9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2022*

*American Diabetes Association Professional Practice Committee**

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PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**

9.3 Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. **B**

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes. 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. However, over the past three 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

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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). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated fewer macrovascular as well as fewer microvascular complications in the group that received intensive treatment (2,4).

Insulin replacement regimens typically consist of basal insulin, mealtime insulin, and correction insulin (5). 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 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 human insulins (6–8). More recently, two new injectable insulin formulations with enhanced rapid action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain (9) (see also subsection "Inhaled Insulin" in PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES), and faster-acting insulin aspart and insulin lisproaabc may reduce prandial excursions better than RAA (10–12). In addition, new 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, for some individuals the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. However, a recent 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). 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 (16). The arrival of continuous glucose monitors (CGM) to clinical practice has proven beneficial in people using insulin therapy. Its use is now considered standard of care for most people with type 1 diabetes (5) (see Section 7, "Diabetes Technology," https://doi.org10.2337/dc22-S007). 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 (16–18). When choosing among insulin delivery systems, patient preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered (see Section 7, "Diabetes Technology," https://doi.org/10.2337/dc22-S007).

The U.S. Food and Drug Administration (FDA) has now approved two hybrid closed-loop pump systems (also called automated insulin delivery [AID] systems). The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (19,20), and recent evidence suggests that a closed-loop system is superior to sensor-augmented pump therapy for glycemic control and reduction of hypoglycemia over 3 months of comparison in children and adults with type 1 diabetes (21). In the International Diabetes Closed Loop (iDCL) trial, a 6-month trial in people with type 1 diabetes at least 14 years of age, the use of a closed-loop system was associated with a greater percentage of time spent in the target glycemic range, reduced mean glucose and A1C levels, and a lower percentage of time spent in hypoglycemia compared with use of a sensor-augmented pump (22).

Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most individuals with type 1 diabetes. AID systems may be considered in individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) in order to improve time in range and reduce A1C and hypoglycemia (22). See Section 7, "Diabetes Technology" (https://doi.org/10.2337/dc22-S007), for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial, but this is dependent on a number of factors, including whether the individual consumes lower or higher carbohydrate meals. 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 are required during puberty, pregnancy, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in individuals with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (23); 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 (24).

Typical multidose regimens for individuals with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight, fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of

prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, 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 of patients on how to adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most patients (25,26). For individuals in whom carbohydrate counting is effective, estimates of the fat and protein content of meals can be incorporated into their prandial dosing for added benefit (27) (see Section 5, "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc22-S005).

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 regimens and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (5).

Insulin Injection Technique

Ensuring that patients and/or caregivers understand correct insulin injection technique is important to optimize glucose control 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 for insulin injection (28). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm. Because insulin absorption from IM sites differs according to the activity of the muscle, inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose, with IM injection being associated with frequent and unexplained hypoglycemia in several reports. Risk for IM insulin delivery is increased in younger, leaner patients 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 (29).

Injection 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. Patients and/or caregivers should receive education about proper injection 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 injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection 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 drugs 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

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

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
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 regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	++++++
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Figure 9.1—Choices of insulin regimens 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 regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Reprinted from Holt et al. (5).

Table 9.1—Examples of subcutaneous insulin regimens

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Regimens that more closely mimic normal insulin secretion				
Insulin pump therapy (hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 40–60% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with pre-meal 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 low-glucose suspend or hybrid closed-loop. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive regimen. 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 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.

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Table 9.1—Continued

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
MDI regimens 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 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.
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.
Regimens with fewer daily injections				
Three injections daily: N+R or N+RAA	Pre-breakfast: ~40% N + ~15% R or RAA. Pre-dinner: ~15% R or RAA. Bedtime: 30% N.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injections 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.

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Table 9.1—Continued

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Twice-daily "split-mixed": N+R or N+RAA	Pre-breakfast: ~40% N + ~15% R or RAA. Pre-dinner: ~30% N + ~15% R or RAA.	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.

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin: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; TDD, total daily insulin dose; URAA, ultra-rapid-acting analog. Reprinted from Holt et al. (5).

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 (30–33). Similarly, 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 caused small reductions in body weight and lipid levels but did not improve A1C (34,35). 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, showing modest A1C reductions (~0.4%), decreases in weight (~5 kg), and reductions in insulin doses (36,37). Similarly, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, showing improvements in A1C, reduced body weight, and improved blood pressure (38–40); however, SGLT2 inhibitor use in type 1 diabetes is associated with an increased rate of diabetic ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on patient selection and precautions (41); only pramlintide is approved for treatment of type 1 diabetes.

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, patients 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 patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (42).

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**) (5).

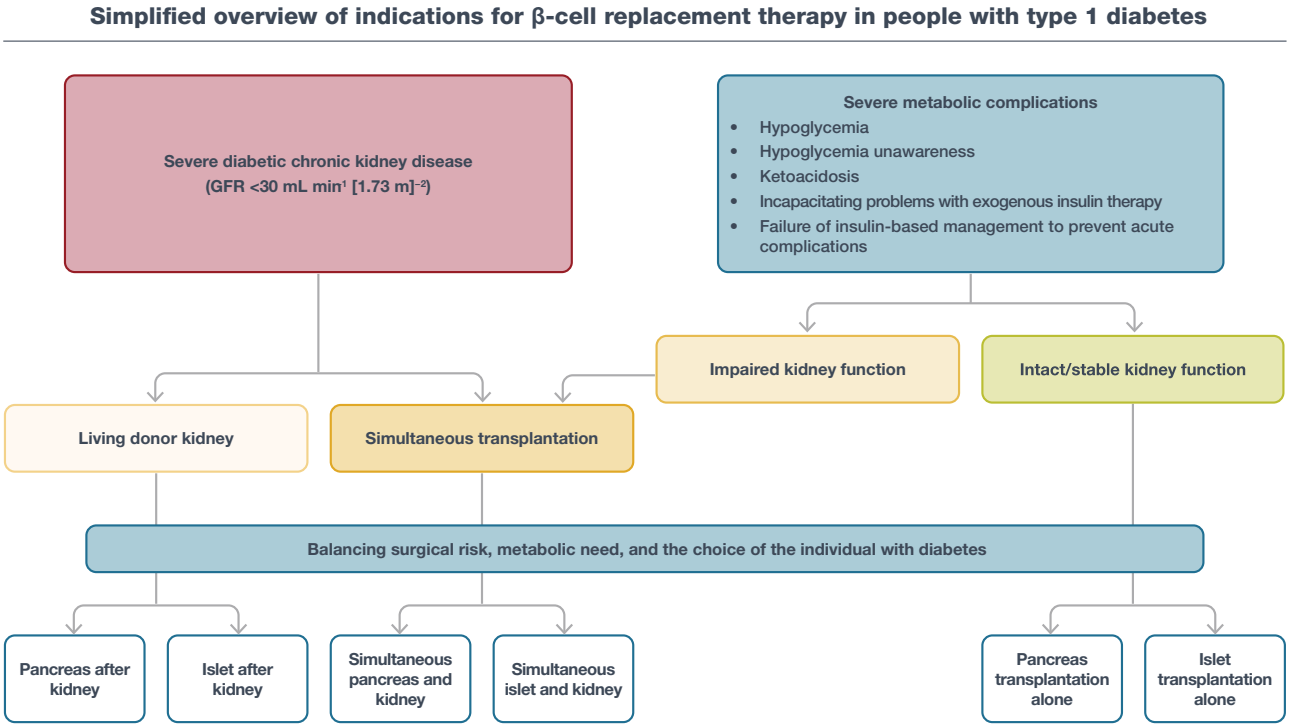


Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation or islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the 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. (5).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.4a First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification. **A**

9.4b Other medications (glucagon-like peptide 1 receptor agonists, sodium–glucose cotransporter 2 inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease (**Fig. 9.3**). **A**

9.5 Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. **A**

9.6 Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. **A**

9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **E**

9.8 A patient-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and patient preferences (**Table 9.2** and **Fig. 9.3**). **E**

9.9 Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Fig. 9.3**, **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, indepenent of A1C and in consideration of patient-specific factors (**Fig. 9.3**) (see Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010, for details on cardiovascular risk reduction recommendations). **A**

9.10 In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**

9.11 If insulin is used, combination therapy with a glucagon-like

peptide 1 receptor agonist is recommended for greater efficacy and durability of treatment effect. **A**

9.12 Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. **A**

9.13 Medication regimen and medication-taking behavior should be reevaluated at regular intervals (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 Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 IU/kg/day, high bedtime-morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. **E**

The ADA/EASD consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2018" and the 2019 update (43,44) recommend a patient-centered approach to choosing appropriate pharmacologic treatment of blood glucose. This includes consideration of efficacy and key patient factors: *1*) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure (HF) (see Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010, and Section 11 "Chronic Kidney Disease and Risk Management," https://doi.org/10.2337/dc22-S011), *2*) hypoglycemia risk, *3*) effects on body weight, *4*) side effects, *5*) cost, and *6*) patient preferences. Lifestyle modifications that improve health (see Section 5, "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc22-S005) should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults" (https://doi.org/10.2337/dc22-S013), and Section 14, "Children and Adolescents" (https://doi.org/10.2337/dc22-S014), have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc22-S010), and Section 11, "Chronic Kidney Disease and Risk Management" (https://doi.org/10.2337/dc22-S011), have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

Initial Therapy

First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs but will generally include metformin and comprehensive lifestyle modification. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for many patients this will be metformin monotherapy in combination with lifestyle modifications. Additional and/or alternative agents may be considered in special circumstances, such as in individuals with established or increased risk of cardiovascular or renal complications (see Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010, and **Fig. 9.3**). Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (45). 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, weight, and cardiovascular mortality (46); there is little systematic data available for other oral agents as initial therapy of type 2 diabetes.

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration. 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 patients with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in patients with eGFR $\geq$30 mL/min/1.73 m^2 (47). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (48). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (49).

In patients with contraindications or intolerance to metformin, initial therapy should be based on patient factors; consider a drug from another class depicted in **Fig. 9.3**. When A1C is $\geq$1.5% (12.5 mmol/mol) above the glycemic target (see Section 6, "Glycemic Targets," https://doi.org/10.2337/dc22-S006, for appropriate targets), many patients will require dual combination therapy to achieve their target A1C level (50). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for patients who present with blood glucose levels $\geq$300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmol/mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible. However, there is evidence that patients with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea (51).

Combination Therapy

Because type 2 diabetes is a progressive disease in many patients, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which combination therapy is necessary. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and

Table 9.2—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
					ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT2 inhibitors		Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin‡, canagliflozin, dapagliflozin‡, ertugliflozin	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin§	▪ See labels for renal dose considerations of individual agents ▪ Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs		High	No	Loss	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	▪ See labels for renal dose considerations of individual agents ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: generally not recommended in chronic kidney disease ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human insulin**	High	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for cardiovascular disease benefit. ‡FDA-approved for heart failure indication. §FDA-approved for chronic kidney disease indication.

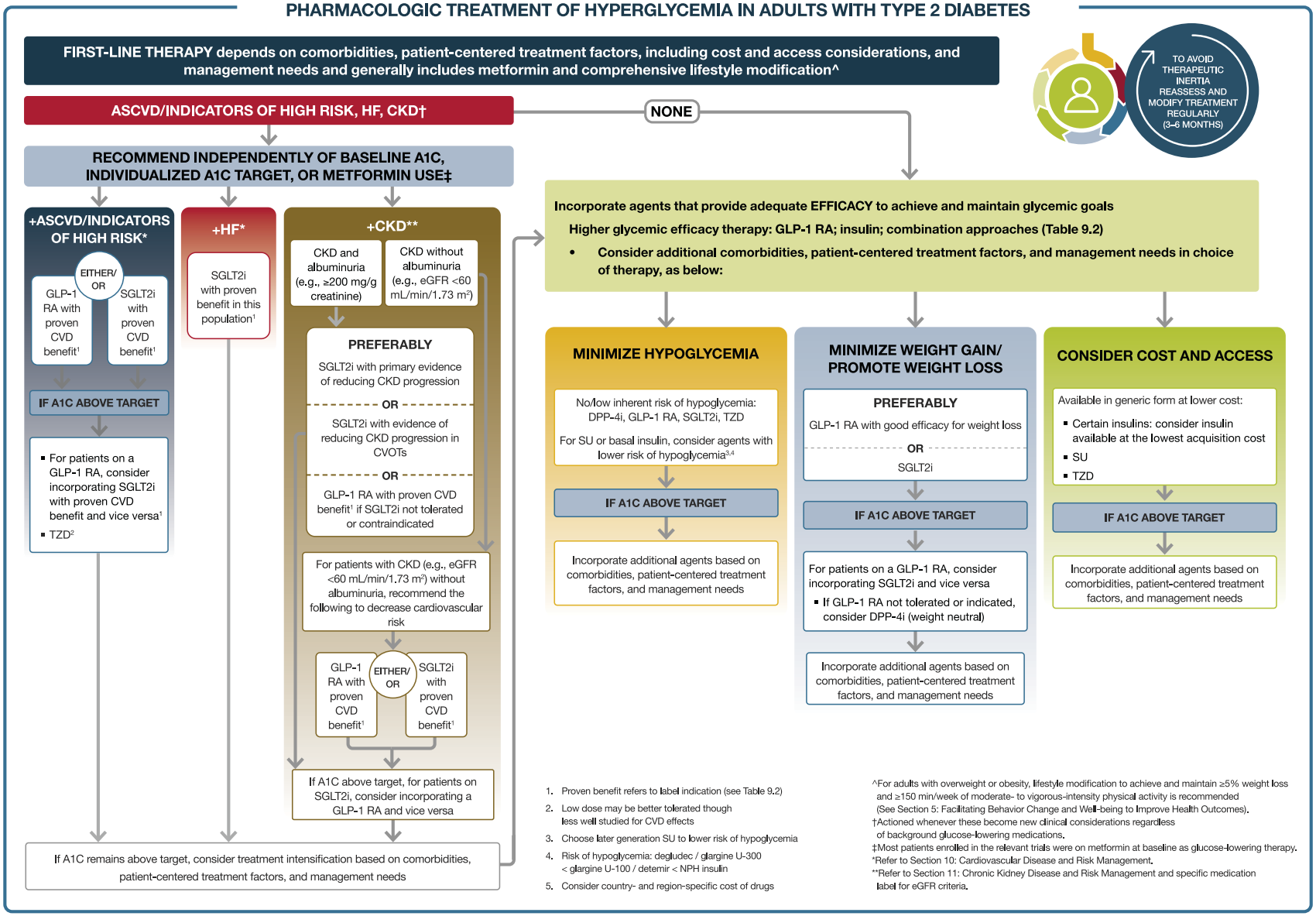


Figure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (43) and Buse et al. (44). For appropriate context, see **Fig. 4.1**. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

reduce potential side effects and expense (52). However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (53,54) and later combination therapy for longer durability of glycemic effect (55). The VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) trial demonstrated that initial combination therapy is superior to sequential addition of medications for extending primary and secondary failure (56). In the VERIFY trial, participants receiving the initial combination of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin had a slower decline of glycemic control compared with metformin alone and with vildagliptin added sequentially to metformin. These results have not been generalized to oral agents other than vildagliptin, but they suggest that more intensive early treatment has some benefits and should be considered through a shared decision-making process with patients, as appropriate. Initial combination therapy should be considered in patients presenting with A1C levels 1.5–2.0% above target. Finally, incorporation of high glycemic efficacy therapies or therapies for cardiovascular/renal risk reduction (e.g., GLP-1 RAs, SGLT2 inhibitors) may allow for weaning of the current regimen, particularly of agents that may increase the risk of hypoglycemia. Thus, treatment intensification may not necessarily follow a pure sequential addition of therapy but instead reflect a tailoring of the regimen in alignment with patient-centered treatment goals (**Fig. 9.3**).

Recommendations for treatment intensification for patients not meeting treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment intensification. The choice of medication added to initial therapy is based on the clinical characteristics of the patient and their preferences. Important clinical characteristics include the presence of established ASCVD or indicators of high ASCVD risk, HF, CKD, other comorbidities, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. A comparative effectiveness meta-analysis suggests that each new class of noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (57,58). (**Fig. 9.3** and **Table 9.2**).

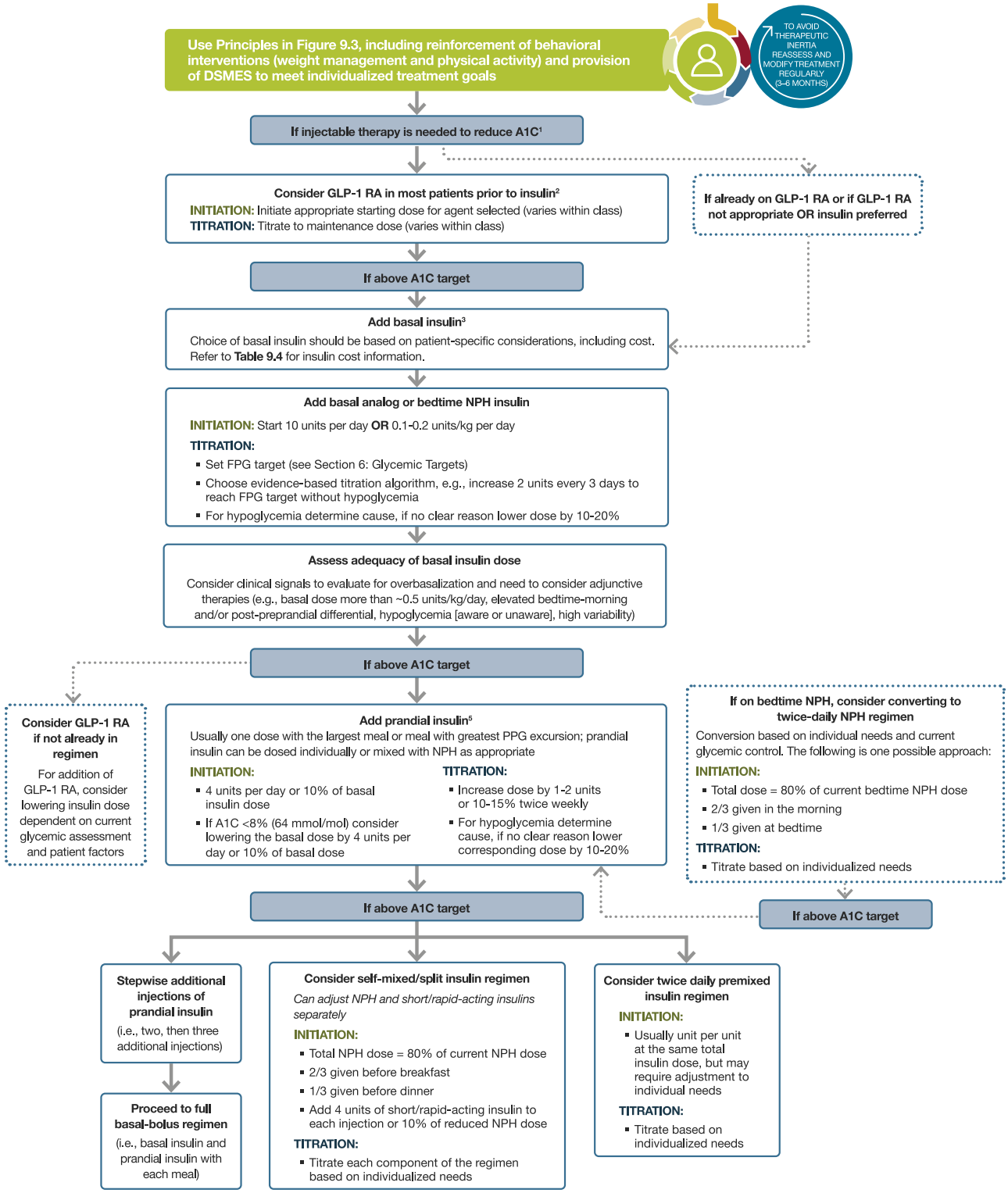
For patients with established ASCVD or indicators of high ASCVD risk (such as patients ≥55 years of age with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy), HF, or CKD, an SGLT2 inhibitor or GLP-1 RA with demonstrated CVD benefit (**Table 9.2**, **Table 10.3*B***, **Table 10.3*C***, and Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010) is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use, and in consideration of patient-specific factors (**Fig. 9.3**). For patients without established ASCVD, indicators of high ASCVD risk, HF, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence comparing across multiple classes. Rather, drug choice is based on efficacy, avoidance of side effects (particularly hypoglycemia and weight gain), cost, and patient preferences (59). Similar considerations are applied in patients who require a third agent to achieve glycemic goals. A recent systematic review and network meta-analysis suggests greatest reductions in A1C level with insulin regimens and specific GLP-1 RAs added to metformin-based background therapy (60). In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and patient burden (**Table 9.2**). In some instances, patients will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 13, "Older Adults" (https://doi.org/10.2337/dc22-S013), 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 regimens is a well-established approach that is effective for many patients. In addition, recent evidence supports the utility of GLP-1 RAs in patients not at glycemic goal. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is now commercially available (61). In trials comparing the addition of an injectable GLP-1 RA or insulin in patients needing further glucose lowering, glycemic efficacy of injectable GLP-1 RA was similar or greater than that of basal insulin (62–68). GLP-1 RAs 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 GLP-1 RAs as the preferred option for patients requiring the potency of an injectable therapy for glucose control (**Fig. 9.4**). In patients who are intensified to insulin therapy, combination therapy with a GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effect than treatment intensification with insulin alone. However, cost and tolerability issues are important considerations in GLP-1 RA use.

Costs for diabetes medications has increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (69). **Table 9.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (70) and National Average Drug Acquisition Costs (NADAC) (71), 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 patient. Medication costs can be a major source of stress for patients with diabetes and contribute to worse adherence to medications (72); cost-reducing strategies may improve adherence in some cases (73).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with an SGLT2 inhibitor or GLP-1 RA; see Section 10, "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc22-S010) for details. Subjects enrolled in many of the cardiovascular outcomes trials had A1C ≥6.5%, with



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For patients 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 patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen 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; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

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	850 mg (IR)	$108 ($5, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($5, $88)	$2	2,000 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$102 ($102, $430)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$3	8 mg
	• Glipizide	10 mg (IR)	$68 ($67, $70)	$3	40 mg
		10 mg (XL/ER)	$48	$12	20 mg
	• Glyburide	6 mg (micronized)	$52 ($48, $71)	$11	12 mg
		5 mg	$82 ($63, $93)	$12	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($7, $349)	$5	45 mg
	• Rosiglitazone	4 mg	N/A	$324	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$26	300 mg
	• Miglitol	100 mg	$284 ($241, $346)	N/A	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$28	360 mg
	• Repaglinide	2 mg	$878 ($58, $897)	$34	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$166	25 mg
	• Saxagliptin	5 mg	$549	$438	5 mg
	• Linagliptin	5 mg	$583	$466	5 mg
	• Sitagliptin	100 mg	$596	$477	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$372	$297	15 mg
	• Dapagliflozin	10 mg	$639	$511	10 mg
	• Canagliflozin	300 mg	$652	$521	300 mg
	• Empagliflozin	25 mg	$658	$526	25 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$909	$727	2 mg**
	• Exenatide	10 μg pen	$933	$746	20 μg
	• Dulaglutide	4.5 mg mL pen	$1,013	$811	4.5 mg**
	• Semaglutide	1 mg pen	$1,022	$822	1 mg**
		14 mg (tablet)	$1,022	$819	14 mg
	• Liraglutide	1.8 mg pen	$1,220	$975	1.8 mg
	• Lixisenatide	20 μg pen	$814	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$710 ($674, $712)	$75	3.75 g
		3.75 g suspension	$674	$222	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$1,036	$833	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,702	N/A	120 μg/injection††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [70] or NADAC [71] 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. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP and NADAC calculated based on 120 μg three times daily.

more than 70% taking metformin at baseline. Thus, a practical extension of these results to clinical practice is to use these drugs preferentially in patients with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these patients, incorporating one of the SGLT2 inhibitors and/or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (**Table 9.2**, **Fig. 9.3**, and Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010). 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 (74). 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" (https://doi.org/10.2337/

Table 9.4—Median cost of insulin products in the U.S. calculated as AWP (70) and NADAC (71) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$125
		U-100 prefilled pen	$202	$161
	• Lispro	U-100 vial	$165†	$132†
		U-100 cartridge	$408	$325
		U-100 prefilled pen	$212†	$170†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	N/A
		U-100 prefilled pen	$424	N/A
		U-200 prefilled pen	$424	N/A
	• Glulisine	U-100 vial	$341	$272
		U-100 prefilled pen	$439	$352
	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridge	$215	$172
		U-100 prefilled pen	$223†	$179†
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	N/A
		U-100 prefilled pen	$447	$356
	• Inhaled insulin	Inhalation cartridges	$1,325	$606
Short-acting	• human regular	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$167
Intermediate-acting	• human NPH	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$167
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$143
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on products	U-100 prefilled pen	$118	$96
		U-100 vial	$190 (118, 261)	$95
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$277
		U-300 prefilled pen	$340	$272
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$296
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$325
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$152	$273
		U-100 prefilled pen	$212	$170
	• Aspart 70/30	U-100 vial	$180	$144
		U-100 prefilled pen	$224	$179
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 μg prefilled pen	$619	$495
	• Degludec/Liraglutide	100/3.6 μg prefilled pen	$917	$732

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; N/A, not available; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.3**. †Generic 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.

dc22-S011) for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See the section INSULIN INJECTION 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 patients, 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 patients in insulin management is beneficial. For example, instruction of patients in self-titration of insulin doses based on glucose monitoring improves glycemic control in patients with type 2 diabetes initiating insulin (75). Comprehensive education regarding self-monitoring of blood glucose, diet, and the avoidance and

appropriate treatment of hypoglycemia are critically important in any patient using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen and can be added to metformin and other oral agents. 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 (76,77). Control of fasting glucose 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 symptomatic and nocturnal hypoglycemia compared with NPH insulin (78–83), although these advantages are modest and may not persist (84). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (85–91). 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-morning or post-preprandial glucose differential (e.g., bedtime-morning glucose differential ≥50 mg/dL), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (92).

The cost of insulin has been rising steadily over the past two decades, at a pace several fold that of other medical expenditures (93). This expense contributes significant burden to patients as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct patient costs contribute to treatment nonadherence (93). Therefore, consideration of cost is an important component of effective management. For many 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 (94). 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. Additionally, approval of follow-on biologics for insulin glargine, the first interchangeable insulin glargine product, and generic versions of analog insulins may expand cost-effective options.

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets. A 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 regimen can then be intensified based on individual needs (see **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 (95). Titration can be based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, 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 with type 2 diabetes have not reported important differences in A1C or hypoglycemia (96,97).

Concentrated Insulins

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 delayed onset and longer duration of action, has characteristics more like an intermediate-acting (NPH) insulin, and can be used as two or three daily injections (98). 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 (99,100). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL) and insulin lispro-aabc (U-200). These concentrated preparations may be more convenient and comfortable for individuals to inject and may improve adherence 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.

Inhaled Insulin

Inhaled insulin is available as a rapid-acting insulin; studies in individuals with type 1 diabetes suggest rapid pharmacokinetics (8). A pilot study found evidence that compared with injectable rapid-acting insulin, supplemental doses of inhaled insulin taken based on postprandial glucose levels may improve blood glucose management without additional hypoglycemia or weight gain (101), although results from a larger study are needed for confirmation. 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.

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 target, consider advancing to combination injectable therapy (**Fig. 9.4**). This approach can use a GLP-1 RA added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (102–106). The DUAL VIII randomized controlled trial demonstrated greater durability of glycemic treatment effect with the combination GLP-1 RA–insulin therapy compared with addition of basal insulin alone (55). In select

individuals, complex insulin regimens can also be simplified with combination GLP-1 RA–insulin therapy in type 2 diabetes (107). 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).

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 regimen with multiple prandial doses if necessary (108). Alternatively, in an individual on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal/prandial regimens 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 combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose control, 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, though potential side effects should be considered. Once a basal/bolus insulin regimen 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). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 13, "Older Adults," https://doi.org/10.2337/dc22-S013).

2022 ADA Professional Practice Committee Updates to Fig. 9.3

The 2022 ADA Professional Practice Committee focused on several key areas in **Fig. 9.3** to reconcile emerging evidence and support harmonization of guidelines. Areas of discussion and updated changes are outlined below.

1. *Title and Purpose of Algorithm.* Given the significant impact the cardiovascular outcomes trials have had on understanding the management of type 2 diabetes and the different guidelines and algorithms being proposed by different societies, it was important to identify the purpose of **Fig. 9.3**, recognizing that no single algorithm covers all circumstances or goals. The purpose of this guidance is to support achievement of glycemic goals to reduce long-term complications, highlighting aspects of therapy that support patient-centered goals. Thus, the scope of this algorithm is defined as the "Pharmacologic Treatment of Hyperglycemia in Adults with Type 2 Diabetes." Toward this goal, glycemic status should be assessed, with treatment modified regularly (e.g., at least twice yearly if stable and more often if not to goal) to achieve patient-centered treatment goals and to avoid therapeutic inertia.
2. *Initial Therapy.* First-line therapy for the treatment of hyperglycemia has traditionally been metformin and comprehensive lifestyle. Recognizing the multiple treatment goals and comorbidities for individuals with type 2 diabetes, alternative initial treatment approaches to metformin are acceptable, depending on comorbidities, patient-centered treatment factors, and glycemic and comorbidity management needs.
3. *+ASCVD/Indicators of High Cardiovascular Risk*. Please see Section 10, "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc22-S010), for comprehensive review of evidence. This pathway has been streamlined to highlight therapies that have evidence to support cardiovascular risk reduction and glycemic management, prioritizing GLP-1 RAs and SGLT2 inhibitors for this population.
4. *+HF*. This pathway highlights the emerging evidence of improvement in cardiovascular outcomes with SGLT2 inhibitors in individuals with type 2 diabetes and existing HF.
5. *+CKD*. This pathway has been updated based on populations studied in renal and cardiovascular outcomes studies and to specify recommendations when further intensification is required (e.g., for patients on an SGLT2 inhibitor, consider incorporating GLP-1 RA and vice versa).
6. *Principle of Incorporation*. Prior algorithms have conveyed sequential addition of therapy. Recognizing the importance of tailoring the therapeutic regimen to the individual's needs and comorbidities, the principle of incorporation is emphasized throughout **Fig. 9.3**. Not all treatment intensification results in sequential add-on therapy, but in some cases it may involve switching therapy or weaning current therapy to accommodate therapeutic changes. For example, discontinuation of the DPP-4 inhibitor is recommended when intensifying from a DPP-4 inhibitor to a GLP-1 RA, given overlapping mechanisms. In addition, when cardioprotective agents (e.g., SGLT2 inhibitors, GLP-1 RAs) are introduced in the regimen, this may require weaning current therapy to minimize hypoglycemia, dependent on baseline A1C status.
7. *Treatment Intensification.* For the individual with high risk or established ASCVD, CKD, or HF whose A1C remains above target, further treatment intensification should be based on comorbidities, patient-centered treatment factors, and management needs as highlighted on the right side of **Fig. 9.3**.
8. *Efficacy.* Agents should be considered that provide adequate efficacy to achieve and maintain glycemic goals (**Table 9.2**) (60) while considering additional patient-centered factors (e.g., focus on minimizing hypoglycemia, focus on minimizing weight gain and promoting weight loss, and access/cost considerations).
9. *Minimize Hypoglycemia*. Agents with no/low inherent risk of hypoglycemia are preferred, with incorporation of additional agents as indicated.

10. *Minimize Weight Gain/Promote Weight Loss*. Agents with good efficacy for weight loss are preferred (109), with incorporation of additional agents as indicated.
11. *Access/Cost Considerations*. Access and cost are universal considerations. Classes with medications currently available in generic form are listed.

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