6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2025

American Diabetes Association Professional Practice Committee*

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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, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

ASSESSMENT OF GLYCEMIC STATUS

Glycemic status is assessed by A1C measurement, blood glucose monitoring (BGM) by capillary (finger-stick) devices, and continuous glucose monitoring (CGM) using time in range (TIR) or mean CGM glucose. Clinical trials of interventions that lower A1C have demonstrated the benefits of improved glycemia. Glucose monitoring via CGM or BGM (discussed in detail in Section 7, "Diabetes Technology") is useful for diabetes self-management, can provide nuanced information on glucose responses to meals, physical activity, and medication changes, and may be particularly useful in individuals taking insulin. CGM serves an increasingly important role in optimizing the effectiveness and safety of treatment in many people with type 1 diabetes, type 2 diabetes, or other forms of diabetes (e.g., cystic fibrosis–related diabetes). Individuals on a variety of insulin treatment plans can benefit from CGM with improved glucose levels, decreased hypoglycemia, and enhanced self-efficacy (Section 7, "Diabetes Technology") (1).

Glycemic Assessment

Recommendations

6.1 Assess glycemic status by A1C **A** and/or continuous glucose monitoring (CGM) metrics such as time in range, time above range, and time below range. **B** Fructosamine or CGM can be used for glycemic monitoring when an alternative to A1C is required. **B**

6.2 Assess glycemic status at least two times a year, and more frequently (e.g., every 3 months) for individuals not meeting glycemic goals or with recent treatment changes, frequent or severe hypoglycemia or hyperglycemia, or changes in health status, or during periods of rapid growth and development in youth. **E**

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Glycemic Assessment by A1C

The A1C test is the primary tool for assessing glycemic status in both clinical practice and clinical trials, and it is strongly linked to diabetes complications (2–4). A1C reflects average glycemia over approximately 2–3 months. The performance of laboratory tests for A1C is generally excellent for National Glycohemoglobin Standardization Program (NGSP)–certified assays (ngsp.org). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether glycemic goals have been reached and maintained. Adults with type 1 or type 2 diabetes who have achieved and are maintaining glucose levels within their target range may only need A1C testing or other glucose assessments twice a year. Individuals with less stable glucose levels, those with intensive care plans, or those not meeting their treatment goals may require more frequent testing, typically every 3 months, with additional assessments as needed. Point-of-care A1C testing can offer timely opportunities for treatment adjustments during appointments with health care professionals.

The A1C test is an indirect measure of average glycemia. Factors that affect hemoglobin or red blood cells may affect A1C. For example, conditions that affect red blood cell turnover (hemolytic anemia and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) can interfere with the accuracy of A1C (5). Some hemoglobin variants can interfere with some A1C assays; however, most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (6). A1C cannot be measured in individuals with sickle cell disease (HbSS) or other homozygous hemoglobin variants (e.g., HbEE), since these individuals lack HbA (7). In individuals with conditions that interfere with the interpretation of A1C, alternative approaches to monitoring glycemic status should be used, including self-monitoring of blood glucose, CGM, and/or the use of glycated serum protein assays (discussed below). A1C does not provide a measure of glycemic variability or hypoglycemia. For individuals prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with insulin deficiency and/or treatment with intensive insulin therapy, glycemic status is best evaluated by the combination of results from BGM or CGM and A1C. Discordant results between A1C and BGM or CGM can occur due to high glycemic variability, inaccurate BGM or CGM measurement, or inaccurate A1C due to the factors discussed above.

As discussed in Section 2, "Diagnosis and Classification of Diabetes," there is controversy regarding the clinical significance of differences in A1C by self-reported race and ethnicity (8–11). There is an emerging understanding of genetic determinants that may modify the association between A1C and glucose levels (12). However, race and ethnicity are not good proxies for these genetic differences that are likely present in a small minority of individuals of all racial groups. Therefore, race and ethnicity should not be considerations for how A1C is used clinically for glycemic monitoring. Limitations of laboratory tests and within-person variability in glucose and A1C underscore the importance of using multiple approaches to glycemic monitoring and further evaluation of discordant results in all racial or ethnic groups.

Serum Glycated Protein Assays as Alternatives to A1C

Fructosamine and glycated albumin are alternative measures of glycemia that are approved for clinical use for monitoring glycemic status in people with diabetes. Fructosamine reflects total glycated serum proteins (mostly albumin). Glycated albumin assays reflect the proportion of total albumin that is glycated. Due to the turnover rate of serum protein, fructosamine and glycated albumin reflect glycemia over the past 2–4 weeks, a shorter-term time frame than that of A1C. Fructosamine and glycated albumin are highly correlated in people with diabetes, and the performance of modern assays is typically excellent. Fructosamine and glycated albumin have been linked to long-term complications in epidemiologic cohort studies (13–17). However, there have been few clinical trials, and the evidence base supporting the use of these biomarkers to monitor glycemic status is much weaker than that for A1C. In people with diabetes who have conditions where the interpretation of A1C may be problematic or when A1C cannot be measured (e.g., homozygous hemoglobin variants), fructosamine or glycated albumin may be useful alternatives to monitor glycemic status (7).

Correlation Between A1C and Blood Glucose Monitoring and Continuous Glucose Monitoring

Table 6.1 provides rough equivalents of A1C and mean glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) study. The ADAG study assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (18,19). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ~2,700 readings per A1C measurement in the ADAG trial.

Caveats in interpretation of **Table 6.1** include that these data are from a single study published in 2008. Mean glucose in the ADAG study was calculated from a combination of measurements from an early CGM system and capillary glucose, intermittently, during a 3-month period. This older system required calibration several times a day using a self-monitoring

Table 6.1—Equivalent A1C levels and estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (18,19). Adapted from Nathan et al. (18).

glucose meter. It is unclear how generalizable these estimates are to mean glucose measurements obtained using modern CGM systems. The comparability of A1C and mean glucose from CGM systems will depend on the number of days of CGM wear, timing of the A1C measurement relative to the CGM wear period, calibration and accuracy of the CGM system, lag time between interstitial glucose and venous glucose, and any factors that affect A1C or red cell turnover (see Section 2, "Diagnosis and Classification of Diabetes").

Glycemic Assessment by Blood Glucose Monitoring

For many people with diabetes, glucose monitoring, either using BGM by capillary (finger-stick) devices or CGM in addition to regular A1C testing, is key for achieving glycemic goals. Major clinical trials of insulin-treated individuals have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (20). BGM is thus an integral component of effective therapy for individuals taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most people with type 1 diabetes. Both approaches to glucose monitoring allow people with diabetes to evaluate individual responses to therapy and assess whether glycemic goals are being safely achieved. The specific needs and goals of individuals with diabetes should dictate BGM frequency and timing. Please refer to Section 7, "Diabetes Technology," for a more complete discussion of the use of BGM and CGM.

Glycemic Assessment by Continuous Glucose Monitoring

CGM is particularly useful in people with diabetes who are at risk for hypoglycemia and is commonly used in people with type 1 diabetes (20). Use of CGM in type 2 diabetes (as well as in several other forms of diabetes) is growing, especially in people who are taking insulin. TIR is a useful metric of glycemic status. A 10- to 14-day CGM assessment of TIR, with CGM wear of 70% or higher, and other CGM metrics can be used to assess glycemic status and are useful in clinical management (21–25). TIR, and especially mean CGM glucose, correlates with A1C (26–30). Time below range (<70 and <54 mg/dL [<3.9 and <3.0 mmol/L]) and time above range (>180 mg/dL [>10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

The international consensus on CGM provides guidance on CGM metrics (**Table 6.2**) and their clinical interpretation (31). To make these metrics actionable, standardized reports with visual summaries, such as the ambulatory glucose profile (**Fig. 6.1**), are recommended (31) and can help individuals with diabetes and health care professionals interpret the data to guide treatment decisions (26,29). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, detect and prevent hypoglycemia, and aid medication management. CGM metrics, including TIR (with time below range and time above range), can provide helpful insights to inform a personalized diabetes management plan. Remote access to glucose data is growing and may help improve diabetes management (32–34).

CGM systems have evolved rapidly in both accuracy and affordability. As such, many individuals with diabetes have these data available to assist with self-management and their health care professionals' assessment of glycemic status. Reports generated from CGM will allow the health care professional and person with diabetes to view TIR and a calculated glucose management indicator and assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a 2019 consensus report, a report formatted as shown in **Fig. 6.1** can be generated (31). Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% (53 mmol/mol) (24,27). Note that the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) serve as values to guide changes in therapy. For older adults using CGM, the recommended percent time spent in target range of 70–180 mg/dL is 50% (or 12 h per day) and the recommended time spent in hypoglycemia of less than 70 mg/dL should not be more than 1%, or 15 min per day, to minimize hypoglycemia risk (35–38). In this population, more permissive hyperglycemia is allowed (up to 50% of the time in 24 h).

GLYCEMIC GOALS

Recommendations

6.3a An A1C goal of <7% (<53 mmol/mol) is appropriate for many nonpregnant adults without severe hypoglycemia or frequent hypoglycemia affecting health or quality of life. **A**

6.3b A goal time in range of >70% in people using CGM is appropriate for many nonpregnant adults. **B**

6.3c A goal percent time <70 mg/dL (<3.9 mmol/L) of <4% (or <1% for older adults) and a goal percent time <54 mg/dL (<3.0 mmol/L) of <1% are recommended in people using CGM to prevent hypoglycemia. Deintensify or modify therapy if these goals are not met. **B**

6.4 Based on health care professional judgment and the preference of the person with diabetes, achievement of lower A1C levels than the goal of 7% (53 mmol/mol) may be acceptable and even beneficial if it can be achieved safely without frequent or severe hypoglycemia or other adverse effects of treatment. **B**

6.5 Less stringent glycemic goals may be appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. **B**

6.6 Deintensify hypoglycemia-causing medications (insulin, sulfonylureas, or meglitinides), or switch to a medication class with lower hypoglycemia risk, for individuals who are at high risk for hypoglycemia, within individualized glycemic goals. **B**

6.7 Deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **B**

6.8 Reassess glycemic goals based on the individualized criteria shown in **Fig. 6.2**. **E**

6.9 Set a glycemic goal during consultations to improve outcomes. **A**

For all populations, it is critical that the glycemic goals be woven into an individualized, person-centered strategy (39). The glycemic goals for many nonpregnant adults are shown in **Table 6.3**, and **Fig. 6.2** summarizes how A1C goals should be individualized by an individual's health, function, and other modifying

Table 6.2—CGM metrics for clinical care in nonpregnant individuals with type 1 or type 2 diabetes

Metric	Interpretation	Goals
Metrics for valid CGM wear		
Wear time	Number of days CGM device is worn	≥14-day wear for pattern management
Active percentage time	Percent of time CGM device is active	70% of time active out of 14 days
Glycemic metrics		
Mean glucose	Mean of glucose values	*
Glucose management indicator (GMI)	Calculated value approximating A1C (not always equivalent)	*
Glucose coefficient of variation (CV)	Spread of glucose values	≤36%†
TAR >250 mg/dL (>13.9 mmol/L)	Percent of time in level 2 hyperglycemia	<5% (most adults); <10% (older adults)
TAR 181–250 mg/dL (10.1–13.9 mmol/L)	Percent of time in level 1 hyperglycemia	<25% (most adults); <50% (older adults)‡
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	Percent of time in range	>70% (most adults); >50% (older adults)
TBR 54–69 mg/dL (3.0–3.8 mmol/L)	Percent of time in level 1 hypoglycemia	<4% (most adults); <1% (older adults)§
TBR <54 mg/dL (<3.0 mmol/L)	Percent of time in level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time in range. *Goals for these values are not standardized. †Some studies suggest that lower coefficient of variation targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. ‡Goals are for level 1 and level 2 hyperglycemia combined. §Goals are for level 1 and level 2 hypoglycemia combined. Adapted from Battelino et al. (31).

factors. For example, less stringent A1C goals are appropriate for individuals with significant functional and cognitive impairments. For more details regarding glycemic goals in older adults, please refer to Section 13, "Older Adults." For glycemic goals in children, please refer to Section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to Section 15, "Management of Diabetes in Pregnancy."

Health care professionals should engage in shared decision-making with the individual (as well as with family members and caregivers) and should consider adjusting goals for simplifying the treatment plan if this change is needed to improve safety and medication-taking behavior. Setting specific glycemic (and other) goals during consultations has been demonstrated to improve glycemic outcomes for individuals with diabetes (40).

Glucose Lowering and Microvascular Complications

Hyperglycemia defines diabetes, and achieving glycemic goals is fundamental to diabetes management. The level of chronic hyperglycemia is the best-established concomitant risk factor associated with microvascular complications (i.e., diabetic retinopathy, nephropathy, and neuropathy). This is best understood by the fact that nerve, retinal, and kidney cells do not require insulin for intracellular glucose entry. Consequently, the exposure of these cells to elevated ambient glucose levels even in the presence of insulin deficiency (absolute or relative) will result in intracellular metabolic dysfunction and increased risk of microvascular complications.

The Diabetes Control and Complications Trial (DCCT) (41), a prospective randomized controlled trial of intensive (mean A1C ∼7% [∼53 mmol/mol]) versus standard (mean A1C ∼9% [∼75 mmol/mol]) glycemic management in people with type 1 diabetes, showed definitively that better glycemic status is associated with 50–76% reductions in rates of development and progression of microvascular complications (retinopathy, neuropathy, and diabetic kidney disease). Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (42,43) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto study (44) and UK Prospective Diabetes Study (UKPDS) (45,46) examined the effects of "intensive glycemic control" among people with short-duration type 2 diabetes, although glycemic lowering in these studies was not intensive by current standards (mean A1C was 7.1% vs. 9.4% in Kumamoto and 7.0% vs. 7.9% in UKPDS). These trials found lower rates of microvascular complications in the intervention arms, with long-term follow-up of the UKPDS cohorts showing enduring effects on most microvascular complications (47). These studies highlight the long-term benefits of early glycemic lowering in type 2 diabetes.

Therefore, improved glycemia has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (2,48). The DCCT (41) and UKPDS (49) studies demonstrated a curvilinear relationship between attained A1C level and microvascular complications. Such results suggest that, on a population level, the greatest number of complications will be averted by taking individuals with diabetes from very high to moderate A1C levels. These analyses also suggest that further lowering of A1C from 7% to 6% (53 mmol/mol to 42 mmol/mol) is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6% and 7% in the setting of low hypoglycemia risk with a long life expectancy. There are newer pharmacologic agents that do not cause hypoglycemia, making it possible to maintain glycemic status without the risk of hypoglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Moreover, CGM use was not as common when these trials were conducted and automated insulin delivery systems were not available; these have been shown to improve glucose levels without increasing hypoglycemia.

Among individuals with type 2 diabetes, three landmark trials (Action to Control

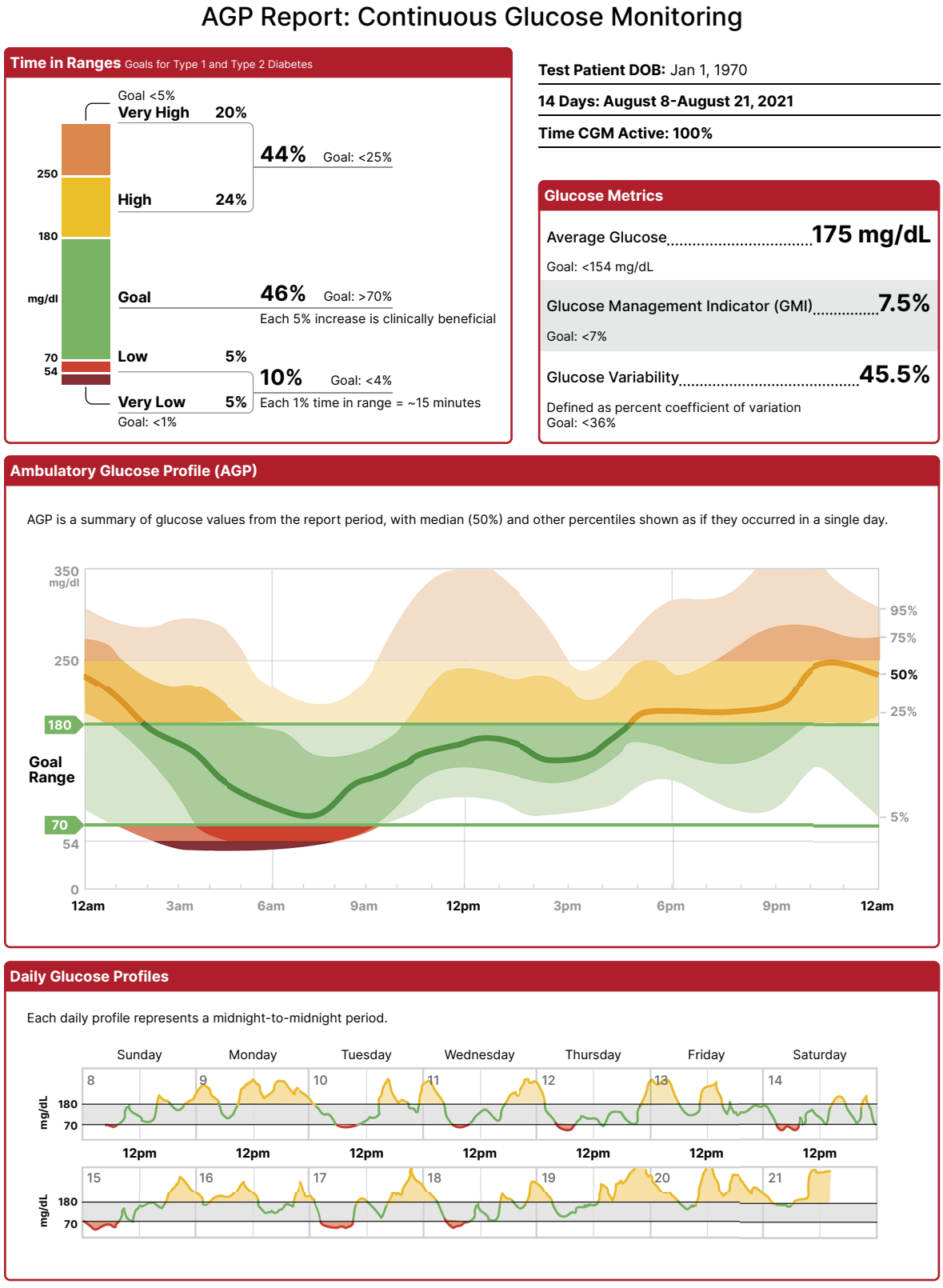
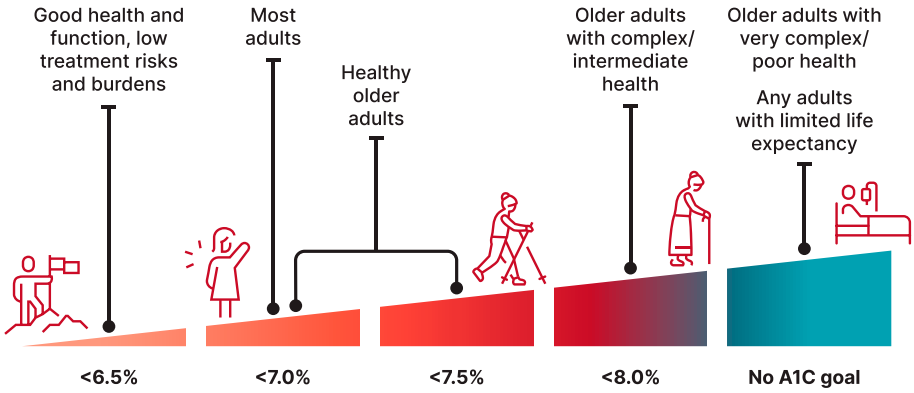


Figure 6.1—Key points included in a standard ambulatory glucose profile (AGP) report. Adapted from Holt et al. (20).

Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes. The ADVANCE and VADT trials found modest reduction in nephropathy with intensive glycemic management; ACCORD was stopped after a median of 3.5 years due to higher mortality in the



Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

Figure 6.2—Individualized A1C goals for nonpregnant adults. Select the glycemic goal based on individual health and function as described at the top of the figure. Consider modifying to a more or less stringent goal according to the factors listed in the table. Older adults are classified as healthy (few coexisting chronic illnesses, intact cognitive and functional status), as having complex/intermediate health (multiple coexisting chronic illnesses, two or more instrumental impairments to activities of daily living, or mild to moderate cognitive impairment), or as having very complex/ poor health (long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment, or two or more impairments to activities of daily living). Select glycemic goals that avoid symptomatic hypoglycemia and hyperglycemia in all individuals. Consider individuals' resources and support systems to safely achieve glycemic goals. Incorporate the preferences and goals of people with diabetes through shared decision-making.

intervention arm (50–54). Importantly, these landmark studies were conducted prior to the approval of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, and intensive glycemic management was achieved predominantly through greater use of insulin. Findings from these studies, including the concerning increase in mortality in the intensive treatment arm of ACCORD, suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes using medications with a high risk for hypoglycemia.

Glucose Lowering and Cardiovascular Disease Outcomes

Cardiovascular disease (CVD) is a more common cause of death than microvascular complications in populations with diabetes. The modern multifaceted management of diabetes, with a focus on the treatment of hypertension and the use of statins, has reduced the prevalence of atherosclerotic CVD to around double compared with that of people without diabetes (55).

The DCCT in individuals with type 1 diabetes and the UKPDS, ACCORD, ADVANCE, and VADT studies in type 2 diabetes all attempted to address whether intensive glycemic management reduced CVD events (41,50,51,53). ACCORD, ADVANCE, and VADT were conducted in relatively older participants with a longer duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. Details of these studies are reviewed extensively in the joint ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (56).

No significant reduction in composite CVD events was demonstrated at the end of the intervention in any of these studies, and ACCORD was stopped prematurely at 3.5 years because of an increase in total mortality, particularly sudden CVD deaths. Serious concerns with the intensive glycemic treatment plan used in

Table 6.3—Summary of glycemic goals for many nonpregnant adults with diabetes

A1C	<7.0% (<53 mmol/mol)*†
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose‡	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for certain individuals. †CGM may be used to assess glycemic status as noted in Recommendations 6.3b and 6.3c and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age and life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, impaired awareness of hypoglycemia, and individual considerations (per **Fig. 6.2**). ‡Postprandial glucose may warrant special attention if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, which is generally the timing for peak levels in people with diabetes.

ACCORD included the rapid escalation of therapies, the early use of large doses of insulin, substantial weight gain, and frequent hypoglycemia. These overall negative results were not unexpected, as blood glucose has subsequently been shown to be a relatively weak CVD risk factor in isolation compared with other CVD risk factors, such as hypertension or hypercholesterolemia. Consequently, even if a wide separation in A1C could be safely obtained, it would take a long time for the CVD benefit to accrue. However, a meta-analysis of individual participant data from UKPDS, ACCORD, ADVANCE, and VADT demonstrated a significant reduction in myocardial infarctions and major CVD events but no difference in stroke, heart failure, or mortality between intensive and less intensive glycemic management (57).

Longer-term epidemiological follow-up has been performed in these studies, and a clear pattern of CVD benefit has emerged (58–60). In the post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction, stroke, or cardiovascular death compared with those previously randomized to the standard arm (58). The benefit of intensive glycemic management in this cohort with type 1 diabetes has been shown to persist for several decades (59) and to be associated with a modest reduction in all-cause mortality (61).

UKPDS post-trial monitoring, with 20 years of total follow-up, has shown reductions in myocardial infarctions and total mortality both in the group of overweight individuals treated with metformin and in the group previously treated intensively with sulfonylureas or insulin (47). Shorter overall follow-up of the VADT (10 years) has shown a significant reduction in the primary outcome of major CVD events, with myocardial infarctions and heart failure being the commonest outcomes (60). In contrast, shorter follow-up of the ADVANCE study in the Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation Post Trial Observational Study (ADVANCE-ON) demonstrated no significant effect on CVD events (62). Even in the epidemiological follow-up of ACCORD in the Action to Control Cardiovascular Risk in Diabetes Follow-On Study (ACCORDION), the excess increase in total mortality that was seen during 3.5 years of intensive treatment was reduced by returning to conventional management, and therefore there was no difference in total mortality after a total of 9 years of follow-up (63). Collectively, the results of these studies confirm that long-term intensive glycemic management reduces CVD events, particularly myocardial infarctions.

As discussed above, these landmark studies in individuals with type 2 diabetes need to be considered with the important caveat that GLP-1 RAs and SGLT2 inhibitors were not yet in clinical use. These agents with established cardiovascular and kidney benefits appear to be safe and beneficial in this group of individuals at high risk for cardiovascular and kidney complications. Randomized clinical trials examining these agents for cardiovascular safety were not designed to test higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering per se by these agents that confers the CVD and kidney benefits (64). Additional beneficial pleotropic effects of these agents may include weight loss, hemodynamic effects, blood pressure lowering, and anti-inflammatory changes.

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (65). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such goals cannot be safely and reasonably achieved. As discussed in Section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of specific SGLT2 inhibitors or GLP-1 RAs that have demonstrated CVD benefit is recommended in individuals with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," the cardiovascular benefits of SGLT2 inhibitors or GLP-1 RAs are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C, A1C goal, or metformin therapy. Based on these considerations, the following two strategies are offered (66):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or a GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 RAs in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C goal.

Setting and Modifying Glycemic Goals

Glycemic goals and management should be individualized and not one size fits all. To prevent both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to individualized goals (56,67).

Numerous factors must be considered when setting a glycemic goal. The ADA proposes general goals that are appropriate for many people but emphasizes the importance of individualization based on key person characteristics. Glycemic goals must be individualized in the context of shared decision-making to address individual needs and preferences and consider characteristics that influence risks and benefits of therapy; this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly in the care of a given individual but to be used as a broad framework to guide clinical decision-making (39) and engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive goals may be recommended if they can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap the benefits of stringent goals. Less stringent goals (e.g., A1C up to 8% [64 mmol/mol]) may be recommended if the individual's life expectancy is such that the benefits of an intensive goal may not be realized or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals.

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed individuals and/or those without comorbidities that limit life expectancy may benefit from intensive glycemic goals proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS suggested that there is metabolic memory, or a legacy effect, in which a finite period of intensive glucose lowering yielded benefits that extended for decades after that period ended. However, there are few recent data on the effects of long-term glucose lowering using modern treatment strategies. Thus, a finite period of intensive treatment to near-normal A1C may yield enduring benefits even if treatment is subsequently deintensified as characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive treatment. Also, with longer disease duration, diabetes may become more difficult to manage, with increasing risks and burdens of therapy. Thus, glycemic goals should be reevaluated over time to balance the risks and benefits.

Accordingly, clinicians should continue to evaluate the balance of risks and benefits of diabetes medications for individuals who have achieved individualized glycemic goals, and they should deintensify (decrease the dose or stop) diabetes medications where their risks exceed their benefits. Hypoglycemia is the major risk to individuals treated with insulin, sulfonylureas, or meglitinides, and it is appropriate to deintensify these medications where there is a high risk for hypoglycemia (see HYPOGLYCEMIA RISK ASSESSMENT, below). Switching a high-hypoglycemia-risk medication to lower-hypoglycemia-risk therapy (see Section 9, "Pharmacologic Approaches to Glycemic Treatment") should be considered if needed to achieve individualized glycemic goals or where individuals have evidence-based indications for alternative medications (e.g., use of SGLT2 inhibitors in the setting of heart failure or diabetic kidney disease and use of GLP-1 RAs in the setting of CVD or obesity). Clinicians should also consider medication burdens other than hypoglycemia, including tolerability, difficulties of administration, impact on education or employment, and financial cost. These factors should be balanced against benefits from glycemic lowering and disease-specific benefits of newer medications that may be independent of glycemic lowering (Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Multiple trials have shown that deintensification of diabetes treatment can be achieved successfully and safely (68–70). It is important to partner with people with diabetes during the deintensification process to understand their goals of diabetes treatment and agree upon appropriate glycemic monitoring, glucose levels, and goals of care (71).

HYPOGLYCEMIA ASSESSMENT, PREVENTION, AND TREATMENT

Recommendations

6.10 Review history of hypoglycemia at every clinical encounter for all individuals at risk for hypoglycemia, and evaluate hypoglycemic events as indicated. **C**

6.11 Screen individuals at risk for hypoglycemia for impaired hypoglycemia awareness at least annually and when clinically appropriate. **E** Refer to a trained health care professional for evidence-based intervention to improve hypoglycemia awareness. **A**

6.12 Screen individuals at high risk for hypoglycemia or with severe and/or frequent hypoglycemia for fear of hypoglycemia at least annually and when clinically appropriate. **E** Refer to a trained health care professional for evidence-based intervention. **A**

6.13 Clinicians should consider an individual's risk for hypoglycemia (see **Table 6.5**) when selecting diabetes medications and glycemic goals. **E**

6.14 Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia. **A**

6.15 Glucose is the preferred treatment for the conscious individual with glucose <70 mg/dL (<3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Avoid using foods or beverages high in fat and/or protein for initial treatment of hypoglycemia. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists. **B**

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

6.17 All individuals taking insulin **A** or at risk for hypoglycemia **C** should receive structured education for hypoglycemia prevention and treatment, with ongoing education for those who experience hypoglycemic events.

6.18 One or more episodes of level 2 or 3 hypoglycemia should prompt reevaluation of the treatment plan, including deintensifying or switching diabetes medications if appropriate. **E**

6.19 Regularly assess cognitive function; if impaired or declining cognition is found, the clinician, person with diabetes, and caregiver should increase vigilance for hypoglycemia. **B**

Hypoglycemia Definitions and Event Rates

Hypoglycemia is often the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (72). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for adrenergic responses to falling glucose in people without diabetes. Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, sweating, and hunger (73). Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience impaired hypoglycemia awareness, a measured glucose level <70 mg/dL (<3.9 mmol/L) is considered clinically important, regardless of symptoms. Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [<3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If an individual has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have impaired

Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)
Level 2	Glucose <54 mg/dL (<3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

Adapted from Agiostratidou et al. (72).

hypoglycemia awareness (discussed further in HYPOGLYCEMIA RISK ASSESSMENT, below). This clinical scenario warrants investigation and review of the treatment plan (74,75). Lastly, level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.

Hypoglycemia has a broad range of negative health consequences (76). Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Level 3 hypoglycemia was associated with mortality in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward (77). An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial and in clinical practice (78,79). Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury (80). Hypoglycemia may also cause substantial anxiety that can reduce the quality of life of individuals with diabetes and their caregivers and may contribute to problems with diabetes self-management and treatment (81–83). Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical treatment plan adjustment, behavioral intervention, delivery of diabetes self-management education and support, and use of technology to assist with hypoglycemia prevention and identification (75,84–87).

Studies of rates of hypoglycemia predominantly rely on claims data for hospitalizations and emergency department visits (88–91). These studies do not capture the level 1 and level 2 hypoglycemia that represent the vast majority of hypoglycemic events, and they also substantially underestimate level 3 hypoglycemia (88,92,93). Nevertheless, they reveal a substantial burden of hypoglycemia-related hospital utilization in the community (88–91). Level 1 and level 2 hypoglycemia can be ascertained from patient self-report (94) and are strong risk factors for subsequent level 3 hypoglycemia.

Hypoglycemia Risk Assessment

Assessment of an individual's risk for hypoglycemia includes evaluating clinical risk factors as well as relevant social, cultural, and economic factors (**Table 6.5**). Recommendations 6.10–6.19 group individuals with diabetes into two hypoglycemia risk categories with clinical significance. Individuals at risk for hypoglycemia are those treated with insulin, sulfonylureas, or meglitinides; clinically significant hypoglycemia is rare among individuals taking other diabetes medication classes (95,96). Individuals at high risk for hypoglycemia are the subset of individuals at risk for hypoglycemia who either have a major hypoglycemia

Table 6.5—Assessment of hypoglycemia risk among individuals treated with insulin, sulfonylureas, or meglitinides

Clinical and biological risk factors	Social, cultural, and economic risk factors
Major risk factors • Recent (within the past 3–6 months) level 2 or 3 hypoglycemia • Intensive insulin therapy* • Impaired hypoglycemia awareness • End-stage kidney disease • Cognitive impairment or dementia	Major risk factors • Food insecurity • Low-income status§ • Housing insecurity • Fasting for religious or cultural reasons • Underinsurance
Other risk factors • Multiple recent episodes of level 1 hypoglycemia • Basal insulin therapy* • Age ≥75 years† • Female sex • High glycemic variability‡ • Polypharmacy • Cardiovascular disease • Chronic kidney disease (eGFR <60 mL/min/1.73 m^2 or albuminuria) • Neuropathy • Retinopathy • Major depressive disorder • Severe mental illness	Other risk factors • Low health literacy • Alcohol or substance use disorder

Major risk factors are those that have a consistent, independent association with a high risk for level 2 or 3 hypoglycemia. Other risk factors are those with less consistent evidence or a weaker association. These risk factors are identified through observational analyses and are intended to be used for hypoglycemia risk stratification. Individuals considered at high risk for hypoglycemia are those with ≥1 major risk factor or who have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (89,90,95,97–100,120,180). Proximal causes of hypoglycemic events (e.g., exercise and sleep) are not included. eGFR, estimated glomerular filtration rate. *Rates of hypoglycemia are highest for individuals treated with intensive insulin therapy (including multiple daily injections of insulin, continuous subcutaneous insulin infusion, or automated insulin delivery systems), followed by basal insulin, followed by sulfonylureas or meglitinides. Combining treatment with insulin and sulfonylureas further increases hypoglycemia risk. †Accounting for treatment plan and diabetes subtype, the oldest individuals (aged ≥75 years) have the highest risk for hypoglycemia in type 2 diabetes; younger individuals with type 1 diabetes are also at very high risk. ‡Tight glycemic management in randomized trials increases hypoglycemia rates. In observational studies, both low and high A1C are associated with hypoglycemia in a J-shaped relationship. §Includes factors associated with low income, such as living in a socioeconomically deprived area.

risk factor or have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (**Table 6.5**). This risk stratification is based on epidemiologic studies of hypoglycemia risk (89,90,95,97–101). Validated tools have been developed to estimate hypoglycemia risk using predominantly electronic health record data (102–104). However, these tools do not include all of the important hypoglycemia risk factors, and more research is needed to determine how they can best be incorporated into clinical care.

Among individuals at risk for hypoglycemia, prior hypoglycemic events, especially level 2 or 3 events, are the strongest risk factors for hypoglycemia recurrence (96,99,105–107). Hypoglycemia history should be assessed at every clinical encounter and should include hypoglycemic event frequency, severity, precipitants, symptoms (or lack thereof), and approach to treatment. It is essential to correlate home glucose readings, both from glucose meters and CGM systems, with symptoms and treatment, as individuals may experience and treat hypoglycemic symptoms without checking their glucose level (108), treat normal glucose values as hypoglycemic, or tolerate hypoglycemia without treatment either because of lack of symptoms or to avoid hyperglycemia.

Individuals at risk for hypoglycemia should also be screened for impaired hypoglycemia awareness (also called hypoglycemia unawareness or hypoglycemia-associated autonomic failure) at least yearly. Impaired hypoglycemia awareness is defined as not experiencing the typical counterregulatory hormone release at low glucose levels or the associated symptoms, which often occurs in individuals with long-standing diabetes or recurrent hypoglycemia (109). Individuals with impaired hypoglycemia awareness may experience confusion as the first sign of hypoglycemia, which can create fear of hypoglycemia and severely impact quality of life (110). Impaired hypoglycemia awareness dramatically increases the risk for level 3 hypoglycemia (111). Validated questionnaires for assessing impaired hypoglycemia awareness include the single-question Pedersen-Bjergaard (112) and Gold (113) tools; the Clarke (114) and HypoA-Q (115) tools are longer questionnaires that evaluate multiple domains of impaired hypoglycemia awareness. Comparisons between these tools largely yield good agreement (116,117). To efficiently screen for impaired hypoglycemia awareness in clinical practice, clinicians can ask a single question based on these tools such as "Can you always feel when your blood sugar is low?" and follow up "No" responses with a more detailed evaluation.

Other notable clinical and biological risk factors for hypoglycemia are older age, multimorbidity, cognitive impairment, chronic kidney disease and end-stage kidney disease in particular, CVD, depression, and neuropathy (95,96). Female sex has also been found to be an independent risk factor for hypoglycemia in multiple studies, although the mechanisms of this relationship are unclear and require further research (95). Cognitive impairment has a strong bidirectional association with hypoglycemia, and recurrent severe hypoglycemic episodes were associated with a greater decline in psychomotor and mental efficiency after long-term follow-up of the DCCT/EDIC cohort (118). Therefore, cognitive function should be routinely assessed among older adults with diabetes.

There are a number of important social, cultural, and economic hypoglycemia risk factors that should be considered. Food insecurity is associated with increased risk of hypoglycemia-related emergency department visits and hospitalizations in low-income households, and this was shown to be mitigated by increased federal nutrition program benefits (119). In general, individuals with low annual household incomes (96), individuals who live in socioeconomically deprived areas (99), and individuals who are underinsured (100) or experiencing housing instability (120) experience higher rates of emergency department visits and hospitalizations for hypoglycemia. Clinicians should also be aware of cultural practices that may influence glycemic management (which are discussed in detail in Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"), such as fasting as part of religious observance. Fasting may increase the risk for hypoglycemia among individuals treated with insulin or insulin secretagogues if not properly planned for, so clinicians need to engage these individuals to codevelop a diabetes treatment plan that is safe and respectful of their traditions (121).

Young children with type 1 diabetes and older adults, including those with type 1 and type 2 diabetes (122,123), are noted as being particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glycemic goals, education, nutrition intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve outcomes (109). Insulin pumps with automated low-glucose suspend and automated insulin delivery systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (124). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, pancreas transplant alone or human islet transplantation may be an option, but these approaches remain experimental (125,126).

Hypoglycemia Treatment

Health care professionals should counsel individuals with diabetes to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less (127–129). Individuals should be counseled to recheck their glucose 15 min after ingesting carbohydrates and to repeat carbohydrate ingestion and seek care for ongoing hypoglycemia. These instructions should be reviewed at each clinical visit.

For most individuals, 15 g carbohydrates should be ingested. Individuals using automated insulin delivery systems should ingest 5–10 g carbohydrates unless there is hypoglycemia in conjunction with exercise or there has been significant overestimation of a carbohydrate/meal bolus (130). The acute glycemic response to food correlates better with the glucose content than with the total carbohydrate content. Pure glucose is the preferred initial treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may slow and then prolong the acute glycemic response. Dietary protein intake may increase insulin secretion and should not be used to treat hypoglycemia (131). Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. All individuals treated with insulin or who are at high risk of hypoglycemia as discussed above should be prescribed glucagon. For these individuals, clinicians should routinely review their access to glucagon, as appropriate glucagon prescribing is very low in current practice (132–134). An individual does not need to be a health care professional to safely administer glucagon. Those in close contact with, or having custodial care of, these individuals (family members, roommates, school personnel, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. It is essential that they be explicitly educated to never administer insulin to individuals experiencing hypoglycemia. Glucagon was traditionally dispensed as a powder that requires reconstitution prior to injection. However, intranasal and ready-to-inject glucagon preparations are now widely available and are preferred due to their ease of administration resulting in more rapid correction of hypoglycemia (135–137). Although the physical and chemical stability of glucagon has improved with newer formulations, care should be taken to replace glucagon products when they reach their expiration date and to store glucagon based on specific product instructions to ensure safe and effective use. For currently available glucagon products and associated costs, see **Table 6.6**. Health insurance providers may prefer only select glucagon products, so it is important to check individuals' insurance coverage and prescribe formulary products whenever possible.

Hypoglycemia Prevention

A multicomponent hypoglycemia prevention plan (**Table 6.7**) is critical to caring for individuals at risk for hypoglycemia. Hypoglycemia prevention begins by establishing an individual's hypoglycemia history and risk factors, as discussed in HYPOGLYCEMIA RISK ASSESSMENT above. Structured education for hypoglycemia prevention and treatment is critical and has been shown to improve hypoglycemia outcomes (138,139). Education should ideally be provided through a diabetes self-management education and support program or by a trained diabetes care and education specialist, although these services are not available in many areas (140,141). If structured education is not available, clinicians should educate individuals at risk for hypoglycemia on hypoglycemia definitions, situations that may precipitate hypoglycemia (fasting, delayed meals, physical activity, and illness), blood glucose self-monitoring, avoidance of driving with hypoglycemia, step-by-step instructions on hypoglycemia treatment as discussed above, and glucagon use as appropriate (138).

CGM can be a valuable tool for detecting and preventing hypoglycemia in many individuals with diabetes, and it is recommended for insulin-treated individuals, especially those using multiple daily insulin injections or continuous subcutaneous insulin infusion. There is clinical trial evidence that CGM reduces rates of hypoglycemia in these populations. CGM can reveal asymptomatic hypoglycemia and help identify patterns and precipitants of hypoglycemic events (142,143). Real-time CGM can provide alarms that can warn individuals of falling glucose so that they can intervene (142,143). For more information on using BGM and CGM for hypoglycemia prevention, see Section 7, "Diabetes Technology."

An essential component of hypoglycemia prevention is appropriate modification to diabetes treatment in the setting of intercurrent illness (discussed in detail below) or to prevent recurrent hypoglycemic events. Level 2 or 3 hypoglycemic events especially should trigger a reevaluation of the individual's diabetes treatment plan, with consideration of deintensification of therapy within individualized glycemic goals.

Individuals with impaired awareness should be offered training to reestablish awareness of hypoglycemia. Fear of hypoglycemia and hypoglycemia unawareness often co-occur, so interventions aimed at treating one often benefit both (144). Several evidence-based training programs have been developed for this purpose and have been demonstrated to reduce rates of hypoglycemia and improve quality of life among people with type 1 diabetes and impaired hypoglycemia awareness (75,145,146). However, these programs are not currently available for clinical use. Similar training can be provided through qualified behavioral health professionals, diabetes care and education specialists, or other professionals with experience in this area, although this approach has not been evaluated in clinical trials. In addition, several weeks of avoidance of hypoglycemia, typically accomplished through a temporary relaxation of glycemic goals, can improve counterregulation and hypoglycemia awareness in many people with diabetes (147). Hence, individuals with impaired hypoglycemia awareness and recurrent hypoglycemic episodes may benefit from short-term relaxation of glycemic goals.

Table 6.6—Median monthly (30-day) AWP and NADAC of glucagon formulations in the U.S.

Product	Form	Median AWP* (min, max)	Median NADAC* (min, max)	Dosage
Glucagon	Injection powder with diluent for reconstitution	$206 ($194, $337)	$235 ($199, $295)	1 mg
Glucagon	Nasal powder	$347	$269	3 mg
Glucagon	Prefilled pen, prefilled syringe	$379	$295	0.5 mg, 1 mg
Dasiglucagon	Prefilled pen, prefilled syringe	$371	$298	0.6 mg

AWP, average wholesale price; max, maximum; min, minimum; NADAC, National Average Drug Acquisition Cost. AWP and NADAC prices are as of 1 July 2024. *Calculated per unit (AWP [181,182] or NADAC [183]; median AWP or NADAC is listed alone when only one product and/or price is described).

INTERCURRENT ILLNESS

Stressful events (e.g., illness, trauma, and surgery) increase the risk for both hyperglycemia and hypoglycemia among individuals with diabetes. In severe cases, they may precipitate diabetic ketoacidosis or a nonketotic hyperglycemic hyperosmolar state, which are life-threatening

Table 6.7—Components of hypoglycemia prevention for individuals at risk for hypoglycemia at initial, follow-up, and annual visits

Hypoglycemia prevention action	Initial visit	Every follow-up visit	Annual visit
Hypoglycemia history assessment	✓	✓	✓
Hypoglycemia awareness assessment	✓		✓
Cognitive function and other hypoglycemia risk factor assessment	✓		✓
Structured patient education for hypoglycemia prevention and treatment	✓	✓*	✓*
Consideration of continuous glucose monitoring needs	✓	✓	✓
Reevaluation of diabetes treatment plan with deintensification, simplification, or agent modification as appropriate	✓	✓†	✓†
Glucagon prescription and training for close contacts for insulin-treated individuals or those at high hypoglycemic risk	✓		✓
Training to reestablish awareness of hypoglycemia	✓‡		✓‡

The listed frequencies are the recommended minimum; actions for hypoglycemia prevention should be taken more often as needed based on clinical judgment. *Indicated with recurrent hypoglycemic events or at initiation of medication with a high risk for hypoglycemia. †Indicated with any level 2 or 3 hypoglycemia, intercurrent illness, or initiating interacting medications. ‡Indicated when impaired hypoglycemia awareness is detected.

conditions that require immediate medical care. Any individuals with diabetes experiencing illness or other stressful events should be assessed for the need for more frequent monitoring of glucose; ketosis-prone individuals also require urine or blood ketone monitoring. Clinicians should reevaluate diabetes treatment during these events and make adjustments as appropriate. Clinicians should be aware of medication interactions that may precipitate hypoglycemia. Notably, sulfonylureas interact with a number of commonly used antimicrobials (fluoroquinolones, clarithromycin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole) that can dramatically increase their effective dose, leading to hypoglycemia (148–150). Clinicians should consider temporarily decreasing or stopping sulfonylureas when these antimicrobials are prescribed.

For further information on management of hyperglycemia in the hospital, see Section 16, "Diabetes Care in the Hospital."

HYPERGLYCEMIC CRISES: DIAGNOSIS, MANAGEMENT, AND PREVENTION

Recommendations

6.20 Review history of hyperglycemic crises (i.e., diabetic ketoacidosis and hyperglycemic hyperosmolar state) at every clinical encounter for all individuals with diabetes at risk for these events. **C**

6.21 Provide structured education on the recognition, prevention, and management of hyperglycemic crisis to all individuals with type 1 diabetes, those with type 2 diabetes who have experienced these events, and people at high risk for these events. **B**

Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) are serious, acute, and life-threatening hyperglycemic emergencies in individuals with diabetes (151) that incur substantial morbidity, mortality, and costs (152). Approximately 1% of all hospitalizations in people with diabetes are for hyperglycemic crises. The diagnostic criteria for DKA and HHS are summarized in **Table 6.8**; all criteria must be met to establish these diagnoses. Importantly, approximately 10% of people experiencing DKA present with euglycemic DKA (plasma glucose <200 mg/dL [11.1 mmol/L]); therefore, DKA diagnosis requires either the presence of hyperglycemia or prior history of diabetes (151). Euglycemic DKA requires insulin deficiency and can be associated with a variety of factors including reduced food intake, pregnancy, alcohol use, liver failure, and/or SGLT2 inhibitor therapy (153). Additionally, DKA and HHS often present concurrently (154), though few studies have examined mixed DKA-HHS events.

There has been a concerning rise in the rate of hyperglycemic crises in people with both type 1 diabetes and type 2 diabetes over the past decade (91,155–161). Recent data suggest hyperglycemic crisis rates of up to 44.5–82.6 per 1,000 person-years among people with type 1 diabetes (91,159) and up to 3.2 per 1,000 person-years among people with type 2 diabetes (91). While DKA mortality decreased in the first decade of the 21st century (156), these improvements have

Table 6.8—Diagnostic criteria for DKA and HHS

DKA	
Diabetes/hyperglycemia	Glucose ≥200 mg/dL (11.1 mmol/L) or prior history of diabetes
Ketosis	β-Hydroxybutyrate concentration ≥3.0 mmol/L or urine ketone strip 2+ or greater
Metabolic acidosis	pH <7.3 and/or bicarbonate concentration <18 mmol/L
HHS	
Hyperglycemia	Plasma glucose ≥600 mg/dL (33.3 mmol/L)
Hyperosmolarity	Calculated effective serum osmolality >300 mOsm/kg (calculated as [2×Na^+ (mmol/L) + glucose (mmol/L)] or total serum osmolality >320 mOsm/kg [2×Na^+ (mmol/L) + glucose (mmol/L) + urea (mmol/L)]
Absence of significant ketonemia	β-Hydroxybutyrate concentration <3.0 mmol/L OR urine ketone strip less than 2+
Absence of acidosis	pH ≥7.3 and bicarbonate concentration ≥15 mmol/L

Adapted from Umpierrez et al. (151).

plateaued in the past decade (155, 159,162). Most recently available data for inpatient mortality during hospital admission for DKA ranges from 0.2% in type 1 diabetes (163) to 1.0% in type 2 diabetes (156,164). Inpatient mortality among people with type 2 diabetes hospitalized for HHS decreased from 1.44% in 2008 to 0.77% in 2018 (165). The only study to have examined inpatient mortality for mixed DKA-HHS found it to be higher than mortality for HHS or DKA alone (154). Mortality rates reported in low- and middle-income countries are much higher than those in developed countries, potentially because of delayed diagnosis and treatment (151). People discharged after an episode of DKA have a 1-year age-corrected mortality rate that is 13 times higher than the general population (166).

There are a number of clinical factors associated with an increased risk of hyperglycemic crises (**Table 6.9**). In addition, several studies have reported DKA at the presentation of newly diagnosed type 1 diabetes during or after a coronavirus disease 2019 (COVID-19) infection. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known, but several complex interrelated processes may be involved. Some drug classes can affect carbohydrate metabolism and precipitate the development of DKA and HHS, including glucocorticoids, antipsychotic medications, checkpoint inhibitors, and SGLT2 inhibitors. The risk of DKA in people with type 1 diabetes using SGLT2 inhibitors can be 5–17 times higher than that in nonusers. In contrast, observational studies and randomized controlled trials have shown that DKA is uncommon in people with type 2 diabetes treated with SGLT2 inhibitors (0.6–4.9 events per 1,000 patient-years) (167). A meta-analysis of four randomized controlled trials found the relative risk of DKA in participants with type 2 diabetes treated with SGLT2 inhibitors versus placebo or active comparator arm to be 2.46 (95% CI 1.16–5.21), while a meta-analysis of five observational studies found the relative risk to be 1.74 (95% CI 1.07–2.83) (168). Risk factors for DKA in individuals with type 2 diabetes treated with SGLT2 inhibitors include very-low-carbohydrate diets and prolonged fasting, dehydration, excessive alcohol intake, and the presence of autoimmunity, in addition to typical precipitating factors (168,169). Up to 2% of pregnancies with pregestational diabetes (most often type 1 diabetes) are complicated by DKA. The incidence of DKA in gestational diabetes is low (<0.1%) (170). Pregnant individuals may present with euglycemic DKA (glucose <200 mg/dL [11.1 mmol/L]), and the diagnosis of DKA may be hindered by the presence of mixed acid-based disturbances, particularly in the setting of hyperemesis. Due to significant risk of feto-maternal harm, pregnant individuals at risk for DKA should be counseled on the signs and symptoms suggestive of DKA and seek immediate medical attention if concern for DKA is present.

Table 6.9—Risk factors for hyperglycemic crises

Type 1 diabetes/absolute insulin deficiency
Younger age
Prior history of hyperglycemic crises
Prior history of hypoglycemic crises
Presence of other diabetes complications
Presence of other chronic health conditions (particularly in people with type 2 diabetes)
Presence of behavioral health conditions (e.g., depression, bipolar disorder, and eating disorders)
Alcohol and/or substance use
High A1C level
Social determinants of health

Data are from McCoy et al. (184), Gibb et al. (185), Randall et al. (186), and Thomas et al. (187).

Hyperglycemic crisis should be considered in all individuals presenting with polyuria, polydipsia, weight loss, vomiting, dehydration, and change in cognitive state (**Table 6.10**). Individuals at risk for DKA should be counseled on the early signs and symptoms of DKA, provided with appropriate tools for accurate ketone measurement (urine and/or blood ketone tests), and educated on timely self-management of hyperglycemia and ketonemia ("sick day advice") (171–173) to prevent clinical deterioration and need for acute care. Individuals treated with intensive insulin therapy should not stop or hold their basal insulin even if not eating, and clinicians should provide detailed instructions on insulin dose adjustments in the setting of illness or fasting to prevent DKA occurrence and worsening. Individuals concerned about or experiencing DKA should be encouraged to contact their diabetes care team immediately. Readily available clinical support can help individuals self-manage hyperglycemia during illness and prevent emergency department and hospital care (174). Individuals at risk for DKA should measure urine or blood ketones in the presence of symptoms and potential precipitating factors (e.g., illness, missed insulin doses), particularly if glucose levels exceed 200 mg/dL (11.1 mmol/L). When hemodynamically and cognitively intact, able to tolerate oral hydration, and able to administer subcutaneous insulin, individuals may treat mild DKA with frequent blood glucose and urine or blood ketone monitoring, noncaloric hydration, and subcutaneous insulin administration. However, individuals should seek immediate medical attention if unable to tolerate oral hydration, blood glucose levels do not improve with insulin administration, altered mental status is present, or any signs of worsening illness occur. Because HHS is associated with greater volume depletion and is typically triggered by an acute illness, individuals with suspected HHS should be immediately evaluated and treated in the inpatient setting.

A substantial proportion of individuals hospitalized with DKA experience recurrent episodes (175,176), which underscores the importance of engaging individuals experiencing these events to identify triggers and prevent recurrence. Structured diabetes self-management education and support that includes problem-solving is effective at reducing DKA admissions, as are psychological interventions, peer

Table 6.10—Clinical presentation in people with diabetes with DKA and HHS

DKA	HHS
Develops over hours to days	Develops over days to a week
Usually alert	Change in cognitive state common
Polyuria, polydipsia, weight loss, and dehydration	
Nausea, vomiting, and abdominal pain	Often copresenting with other acute illness
Kussmaul respiration	
One-third of hyperglycemic emergencies have a hybrid DKA-HHS presentation	

Adapted from Umpierrez et al. (151).

support, individual coaching, and behavioral family systems therapy (177,178). Individuals who have experienced DKA or HHS should be screened for social determinants of health that can contribute to or trigger these complications, including inadequate access to insulin, other glucose-lowering medications, and diabetes durable medical equipment (i.e., glucose monitoring and insulin administration devices), and referred to appropriate health care and/or community services to mitigate these barriers to care (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional details). Access to CGM may also decrease risk of DKA recurrence (179).

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