management"). Emerging data suggest that use of both classes of drugs will provide additional cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 RA may be considered to provide the complementary outcomes benefits associated with these classes of medication (121). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD, while dedicated renal outcomes studies have demonstrated benefit of specific SGLT2 inhibitors. See Section 11, "Chronic Kidney Disease and Risk Management," for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Individuals at low risk for ASCVD may benefit from GLP-1 RA therapy to reduce their risk of future ASCVD events, although the evidence is currently limited. The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study (GRADE), which was designed to examine the comparative effectiveness of insulin glargine U-100, glimepiride, liraglutide, and sitagliptin in individuals with short duration of diabetes with respect to achieving and maintaining glycemic control, found that individuals treated with liraglutide had a slightly lower risk of cardiovascular disease compared with individuals receiving the other three treatments (hazard ratio 0.7 [95% CI 0.6–0.9]), although no significant differences were found for major adverse cardiovascular events, hospitalization for HF, or cardiovascular death (122).

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Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See the section 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 or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents 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 in self-titration of insulin doses based on glucose monitoring improves glycemic management (123). Comprehensive education regarding blood glucose monitoring, nutrition, and the avoidance and appropriate treatment of hypoglycemia are critically important in any individual using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to metformin and other noninsulin injectables for individuals with type 2 diabetes. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (124,125). 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 or detemir) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin (126). Longer-acting basal analogs (U-300 glargine or degludec) convey a lower nocturnal hypoglycemia risk compared with U-100 glargine (127,128). Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ~0.5 units/kg, high bedtime-to-morning or preprandial-to-postprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL [≥2.8 mmol/L]), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (129).

The cost of insulin has been rising steadily over the past two decades, at a pace severalfold that of other medical expenditures. This expense contributes significant burden to people with diabetes, as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct costs contribute to decrease in medication-taking behavior (130). As of January 2023, the cost of individual insulins was capped for enrollees in Medicare Part D plans (131), and at least 20 states and the District of Columbia have also capped insulin costs for enrollees in state-sponsored plans and, in select states, for those without insurance. In 2023, the three major U.S. insulin manufacturers also announced plans to reduce insulin prices; some plans go into effect in January 2024, and another has already occurred. The summary of the cost of insulin products in **Table 9.4** provides a comparison but is not reflective of the Medicare or state-level caps or the recent manufacturer price reductions. However, the information in **Table 9.4** reflects how the approval of unbranded versions (insulin aspart, lispro, degludec, glargine U-100, and some premixed products), follow-on products (insulin lispro and glargine), and interchangeable biosimilars (insulin glargine) have led to lower costs compared with other products. For some individuals with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (132). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.4** at select pharmacies. It is important to note that although these caps, price reductions, use of unbranded or biosimilar versions of analogs, or use of human insulins may impact the cost of insulin products, there are no caps on the costs of the other tools individuals with diabetes need for monitoring or treatment (including glucose monitoring supplies [strips or sensors], administration tools [pen needles, syringes, and insulin pumps], ketone testing supplies, and glucagon). Therefore, routine assessment of financial obstacles that may impact diabetes management is an important component of effective care of people with diabetes. Collaboration between members of the health care team and with social service professionals to identify and implement cost reduction strategies to support and improve access to evidence-based care is important (120,130).

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic goals. 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 prandial insulin to further address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy (84,114). For individuals who advance to prandial insulin, 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 is a safe estimate for initiating therapy. The prandial insulin plan can then be intensified based on individual needs (**Fig. 9.4**). 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 (133). Titration 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. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported important differences in A1C or hypoglycemia (134,135).

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular

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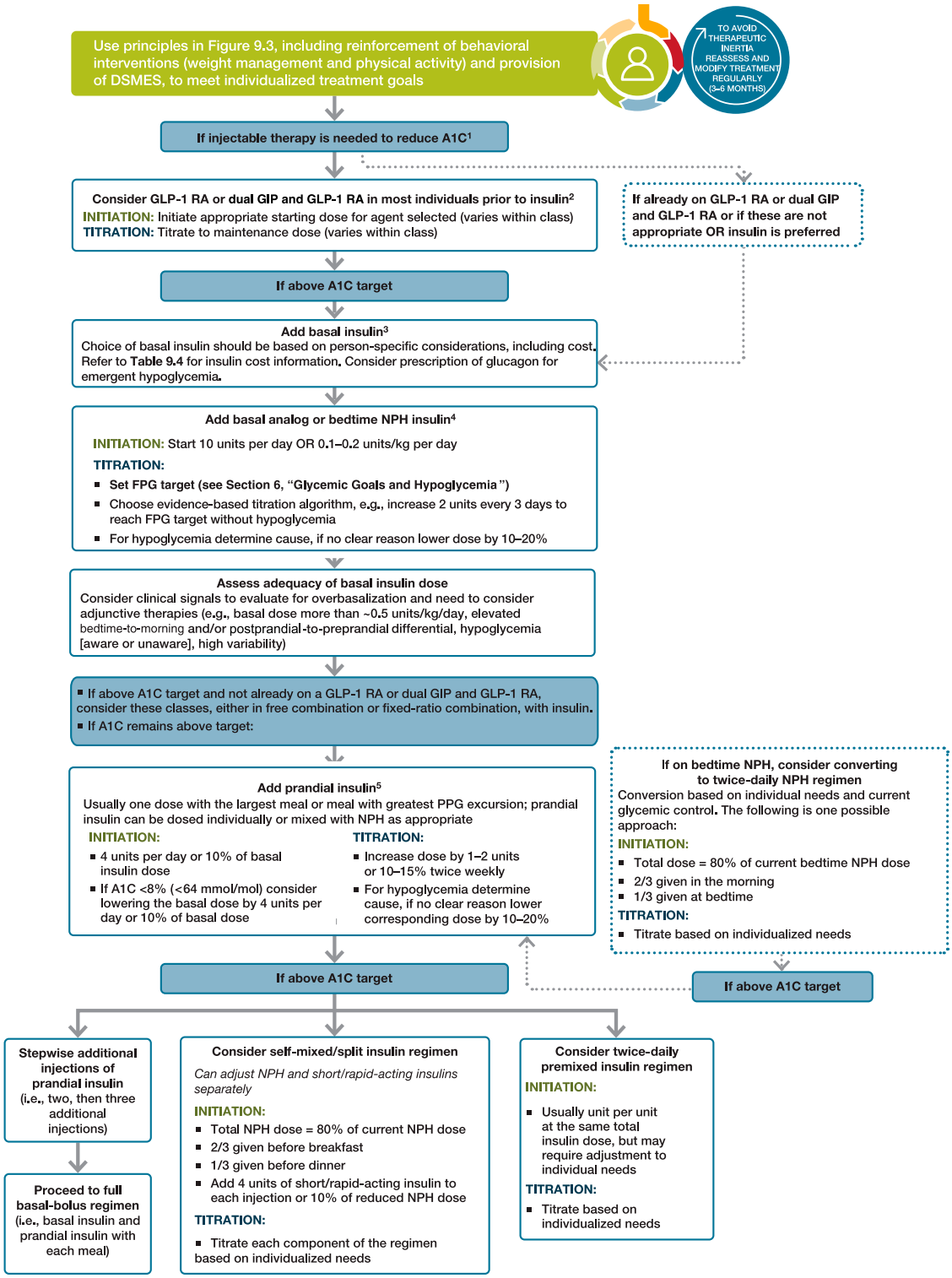

1. Consider insulin as the first injectable if evidence of ongoing catabolism is present, symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVO is present. consider GLP-1 RA with proven CVO 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 wtth an A.M. dose of a long-acting basal Insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; dual GIP and GLP-1 RA, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (151).

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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(s)	Dosage strength/ product (if applicable)	Median AWP (min, max)*	Median NADAC (min, max)*	Maximum approved daily dose†
Biguanides	• Metformin	500 mg (ER)	$89 ($45, $6,719)	$5	2,000 mg
		850 mg (IR)	$108 ($5, $189)	$2	2,550 mg
		1,000 mg (IR)	$87 ($3, $144)	$2	2,000 mg
		1,000 mg (ER)	$1,884 ($242, $7,214)	$31 ($31, $226)	2,000 mg
		500 mg (Sol)	$405 ($405, $739)	$535	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$73 ($72, $198)	$3	8 mg
	• Glipizide	10 mg (IR)	$72 ($67, $91)	$6	40 mg
		10 mg (XL/ER)	$48 ($46, $48)	$10	20 mg
	• Glyburide	6 mg (micronized)	$54 ($48, $71)	$12	12 mg
		5 mg	$82 ($63, $432)	$8	20 mg
Thiazolidinedione	• Pioglitazone	45 mg	$348 ($7, $349)	$4	45 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $378)	$27	300 mg
	• Miglitol	100 mg	$294 ($241, $346)	NA	300 mg
Meglitinides	• Nateglinide	120 mg	$155	$27	360 mg
	• Repaglinide	2 mg	$878 ($58, $897)	$31	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$161	25 mg
	• Linagliptin	5 mg	$630	$504	5 mg
	• Saxagliptin	5 mg	$524	$466	5 mg
	• Sitagliptin	100 mg	$657	$525	100 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$718	$574	300 mg
	• Dapagliflozin	10 mg	$678	$543	10 mg
	• Empagliflozin	25 mg	$712	$569	25 mg
	• Ertugliflozin	15 mg	$408	$328	15 mg
GLP-1 RAs	• Dulaglutide	4.5 mg pen	$1,117	$895	4.5 mg‡
	• Exenatide	10 μg pen	$964	$771	20 μg
	• Exenatide (extended release)	2 mg pen	$990	$793	2 mg‡
	• Liraglutide	1.8 mg pen	$1,340	$1,072	1.8 mg
	• Semaglutide	1 mg pen	$1,123	$903	2 mg‡
		14 mg (tablet)	$1,097 ($1,070, $1,123)	$899	14 mg
Dual GIP and GLP-1 receptor agonist	• Tirzepatide	15 mg pen	$1,228	$982	15 mg‡
Bile acid sequestrant	• Colesevelam	625 mg tabs	$711 ($674, $712)	$64	3.75 g
		3.75 g suspension	$674 ($673, $675)	$130	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$1,200	$965	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,866	NA	120 μg/injection§

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. AWP and NADAC prices as of July 2023. *Calculated for 30-day supply (AWP [116] or NADAC [117] 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. Prices for bexagliflozin were not available at the time of this update. ‡Administered once weekly. §AWP and NADAC calculated based on 120 μg three times daily.

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 (136,137). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations, respectively, 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 (138–140). The U-200 formulations of insulin degludec, insulin lispro, and insulin lispro-aabc have similar pharmacokinetics to their U-100 counterparts (141–143). These concentrated preparations may be more convenient (fewer injections to achieve target dose) and comfortable (less volume to inject target 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. 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

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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*
Rapid-acting	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridge	$215†	$172†
		U-100 prefilled pen	$224†	$179†
	• Aspart ("faster acting product")	U-100 vial	$347	$277
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$351
	• Inhaled insulin	Inhalation cartridges	$1,503	NA
	• Lispro	U-100 vial	$30†	$24†
		U-100 cartridge	$408	$326
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$261
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	$338
	• Lispro follow-on product	U-100 vial	$118	$94
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$172 ($165, $178)‡	$137 ($132, $142)‡
		U-100 prefilled pen	$208	$166
Intermediate-acting	• Human NPH	U-100 vial	$172 ($165, $178)‡	$137 ($132, $143)‡
		U-100 prefilled pen	$208 ($208, $377)	$234 ($166, $303)
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial	$142†	$327
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$85†	$113†
	• Glargine	U-100 vial; U-100 prefilled pen	$136†	$109†
		U-300 prefilled pen	$363	$290
	• Glargine biosimilar/ follow-on products	U-100 prefilled pen	$190 ($74, $323)	$95†
		U-100 vial	$118†	$95†
Premixed insulin products	• Aspart 70/30	U-100 vial	$180†	$145†
		U-100 prefilled pen	$224†	$179†
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$341
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$127†	$102†
	• NPH/regular 70/30	U-100 vial	$172 ($165, $178)‡	$138 ($132, $143)‡
		U-100 prefilled pen	$208 ($208, $377)	$234 ($166, $302)
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 μg prefilled pen	$991	$795
	• Glargine/lixisenatide	100/33 μg prefilled pen	$679	$543

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (116) and NADAC (117) prices as of July 2023. *AWP or NADAC calculated as in **Table 9.3**. †Unbranded product prices used when available. ‡AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

regular insulin vials are prescribed, the prescription should be accompanied by a prescription for U-500 syringes to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulin is primarily administered via subcutaneous injection or infusion. Administration devices provide some additional variation in the subcutaneous delivery beyond vial versus insulin pen. Those devices include continuous insulin pumps (programmable basal and bolus settings and fixed basal and bolus settings) and bolus-only insulin patch pump. In addition, prandial or correction insulin doses may be administered using inhaled human insulin. Inhaled insulin is available as monomers of regular human insulin; studies in individuals with type 1 diabetes suggest that inhaled insulin has pharmacokinetics similar to RAA (7). 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 (144–146). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 second [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.

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Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above goal, consider advancing to combination injectable therapy (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin (114,147). The combination of basal insulin and GLP-1 RA (administered via separate injections of individual products or single injection of a fixed-ratio product) has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin plans (148). Two different once-daily, fixed dual combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide (iGlarLixi) and insulin degludec plus liraglutide (IDegLira). In select individuals with type 2 diabetes, complex insulin plans can also be simplified with fixed-ratio GLP-1 RA-insulin product (149).

Intensification of insulin treatment can be done by 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 (150). Alternatively, for an individual on basal insulin in whom additional prandial coverage is desired but administering insulin prior to one or more meal(s) 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. 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 (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.4** outlines these options as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating intensification of insulin therapy, metformin, SGLT2 inhibitors, and GLP-1 RA (or dual GIP and GLP-1 RA) should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose management, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, although potential side effects should be considered. Once a basal-bolus insulin plan is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the 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").

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