9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people 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 Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. **C**

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 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

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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 less macrovascular as well as less microvascular complications in the group that received intensive treatment (2,4).

Over the last 25 years, rapid-acting and long-acting insulin analogs have been developed that have distinct pharmacokinetics compared with recombinant human insulins: 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 (5–7). 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 (8), and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA (9,9a,9b); further investigation is needed to establish a clear place for these agents in diabetes management. In addition, new longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in patients with type 1 diabetes (10,11). Despite the advantages of insulin analogs in patients with type 1 diabetes, for some patients 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 patient to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the patient'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 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 (12). However, there is no consensus to guide the choice of injection or pump therapy in a given patient, and research to guide this decision-making is needed (13). The arrival of continuous glucose monitors to clinical practice has proven beneficial in specific circumstances. Reduction of nocturnal hypoglycemia in people with type 1 diabetes using insulin pumps with glucose sensors is improved by automatic suspension of insulin delivery at a preset glucose level (13–15). 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/dc21-S007).

The U.S. Food and Drug Administration (FDA) has now approved two hybrid closed-loop pump systems. The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (16,17), 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 (18). In the International Diabetes Closed Loop (iDCL) trial, a 6-month trial in patients 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 lower percentage of time spent in hypoglycemia compared with use of a sensor-augmented pump (19).

Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most patients. Automated insulin delivery systems may be considered in adults with type 1 diabetes who have the skills to use them in order to improve time in range and reduce A1C and hypoglycemia (19). See Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc21-S007) for a full discussion of insulin delivery devices.

In general, patients with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial. 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 patients 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 (20); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (21).

Typical multidose regimens for patients with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation, usually at night. 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, 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 (22,23). 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 (24).

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 (25). 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 (26).

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 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 with type 1 diabetes. Results from randomized controlled studies show variable reductions of A1C (0–0.3%) and body weight (1–2 kg) with addition of pramlintide to insulin (27,28). 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 (29,30). The addition of the glucagon-like peptide 1 (GLP-1) receptor agonist (RA) liraglutide or exenatide to insulin therapy caused small (0.2%) reductions in A1C compared with insulin alone in people with type 1 diabetes and also reduced body weight by ~3 kg (31). Similarly, the addition of a sodium–glucose cotransporter 2 (SGLT2) inhibitor to insulin therapy has been associated with improvements in A1C and body weight when compared with insulin alone (32,33); however, SGLT2 inhibitor use in type 1 diabetes is associated with a two- to fourfold increase in ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, but 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 (34).

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Recommendations

- **9.4** Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**
- **9.5** Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **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 be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (**Table 9.1** and **Fig. 9.1**). **E**
- **9.9** Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 9.1**, **Table 10.3*B***, **Table 10.3*C***) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors (**Fig. 9.1** and Section 10). **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** Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. **A**

9.12 The 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 9.1**). **E**

9.13 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, high bedtime-morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. **E**

The American Diabetes Association/European Association for the Study of Diabetes consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2018" and the 2019 update (35,36) 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 (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc21-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/dc21-S005) should be emphasized along with any pharmacologic therapy. Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) and Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013) 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/dc21-S010) and Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc21-S011) have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

Initial Therapy

Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for many patients this will be 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/dc21-S010, and **Fig. 9.1**). Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (37). 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 (38); 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 (39). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (40). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (41).

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. 9.1**. When A1C is $\geq$1.5% (12.5 mmol/mol) above the glycemic target (see Section 6 "Glycemic Targets," https://doi.org/10.2337/dc21-S006, for appropriate targets), many patients will require dual combination therapy to achieve their target A1C level (42). 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. 9.2**). As glucose toxicity resolves, simplifying the regimen and/or changing to oral 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 (43).

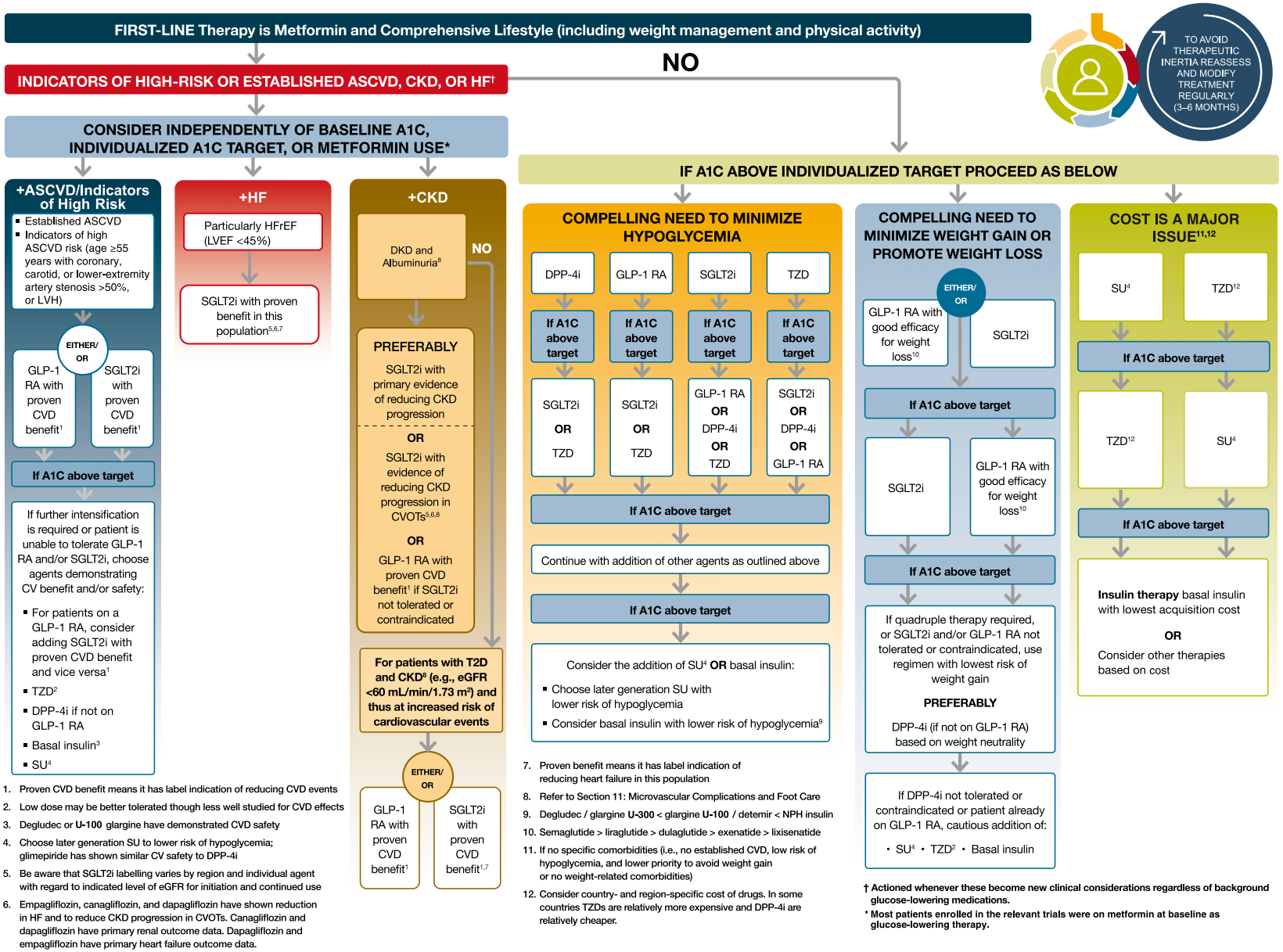
Combination Therapy

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. Current recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. This allows a clearer assessment of the positive and negative effects of new drugs and reduces patient risk and expense (44); based on these factors, sequential addition of oral agents to metformin has been the standard of care. However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (45,46) and later combination therapy for longer durability of glycemic effect (47). 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 (48). 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

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy	Hypoglycemia	Weight change	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
SGLT-2 inhibitors		Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ 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	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m^2 ▪ 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, albiglutide, 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: not recommended ▪ 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	Highest	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.

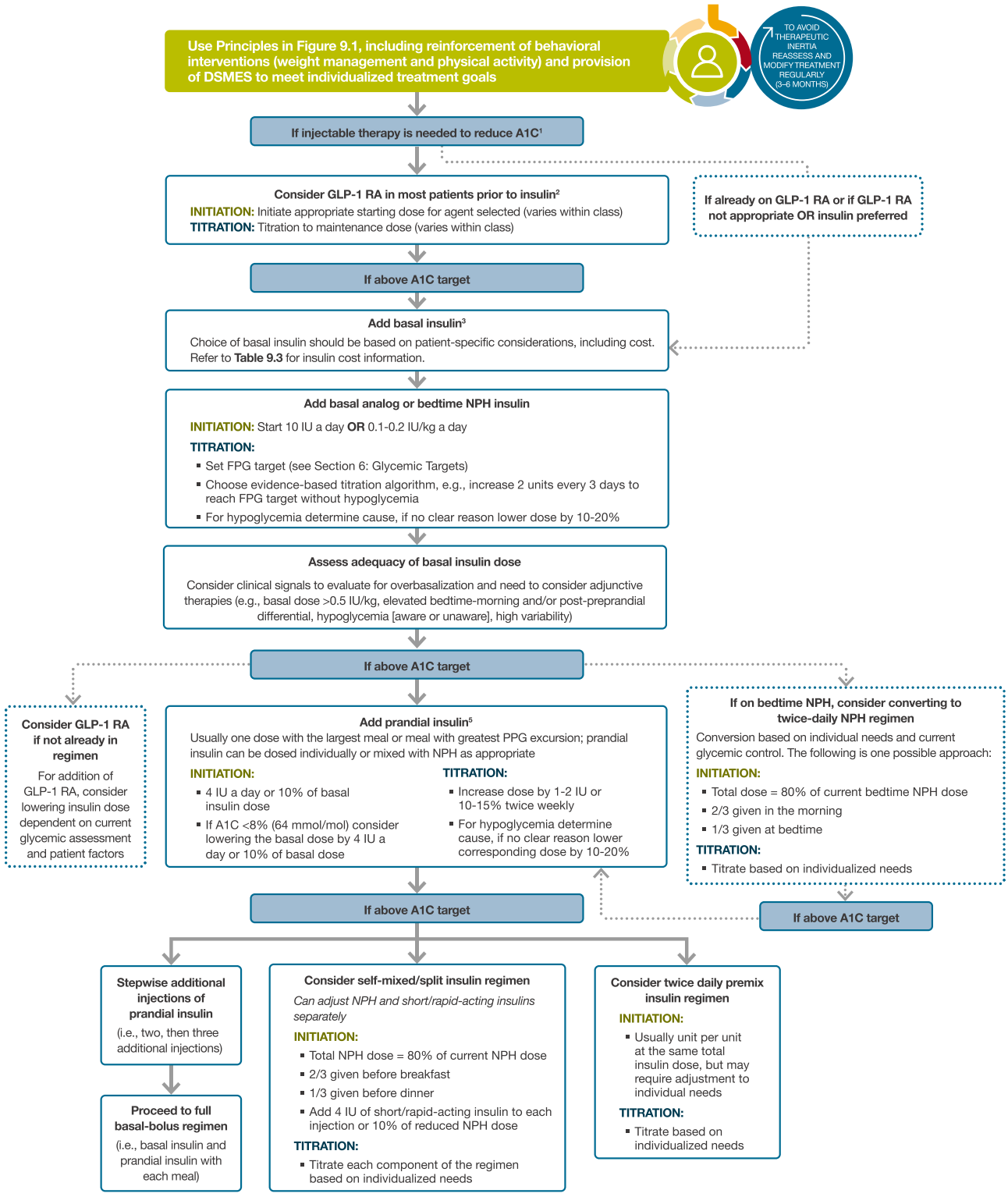


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

*** Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

Figure 9.1—Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (35) and Buse et al. (36). For appropriate context, see **Fig. 4.1**. The 2021 ADA PPC adaptation of the **Fig. 9.1** "Indicators of high-risk or established ASCVD, CKD, or HF" pathway has been adapted based on trial populations studied. 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; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.



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 9.2—Intensifying to injectable therapies. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (35).

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. Moreover, since the absolute effectiveness of most oral medications rarely exceeds 1%, initial combination therapy should be considered in patients presenting with A1C levels 1.5–2.0% above target.

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 metformin 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, heart failure, CKD, other comorbidities, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. Although there are numerous trials comparing dual therapy with metformin alone, there is little evidence to support one combination over another. 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% (49,50). If the A1C target is not achieved after approximately 3 months, metformin can be combined with any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin; the choice of which agent to add is based on drug-specific effects and patient factors (**Fig. 9.1** and **Table 9.1**).

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), heart failure, or CKD, an SGLT2 inhibitor or GLP-1 RA with demonstrated CVD benefit (**Table 9.1**, **Table 10.3*B***, **Table 10.3*C***, and Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-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. 9.1**). For patients without established ASCVD, indicators of high ASCVD risk, heart failure, 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 (51). 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 (52). In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and patient burden (**Table 9.1**). 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 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) 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 (53). 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 (54–60). 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. 9.2**). However, high costs and tolerability issues are important barriers to GLP-1 RA use.

Cost for diabetes medicine has increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (61). **Table 9.2** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (62) and National Average Drug Acquisition Costs (NADAC) (63), 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 (64); cost-reducing strategies may improve adherence in some cases (65).

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 (empagliflozin, canagliflozin, dapagliflozin) or GLP-1 RA (liraglutide, semaglutide, dulaglutide); see Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) for details. The subjects enrolled in the cardiovascular outcomes trials using empagliflozin, canagliflozin, dapagliflozin, liraglutide, and semaglutide had A1C ≥6.5%, and more than 70% were 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 or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (**Table 9.1**). 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 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc21-S011) for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Table 9.2—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 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$188 ($188, $572)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$4	8 mg
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$5	40 mg (IR)
		10 mg (XL)	$48	$11	20 mg (XL)
	• Glyburide	6 mg (micronized)	$52 ($48, $71)	$10	12 mg (micronized)
		5 mg	$93 ($63, $103)	$11	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$5	45 mg
	• Rosiglitazone	4 mg	$407	$330	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$28	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$31	360 mg
	• Repaglinide	2 mg	$878 ($162, $897)	$38	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$175	25 mg
	• Saxagliptin	5 mg	$530	$424	5 mg
	• Linagliptin	5 mg	$555	$444	5 mg
	• Sitagliptin	100 mg	$568	$456	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$354	$284	15 mg
	• Dapagliflozin	10 mg	$621	$496	10 mg
	• Empagliflozin	25 mg	$627	$501	25 mg
	• Canagliflozin	300 mg	$622	$499	300 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$882	$706	2 mg**
	• Exenatide	10 μg pen	$752	$720	20 μg
	• Dulaglutide	4.5/0.5 mL pen	$957	$766	4.5 mg**
	• Semaglutide	1 mg pen	$973	$779	1 mg**
		14 mg (tablet)	$927	$738	14 mg
	• Liraglutide	18 mg/3 mL pen	$1,161	$930	1.8 mg
	• Lixisenatide	300 μg/3 mL pen	$774	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$710 ($674, $712)	$105	3.75 g
		3.75 g suspension	$804	$318	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$960	$772	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2702	$2,097	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 [62] or NADAC [63] 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 mg three times daily.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.2**). 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 providers 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 (66). 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 (67,68). 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 (69–74), although these advantages are modest and may not persist (75). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (62) and NADAC (63) 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 cartridges	$408	$326
		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	$350
	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridges	$215	$344
		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	$924	$606
Short-acting	• human regular	U-100 vial	$165††	$133††
Intermediate-acting	• human NPH	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$143
		U-500 prefilled pen	$229	$183
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$190 (118, 261)	$210
		U-100 vial	$190 (118, 261)	N/A
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		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	$273
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$212	$340
	• Aspart 70/30	U-100 vial	$180	$144
		U-100 prefilled pen	$224	$179
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$589	$471
	• Degludec/Liraglutide	100/3.6 prefilled pen	$874	$701

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 9.2**. †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.

combination with oral agents (76–82). Despite evidence for reduced hypoglycemia with newer, longer-acting basal insulin analogs in clinical trial settings, in practice these effects may be modest compared with NPH insulin (83). 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 IU/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 (84).

The cost of insulin has been rising steadily over the past two decades, at a pace several fold that of other medical expenditures (85). 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 (85). Therefore, consideration of cost is an important component of effective management. For many patients 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 (83). 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 9.3** at select pharmacies.

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 patient needs (see **Fig. 9.2**). People 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 (86). 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 patients with type 2 diabetes have not reported important differences in A1C or hypoglycemia (87,88).

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. Regular U-500 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 (89). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (90,91). 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 patients 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 people 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 (92), although results from a larger study are needed for confirmation. Inhaled insulin is contraindicated in patients with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in patients who smoke or who recently stopped smoking. All patients require spirometry (forced expiratory volume in 1 s [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. 9.2**). 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 (93–95), with one study suggesting greater durability of glycemic effect compared with addition of basal insulin alone (47). Two different once-daily, fixed dual-combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide and insulin degludec plus liraglutide.

Intensification of insulin treatment can be done by adding doses of prandial 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 (96). Alternatively, in a patient 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 patients 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 9.2** 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 patients 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 (pattern control). 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 12 "Older Adults," https://doi.org/10.2337/dc21-S012).

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