9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*

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

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 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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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 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 ALTERNATIVE INSULIN ROUTES in PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES), and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14). Despite the advantages of insulin analogs in individuals with type 1 diabetes, 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 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 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"). 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, individual preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered (see Section 7, "Diabetes Technology").

The U.S. Food and Drug Administration (FDA) has now approved multiple 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 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).

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," 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 and 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

adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most individuals (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 Positive Health Behaviors and Well-being to Improve Health Outcomes").

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 individuals 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. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (29).

Injection site rotation is additionally necessary to avoid lipohypertrophy, which is the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection 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 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 consen-

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous 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).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.4a Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. **A**

9.4b In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (**Fig. 9.3** and **Table 9.2**). **A**

9.4c Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy (**Fig. 9.3** and **Table 9.2**). **A**

9.4d Weight management is an impactful component of glucose-lowering management in type 2

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).

treatment regimen should consider approaches that support weight management goals (**Fig. 9.3** and **Table 9.2**). **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 individuals 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 person-centered approach should guide the choice of pharmacologic therapy, considering effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (**Fig. 9.3** and **Table 9.2**). **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, independent of A1C and in consideration of person-specific factors (**Fig. 9.3**) (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.10 In adults 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, durability of treatment effect, and weight and hypoglycemia benefit. **A**

9.12 Recommendation for treatment intensification for individuals 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 units/kg/day, high bedtime–morning or postprepradial 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, 2022" (43–45) recommends a holistic, multifactorial person-centered approach accounting for the lifelong nature of type 2 diabetes. Person-specific factors that affect choice of treatment include individualized glycemic and weight goals, impact on weight, hypoglycemia and cardiorenal protection (see Section 10, "Cardiovascular Disease and Risk Management," and Section 11 "Chronic Kidney Disease and Risk Management"), underlying physiologic factors, side effect profiles of medications, complexity of regimen, regimen choice to optimize medication use and reduce treat-

le 9.1—Examples of subcutaneous insulin regimens

men	Timing and distribution	Advantages	Disadvantages	Adjusting doses
mens that more closely mimic normal insulin secretion				
lin pump therapy (hybrid osed-loop, low-glucose uspend, CGM-augmented pen-loop, BGM-augmented pen-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.
: LAA + flexible doses of URAA r 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.
regimens with less flexibility				
injections daily with fixed oses of N and RAA	Pre-breakfast: RAA ∼20% of TDD. Pre-lunch: RAA ∼10% of TDD. Pre-dinner: RAA ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

Continued on p. S145

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