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

*American Diabetes Association Professional Practice Committee**

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## 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**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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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

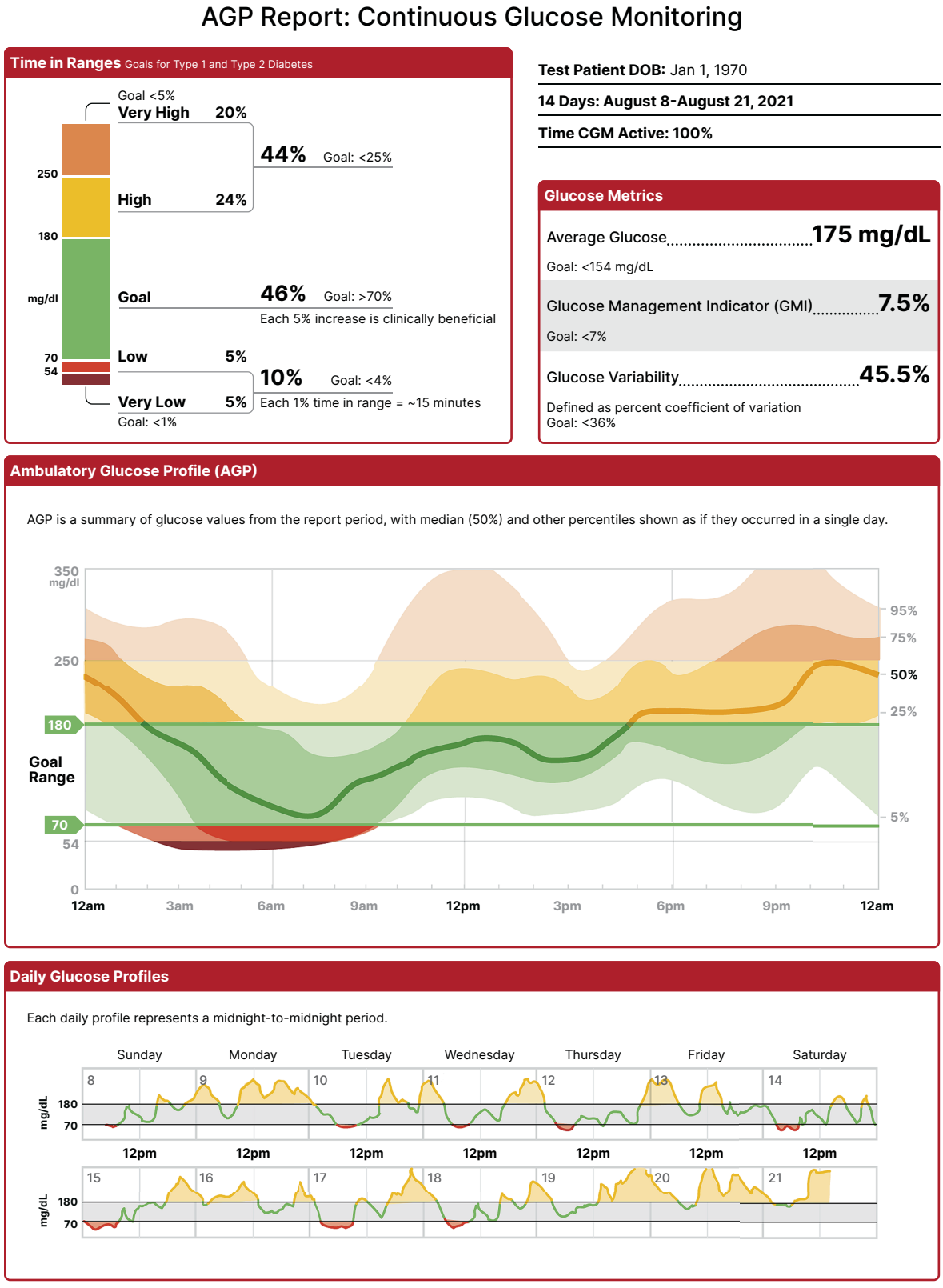
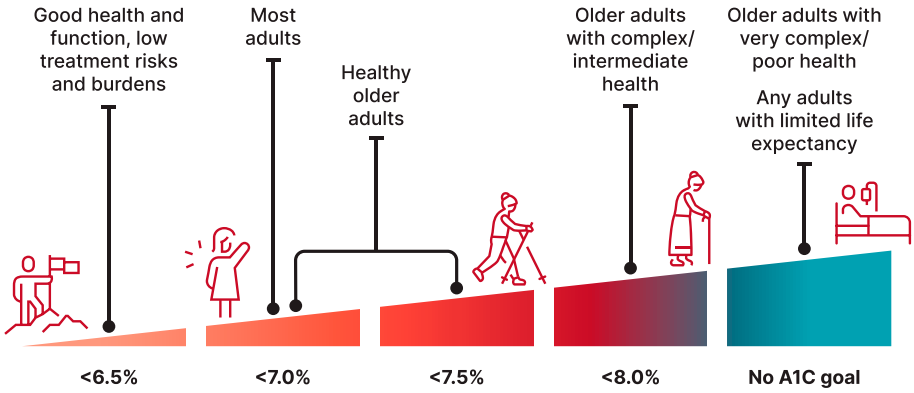



**Figure 6.1**—Key points included in a standard ambulatory glucose profile (AGP) report. Adapted from Holt et al. (20).

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

## References


1. Deshmukh H, Wilmot EG, Gregory R, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. Diabetes Care 2020;43:2153–2160
2. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study). Diabetes Care 2019;42:416–426
3. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
4. Little RR, Rohlfing CL, Sacks DB; National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. Clin Chem 2011;57:205–214
5. Kidney Disease: Improving Global Outcomes (KDIGO) Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102:S1–S127
6. National Glycohemoglobin Standardization Program. HbA1c Assay Interferences. HbA1c methods: effects of hemoglobin variants (HbC, HbS, HbE and HbD traits) and elevated fetal hemoglobin (HbF). 2022. Accessed 14 Aug 2024. Available from https://ngsp.org/interf.asp
7. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2023;46:e151–e199
8. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. Ann Intern Med 2017;167:95–102
9. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457
10. Saaddine JB, Fagot-Campagna A, Rolka D, et al. Distribution of HbA(1c) levels for children and young adults in the U.S.: Third National Health and Nutrition Examination Survey. Diabetes Care 2002;25:1326–1330
11. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 2011;154:303–309
12. Wheeler E, Leong A, Liu C-T, et al.; EPIC-CVD Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. PLoS Med 2017;14:e1002383
13. Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr Diab Rep 2014;14:548
14. Rooney MR, Daya N, Tang O, et al. Glycated albumin and risk of mortality in the US adult population. Clin Chem 2022;68:422–430
15. Selvin E, Rawlings AM, Lutsey PL, et al. Fructosamine and glycated albumin and the risk of cardiovascular outcomes and death. Circulation 2015;132:269–277
16. Selvin E, Rawlings AM, Grams M, et al. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol 2014;2:279–288
17. Nathan DM, McGee P, Steffes MW, Lachin JM; DCCT/EDIC Research Group. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. Diabetes 2014;63:282–290
18. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478
19. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. Diabetes Care 2014;37:1048–1051
20. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625
21. Valenzano M, Cibrario Bertolotti I, Valenzano A, Grassi G. Time in range-A1c hemoglobin relationship in continuous glucose monitoring of type 1 diabetes: a real-world study. BMJ Open Diabetes Res Care 2021;9
22. Fabris C, Heinemann L, Beck R, Cobelli C, Kovatchev B. Estimation of hemoglobin A1c from continuous glucose monitoring data in individuals with type 1 diabetes: is time in range all we need? Diabetes Technol Ther 2020;22:501–508
23. Ranjan AG, Rosenlund SV, Hansen TW, Rossing P, Andersen S, Nørgaard K. improved time in range over 1 year is associated with reduced albuminuria in individuals with sensor-augmented insulin pump-treated type 1 diabetes. Diabetes Care 2020;43:2882–2885
24. Beck RW, Bergenstal RM, Cheng P, et al. the relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol 2019;13:614–626
25. Šoupal J, Petruželková L, Grunberger G, et al. Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR STUDY. Diabetes Care 2020;43:37–43
26. Advani A. Positioning time in range in diabetes management. Diabetologia 2020;63:242–252
27. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21:81–85
28. Avari P, Uduku C, George D, Herrero P, Reddy M, Oliver N. Differences for percentage times in glycemic range between continuous glucose monitoring and capillary blood glucose monitoring in adults with type 1 diabetes: analysis of the REPLACE-BG dataset. Diabetes Technol Ther 2020;22:222–227
29. Kröger J, Reichel A, Siegmund T, Ziegler R. Clinical recommendations for the use of the ambulatory glucose profile in diabetes care. J Diabetes Sci Technol 2020;14:586–594
30. Livingstone R, Boyle JG, Petrie JR. How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes? Diabet Med 2020;37:513–521
31. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603
32. Tchero H, Kangambega P, Briatte C, Brunet-Houdard S, Retali G-R, Rusch E. Clinical effectiveness of telemedicine in diabetes mellitus: a meta-analysis of 42 randomized controlled trials. Telemed J E Health 2019;25:569–583

33. Salabelle C, Ly Sall K, Eroukhmanoff J, et al. COVID-19 pandemic lockdown in young people with type 1 diabetes: positive results of an unprecedented challenge for patients through telemedicine and change in use of continuous glucose monitoring. Prim Care Diabetes 2021; 15:884–886
34. Prabhu Navis J, Leelarathna L, Mubita W, et al. Impact of COVID-19 lockdown on flash and real-time glucose sensor users with type 1 diabetes in England. Acta Diabetol 2021;58: 231–237
35. Weinstock RS, DuBose SN, Bergenstal RM, et al.; T1D Exchange Severe Hypoglycemia in Older Adults With Type 1 Diabetes Study Group. Risk factors associated with severe hypoglycemia in older adults with type 1 diabetes. Diabetes Care 2016;39:603–610
36. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35: 787–793
37. Cariou B, Fontaine P, Eschwege E, et al. Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the DIALOG study. Diabetes Metab 2015;41:116–125
38. Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. Diabetes Care 2009;32: 1513–1517
39. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
40. Whitehead L, Glass C, Coppell K. The effectiveness of goal setting on glycaemic control for people with type 2 diabetes and prediabetes: a systematic review and meta-analysis. J Adv Nurs 2022;78:1212–1227
41. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
42. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389
43. Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, Nathan DM; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631–642
44. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117
45. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
46. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
47. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
48. Lind M, Pivodic A, Svensson A-M, Ólafsdóttir AF, Wedel H, Ludvigsson J. $HbA_{1c}$ level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. BMJ 2019;366:l4894
49. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412–419
50. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
51. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358: 2560–2572
52. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
53. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
54. Agrawal L, Azad N, Bahn GD, et al.; VADT Study Group. Intensive glycemic control improves long-term renal outcomes in type 2 diabetes in the Veterans Affairs Diabetes Trial (VADT). Diabetes Care 2019;42:e181–e182
55. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376: 1407–1418
56. Skyler JS, Bergenstal R, Bonow RO, et al.; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192
57. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298
58. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care 2016;39: 686–693
59. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). Arch Intern Med 2009; 169:1307–1316
60. Hayward RA, Reaven PD, Wiitala WL, et al.; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372:2197–2206
61. Di Angelantonio E, Kaptoge S, Wormser D, et al.; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality. JAMA 2015;314:52–60
62. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
63. ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39: 701–708
64. Buse JB, Bain SC, Mann JFE, et al.; LEADER Trial Investigators. Cardiovascular risk reduction with liraglutide: an exploratory mediation analysis of the LEADER trial. Diabetes Care 2020;43:1546–1552
65. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. Diabetes Care 2018;41: 104–111
66. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
67. Zoungas S, Woodward M, Li Q, et al.; ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia 2014;57:2465–2474
68. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of Insulin Regimen in Older Adults and Risk of Hypoglycemia. JAMA Intern Med 2016;176:1023–1025
69. Pratley RE, Rosenstock J, Heller SR, et al. Reduced glucose variability with glucose-dependent versus glucose-independent therapies despite similar glucose control and hypoglycemia rates in a randomized, controlled study of older patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2018;12:1184–1191
70. Heller SR, Pratley RE, Sinclair A, et al. Glycaemic outcomes of an individualized treatment approach for older vulnerable patients: a randomized, controlled study in type 2 diabetes mellitus (IMPERIUM). Diabetes Obes Metab 2018; 20:148–156
71. Pilla SJ, Meza KA, Schoenborn NL, Boyd CM, Maruthur NM, Chander G. A qualitative study of

perspectives of older adults on deintensifying diabetes medications. J Gen Intern Med 2023; 38:1008–1015
72. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond $HbA_{1c}$ for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40: 1622–1630
73. Hepburn DA, Deary IJ, MacLeod KM, Frier BM. Structural equation modeling of symptoms, awareness and fear of hypoglycemia, and personality in patients with insulin-treated diabetes. Diabetes Care 1994;17:1273–1280
74. Polonsky WH, Fortmann AL, Price D, Fisher L. "Hyperglycemia aversiveness": investigating an overlooked problem among adults with type 1 diabetes. J Diabetes Complications 2021;35: 107925
75. Amiel SA, Potts L, Goldsmith K, et al. A parallel randomised controlled trial of the Hypoglycaemia Awareness Restoration Programme for adults with type 1 diabetes and problematic hypoglycaemia despite optimised self-care (HARPdoc). Nat Commun 2022;13:2229
76. Sreenan S, Andersen M, Thorsted BL, Wolden ML, Evans M. Increased risk of severe hypoglycemic events with increasing frequency of non-severe hypoglycemic events in patients with type 1 and type 2 diabetes. Diabetes Ther 2014;5:447–458
77. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. Bmj 2010;340:b4909
78. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
79. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897–1901
80. Bloomfield HE, Greer N, Newman D, et al. *Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence*. Washington, DC, Department of Veterans Affairs, 2012. Accessed 9 September 2024. Available from https://www.ncbi.nlm.nih.gov/books/NBK114893/
81. Rossi MC, Nicolucci A, Ozzello A, et al.; HYPOS-1 Study Group of AMD. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. Nutr Metab Cardiovasc Dis 2019;29: 736–743
82. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. Endocr Pract 2013;19:792–799
83. Leiter LA, Boras D, Woo VC. Dosing irregularities and self-treated hypoglycemia in type 2 diabetes: results from the Canadian cohort of an international survey of patients and healthcare professionals. Can J Diabetes 2014;38: 38–44
84. Ghandi K, Pieri B, Dornhorst A, Hussain S. A comparison of validated methods used to assess impaired awareness of hypoglycaemia in type 1 diabetes: an observational study. Diabetes Ther 2021;12:441–451
85. Khunti K, Alsifri S, Aronson R, et al.; HAT Investigator Group. Impact of hypoglycaemia on patient-reported outcomes from a global, 24-country study of 27,585 people with type 1 and insulin-treated type 2 diabetes. Diabetes Res Clin Pract 2017;130:121–129
86. Choudhary P, Amiel SA. Hypoglycaemia in type 1 diabetes: technological treatments, their limitations and the place of psychology. Diabetologia 2018;61:761–769
87. Hopkins D, Lawrence I, Mansell P, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012;35:1638–1642
88. Karter AJ, Moffet HH, Liu JY, Lipska KJ. Surveillance of hypoglycemia-limitations of emergency department and hospital utilization data. JAMA Intern Med 2018;178:987–988
89. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2017;40:1661–1667
90. Pilla SJ, Kraschnewski JL, Lehman EB, et al. Hospital utilization for hypoglycemia among patients with type 2 diabetes using pooled data from six health systems. BMJ Open Diabetes Res Care 2021;9
91. McCoy RG, Herrin J, Galindo RJ, et al. Rates of hypoglycemic and hyperglycemic emergencies among U.S. adults with diabetes, 2011-2020. Diabetes Care 2023;46:e69–e71
92. Mattishent K, Loke YK. Detection of asymptomatic drug-induced hypoglycemia using continuous glucose monitoring in older people—systematic review. J Diabetes Complications 2018; 32:805–812
93. Ratzki-Leewing A, Black JE, Kahkoska AR, et al. Severe (level 3) hypoglycaemia occurrence in a real-world cohort of adults with type 1 or 2 diabetes mellitus (iNPHORM, United States). Diabetes Obes Metab 2023;25:3736–3747
94. Au NH, Ratzki-Leewing A, Zou G, et al. Real-world incidence and risk factors for daytime and nocturnal non-severe hypoglycemia in adults with type 2 diabetes mellitus on insulin and/or secretagogues (InHypo-DM Study, Canada). Can J Diabetes 2022;46:196–203 e192
95. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors, and prevention strategies. Curr Diab Rep 2018;18:53
96. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Association of cumulative multimorbidity, glycemic control, and medication use with hypoglycemia-related emergency department visits and hospitalizations among adults with diabetes. JAMA Netw Open 2020;3:e1919099
97. Yun J-S, Ko S-H, Ko S-H, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care 2013;36:1283–1289
98. Galindo RJ, Ali MK, Funni SA, et al. Hypoglycemic and hyperglycemic crises among U.S. adults with diabetes and end-stage kidney disease: population-based study, 2013-2017. Diabetes Care 2022;45:100–107
99. Kurani SS, Heien HC, Sangaralingham LR, et al. Association of area-level socioeconomic deprivation with hypoglycemic and hyperglycemic crises in US adults with diabetes. JAMA Netw Open 2022;5: e2143597
100. Jiang DH, Herrin J, Van Houten HK, McCoy RG. Evaluation of high-deductible health plans and acute glycemic complications among adults with diabetes. JAMA Netw Open 2023;6:e2250602
101. Scheuer SH, Andersen GS, Carstensen B, et al. Trends in incidence of hospitalization for hypoglycemia and diabetic ketoacidosis in individuals with type 1 or type 2 diabetes with and without severe mental illness in Denmark from 1996 to 2020: a nationwide study. Diabetes Care 2024;47:1065–1073
102. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA Intern Med 2017;177:1461–1470
103. Karter AJ, Warton EM, Moffet HH, et al. Revalidation of the hypoglycemia risk stratification tool using ICD-10 codes. Diabetes Care 2019;42: e58–e59
104. Chow LS, Zmora R, Ma S, Seaquist ER, Schreiner PJ. Development of a model to predict 5-year risk of severe hypoglycemia in patients with type 2 diabetes. BMJ Open Diabetes Res Care 2018;6:e000527
105. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med 2001;161:1653–1659
106. Davis TME, Brown SGA, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. J Clin Endocrinol Metab 2010;95:2240–2247
107. Quilliam BJ, Simeone JC, Ozbay AB. Risk factors for hypoglycemia-related hospitalization in patients with type 2 diabetes: a nested case-control study. Clin Ther 2011;33:1781–1791
108. Pilla SJ, Park J, Schwartz JL, et al. Hypoglycemia communication in primary care visits for patients with diabetes. J Gen Intern Med 2021;36:1533–1542
109. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013; 36:1384–1395
110. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. Patient Educ Couns 2007;68:10–15
111. Schopman JE, Geddes J, Frier BM. Prevalence of impaired awareness of hypoglycaemia and frequency of hypoglycaemia in insulin-treated type 2 diabetes. Diabetes Res Clin Pract 2010; 87:64–68
112. Pedersen-Bjergaard U, Færch L, Thorsteinsson B. The updated Pedersen-Bjergaard method for

assessment of awareness of hypoglycaemia in type 1 diabetes. Dan Med J 2022;69
113. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697–703
114. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995; 18:517–522
115. Speight J, Barendse SM, Singh H, et al. Characterizing problematic hypoglycaemia: iterative design and preliminary psychometric validation of the Hypoglycaemia Awareness Questionnaire (HypoA-Q). Diabet Med 2016;33:376–385
116. Høi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. Classification of hypoglycemia awareness in people with type 1 diabetes in clinical practice. J Diabetes Complications 2010; 24:392–397
117. Henao-Carrillo DC, Sierra-Matamoros FA, Carrillo Algarra AJ, García-Lugo JP, Hernández-Zambrano SM. Validation of the hypoglycemia awareness questionnaire to assess hypoglycemia awareness in patients with type 2 diabetes treated with insulin. Diabetes Metab Syndr 2023;17:102917
118. Jacobson AM, Ryan CM, Braffett BH, et al.; DCCT/EDIC Research Group. Cognitive performance declines in older adults with type 1 diabetes: results from 32 years of follow-up in the DCCT and EDIC Study. Lancet Diabetes Endocrinol 2021;9: 436–445
119. Basu S, Berkowitz SA, Seligman H. The monthly cycle of hypoglycemia: an observational claims-based study of emergency room visits, hospital admissions, and costs in a commercially insured population. Med Care 2017;55:639–645
120. Sharan R, Wiens K, Ronksley PE, et al. The association of homelessness with rates of diabetes complications: a population-based cohort study. Diabetes Care 2023;46:1469–1476
121. Ibrahim M, Davies MJ, Ahmad E, et al. Recommendations for management of diabetes during Ramadan: update 2020, applying the principles of the ADA/EASD consensus. BMJ Open Diabetes Res Care 2020;8
122. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572
123. DuBose SN, Weinstock RS, Beck RW, et al. Hypoglycemia in older adults with type 1 diabetes. Diabetes Technol Ther 2016;18:765–771
124. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
125. Hering BJ, Clarke WR, Bridges ND, et al.; Clinical Islet Transplantation Consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care 2016;39:1230–1240
126. Boggi U, Baronti W, Amorese G, et al. Treating type 1 diabetes by pancreas transplant alone: a cohort study on actual long-term (10 years) efficacy and safety. Transplantation 2022;106: 147–157
127. McTavish L, Corley B, Weatherall M, Wiltshire E, Krebs JD. Weight-based carbohydrate treatment of hypoglycaemia in people with type 1 diabetes using insulin pump therapy: a randomized crossover clinical trial. Diabet Med 2018;35:339–346
128. McTavish L, Wiltshire E. Effective treatment of hypoglycemia in children with type 1 diabetes: a randomized controlled clinical trial. Pediatr Diabetes 2011;12:381–387
129. Georgakopoulos K, Katsilambros N, Fragaki M, et al. Recovery from insulin-induced hypoglycemia after saccharose or glucose administration. Clin Physiol Biochem 1990;8:267–272
130. Phillip M, Nimri R, Bergenstal RM, et al. Consensus recommendations for the use of automated insulin delivery technologies in clinical practice. Endocr Rev 2023;44:254–280
131. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. Am J Clin Nutr 2008;87:1571s–1575s
132. Kahn PA, Liu S, McCoy R, Gabbay RA, Lipska K. Glucagon use by U.S. adults with type 1 and type 2 diabetes. J Diabetes Complications 2021; 35:107882
133. Herges JR, Galindo RJ, Neumiller JJ, Heien HC, Umpierrez GE, McCoy RG. Glucagon prescribing and costs among u.s. adults with diabetes, 2011-2021. Diabetes Care 2023;46:620–627
134. Benning TJ, Heien HC, Herges JR, Creo AL, Al Nofal A, McCoy RG. Glucagon fill rates and cost among children and adolescents with type 1 diabetes in the United States, 2011-2021. Diabetes Res Clin Pract 2023;206:111026
135. Matsuhisa M, Takita Y, Nasu R, Nagai Y, Ohwaki K, Nagashima H. Nasal glucagon as a viable alternative for treating insulin-induced hypoglycaemia in Japanese patients with type 1 or type 2 diabetes: a phase 3 randomized crossover study. Diabetes Obes Metab 2020;22:1167–1175
136. Suico JG, Hövelmann U, Zhang S, et al. Glucagon administration by nasal and intramuscular routes in adults with type 1 diabetes during insulin-induced hypoglycaemia: a randomised, open-label, crossover study. Diabetes Ther 2020;11:1591–1603
137. Pieber TR, Aronson R, Christiansen MP, Bode B, Junaidi K, Conoscenti V. Efficacy, safety, tolerability, and noninferiority phase 3 study of glucagon as a ready-to-use room temperature liquid stable formulation versus a lyophilised formulation for the biochemical recovery and symptomatic relief of insulin-induced severe hypoglycaemia in adults with type 1 diabetes. Diabetes Obes Metab 2022;24:1394–1397
138. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. Diabetes Care 2020;43:1636–1649
139. LaManna J, Litchman ML, Dickinson JK, et al. Diabetes education impact on hypoglycemia outcomes: a systematic review of evidence and gaps in the literature. Diabetes Educ 2019;45: 349–369
140. Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. Use of Medicare's diabetes self-management training benefit. Health Educ Behav 2015;42:530–538
141. Rutledge SA, Masalovich S, Blacher RJ, Saunders MM. Diabetes self-management education programs in nonmetropolitan counties - United States, 2016. MMWR Surveill Summ 2017;66:1–6
142. Hermanns N, Heinemann L, Freckmann G, Waldenmaier D, Ehrmann D. Impact of CGM on the management of hypoglycemia problems: overview and secondary analysis of the HypoDE study. J Diabetes Sci Technol 2019;13:636–644
143. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367–1377
144. Yeoh E, Choudhary P, Nwokolo M, Ayis S, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. Diabetes Care 2015;38:1592–1609
145. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes Care 2001;24:637–642
146. Little SA, Speight J, Leelarathna L, et al. Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: two-year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Care 2018;41:1600–1607
147. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004;350:2272–2279
148. Parekh TM, Raji M, Lin Y-L, Tan A, Kuo Y-F, Goodwin JS. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. JAMA Intern Med 2014;174:1605–1612
149. Lee S, Ock M, Kim H-S, Kim H. Effects of co-administration of sulfonylureas and antimicrobial drugs on hypoglycemia in patients with type 2 diabetes using a case-crossover design. Pharmacotherapy 2020;40:902–912
150. Pilla SJ, Pitts SI, Maruthur NM. High concurrent use of sulfonylureas and antimicrobials with drug interactions causing hypoglycemia. J Patient Saf 2022;18:e217–e224
151. Umpierrez GE, Davis GM, ElSayed NA, et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024;47:1257–1275
152. Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health care utilization and burden of diabetic ketoacidosis in the U.S. over the past decade: a nationwide analysis. Diabetes Care 2018;41:1631–1638
153. Long B, Lentz S, Koyfman A, Gottlieb M. Euglycemic diabetic ketoacidosis: etiologies, evaluation, and management. Am J Emerg Med 2021;44:157–160
154. Pasquel FJ, Tsegka K, Wang H, et al. Clinical outcomes in patients with isolated or combined diabetic ketoacidosis and hyperosmolar hyperglycemic state: a retrospective, hospital-based cohort study. Diabetes Care 2020;43:349–357
155. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998-2013: a retrospective cohort study. Diabetes Care 2018;41:1870–1877
156. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in diabetic ketoacidosis

hospitalizations and in-hospital mortality - United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2018;67:362–365
157. Benoit SR, Hora I, Pasquel FJ, Gregg EW, Albright AL, Imperatore G. Trends in Emergency Department Visits and Inpatient Admissions for Hyperglycemic Crises in Adults With Diabetes in the U.S., 2006-2015. Diabetes Care 2020;43:1057–1064
158. Desai R, Singh S, Syed MH, et al. Temporal trends in the prevalence of diabetes decompensation (diabetic ketoacidosis and hyperosmolar hyperglycemic state) among adult patients hospitalized with diabetes mellitus: a nationwide analysis stratified by age, gender, and race. Cureus 2019;11:e4353
159. O'Reilly JE, Jeyam A, Caparrotta TM, et al.; Scottish Diabetes Research Network Epidemiology Group. Rising rates and widening socioeconomic disparities in diabetic ketoacidosis in type 1 diabetes in Scotland: A nationwide retrospective cohort observational study. Diabetes Care 2021;44:2010–2017
160. Fazeli Farsani S, Brodovicz K, Soleymanlou N, Marquard J, Wissinger E, Maiese BA. Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. BMJ Open 2017;7:e016587
161. Everett EM, Copeland TP, Moin T, Wisk LE. National trends in pediatric admissions for diabetic ketoacidosis, 2006-2016. J Clin Endocrinol Metab 2021;106:2343–2354
162. McCoy RG, Herrin J, Galindo RJ, et al. All-cause mortality after hypoglycemic and hyperglycemic emergencies among U.S. adults with diabetes, 2011-2020. Diabetes Res Clin Pract 2023;197:110263
163. EL-Mohandes N, Yee G, Bhutta BS, Huecker MR. Pediatric diabetic ketoacidosis. In *StatPearls*. StatPearls Publishing, 2024
164. Shaka H, Wani F, El-Amir Z, et al. Comparing patient characteristics and outcomes in type 1 versus type 2 diabetes with diabetic ketoacidosis: a review and a propensity-matched nationwide analysis. J Investig Med 2021;69:1196–1200
165. Shaka H, El-Amir Z, Wani F, et al. Hospitalizations and inpatient mortality for hyperosmolar hyperglycemic state over a decade. Diabetes Res Clin Pract 2022;185:109230
166. Shand JAD, Morrow P, Braatvedt G. Mortality after discharge from hospital following an episode of diabetic ketoacidosis. Acta Diabetol 2022;59:1485–1492
167. Colacci M, Fralick J, Odutayo A, Fralick M. Sodium-glucose cotransporter-2 inhibitors and risk of diabetic ketoacidosis among adults with type 2 diabetes: a systematic review and meta-analysis. Can J Diabetes 2022;46:10–15.e12
168. Bamgboye AO, Oni IO, Collier A. Predisposing factors for the development of diabetic ketoacidosis with lower than anticipated glucose levels in type 2 diabetes patients on SGLT2-inhibitors: a review. Eur J Clin Pharmacol 2021;77:651–657
169. Wu X-Y, She D-M, Wang F, et al. Clinical profiles, outcomes and risk factors among type 2 diabetic inpatients with diabetic ketoacidosis and hyperglycemic hyperosmolar state: a hospital-based analysis over a 6-year period. BMC Endocr Disord 2020;20:182
170. Dhanasekaran M, Mohan S, Erickson D, et al. Diabetic ketoacidosis in pregnancy: clinical risk factors, presentation, and outcomes. J Clin Endocrinol Metab 2022;107:3137–3143
171. Be prepared: sick day management. Diabetes Spectrum 2002;15:54–54
172. Watson KE, Dhaliwal K, McMurtry E, et al. Sick day medication guidance for people with diabetes, kidney disease, or cardiovascular disease: a systematic scoping review. Kidney Med 2022;4:100491
173. American Diabetes Association. Getting sick: planning for sick days. Accessed 6 July 2024. Available from https://diabetes.org/getting-sick-with-diabetes/sick-days
174. Farrell K, Brunero S, Holmes-Walker DJ, Griffiths R, Salamonson Y. Self-management of sick days in young people with type 1 diabetes enhanced by phone support: a qualitative study. Contemp Nurse 2019;55:171–184
175. Mays JA, Jackson KL, Derby TA, et al. An evaluation of recurrent diabetic ketoacidosis, fragmentation of care, and mortality across Chicago, Illinois. Diabetes Care 2016;39:1671–1676
176. McCoy RG, Herrin J, Lipska KJ, Shah ND. Recurrent hospitalizations for severe hypoglycemia and hyperglycemia among U.S. adults with diabetes. J Diabetes Complications 2018;32:693–701
177. Ehrmann D, Kulzer B, Roos T, Haak T, Al-Khatib M, Hermanns N. Risk factors and prevention strategies for diabetic ketoacidosis in people with established type 1 diabetes. Lancet Diabetes Endocrinol 2020;8:436–446
178. Elliott J, Jacques RM, Kruger J, et al. Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with type 1 diabetes. Diabet Med 2014;31:847–853
179. Riveline J-P, Roussel R, Vicaut E, et al. Reduced rate of acute diabetes events with flash glucose monitoring is sustained for 2 years after initiation: extended outcomes from the RELIEF study. Diabetes Technol Ther 2022;24:611–618
180. Misra-Hebert AD, Pantalone KM, Ji X, et al. Patient characteristics associated with severe hypoglycemia in a type 2 diabetes cohort in a large, integrated health care system from 2006 to 2015. Diabetes Care 2018;41:1164–1171
181. Merative. Micromedex RED BOOK (electronic version). Ann Arbor, Michigan, Merative. Accessed 22 August 2024. Available from https://www.merative.com/clinical-decision-support
182. HealthData.gov. NADAC (National Average Drug Acquisition Cost) 2024. Accessed 1 July 2024. Available from https://healthdata.gov/dataset/NADAC-National-Average-Drug-Acquisition-Cost-2024/3tha-57c6/about_data
183. Data.Medicaid.gov. NADAC (National Average Drug Acquisition Cost) 2023. Accessed 22 August 2024. Available from https://data.medicaid.gov/dataset/4a00010a-132b-4e4d-a611-543c9521280f
184. McCoy RG, Galindo RJ, Swarna KS, et al. Sociodemographic, clinical, and treatment-related factors associated with hyperglycemic crises among adults with type 1 or type 2 diabetes in the US From 2014 to 2020. JAMA Netw Open 2021;4:e2123471
185. Gibb FW, Teoh WL, Graham J, Lockman KA. Risk of death following admission to a UK hospital with diabetic ketoacidosis. Diabetologia 2016;59:2082–2087
186. Randall L, Begovic J, Hudson M, et al. Recurrent mental ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. Diabetes Care 2011;34:1891–1896
187. Thomas M, Harjutsalo V, Feodoroff M, Forsblom C, Gordin D, Groop P-H. The long-term incidence of hospitalization for ketoacidosis in adults with established T1D—a prospective cohort study. J Clin Endocrinol Metab 2020;105:dgz003