6. Glycemic Goals and Hypoglycemia: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S111–S125 | https://doi.org/10.2337/dc24-S006

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

ASSESSMENT OF GLYCEMIC STATUS

Glycemic status is assessed by A1C measurement, blood glucose monitoring (BGM) by capillary (finger-stick) devices, and continuous glucose monitoring (CGM) using time in range (TIR) or mean CGM glucose. Clinical trials of interventions that lower A1C have demonstrated the benefits of improved glycemia. Glucose monitoring via CGM or BGM (discussed in detail in Section 7, "Diabetes Technology") is useful for diabetes self-management, can provide nuanced information on glucose responses to meals, physical activity, and medication changes, and may be particularly useful in individuals taking insulin. CGM serves an increasingly important role in optimizing the effectiveness and safety of treatment in many people with type 1 diabetes and in selected people with 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 and/or appropriate continuous glucose monitoring (CGM) metrics at least two times a year. Assess more frequently (e.g., every 3 months) for individuals not meeting treatment goals, with frequent or severe hypoglycemia or hyperglycemia, changing health status, or growth and development in youth. **E**

6.2 Assess glycemic status at least quarterly and as needed in individuals whose therapy has recently changed and/or who are not meeting glycemic goals. **E**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

Suggested citation: American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: Standards of Care in Diabetes—2024. *Diabetes Care 2024;47(Suppl. 1):S111–S125*

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 diabetes or type 2 diabetes with stable glycemia within goal may do well with A1C testing or other glucose assessment only twice per year. Unstable or intensively managed individuals or people not at goal with treatment adjustments may require testing more frequently (every 3 months, with interim assessments as needed) (5). The use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters between individuals with diabetes and health care professionals.

The A1C test is an indirect measure of average glycemia. Factors that affect hemoglobin or red blood cell characteristics or turnover 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 (6). 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 (7). A1C cannot be measured in individuals with sickle cell disease (HbSS) or other homozygous hemoglobin variants (e.g., HbEE), since these individuals lack HbA (8). 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 severe insulin deficiency, glycemic status is best evaluated by the combination of results from BGM or CGM and A1C. Discordant results between BGM/CGM and A1C can be the result of the conditions outlined above or glycemic variability, with BGM/CGM missing the extremes.

As discussed in Section 2, "Diagnosis and Classification of Diabetes," there is controversy regarding the clinical significance of racial differences in A1C (9–12). There is an emerging understanding of genetic determinants that may modify the association between A1C and glucose levels (13). However, race is not a good proxy for these genetic differences that are likely present in a small minority of individuals of all racial groups. Therefore, race should not be a consideration 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 (14–18). 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 (8).

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 (19,20). 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.

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 control on diabetes

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 (19,20). Adapted from Nathan et al. (19).

complications (21). 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

Recommendations

6.3 Standardized, single-page glucose reports from CGM devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**

6.4 Time in range (TIR) is associated with the risk of microvascular complications and can be used for assessment of glycemic status. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (**Table 6.2**). **C**

CGM is particularly useful in people with diabetes who are at risk for hypoglycemia and is commonly used in people with type 1 diabetes (21). 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 (22–26). TIR, especially mean CGM glucose, correlates with A1C (27–31). 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 standardized CGM metrics (**Table 6.2**) and their clinical interpretation (32). To make these metrics actionable, standardized reports with visual summaries, such as the ambulatory glucose profile (**Fig. 6.1**), are recommended (32) and can help individuals with diabetes and health care professionals interpret the data to guide treatment decisions (27,30). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, 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 (33–35).

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 can be generated from CGM that will allow the health care professional and person with diabetes to view TIR, 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 (32). 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% (25,28). Note the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) as values to guide changes in therapy.

GLYCEMIC GOALS

Recommendations

6.5a An A1C goal for many nonpregnant adults of <7% (<53 mmol/mol)

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

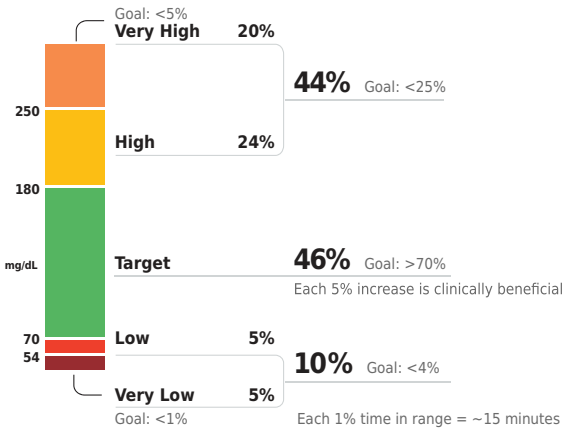
Metric	Interpretation	Goals
1. Number of days CGM device is worn		14-day wear for pattern management
2. Percentage of time CGM device is active		70% of data from 14 days
3. Mean glucose	Simple average of glucose values	*
4. Glucose management indicator	Calculated value approximating A1C (not always equivalent)	*
5. Glycemic variability (%CV) target	Spread of glucose values	≤36%†
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia	<5% (most adults); <10% (older adults)
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia	<25% (most adults); <50% (older adults)‡
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range	>70% (most adults); >50% (older adults)
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia	<4% (most adults); <1% (older adults)§
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Goals for these values are not standardized. †Some studies suggest that lower %CV 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. (32).

AGP Report: Continuous Glucose Monitoring

Time in Ranges

Goals for Type 1 and Type 2 Diabetes



Test Patient DOB: Jan 1, 1970

14 Days: August 8–August 21, 2021

Time CGM Active: 100%

Glucose Metrics

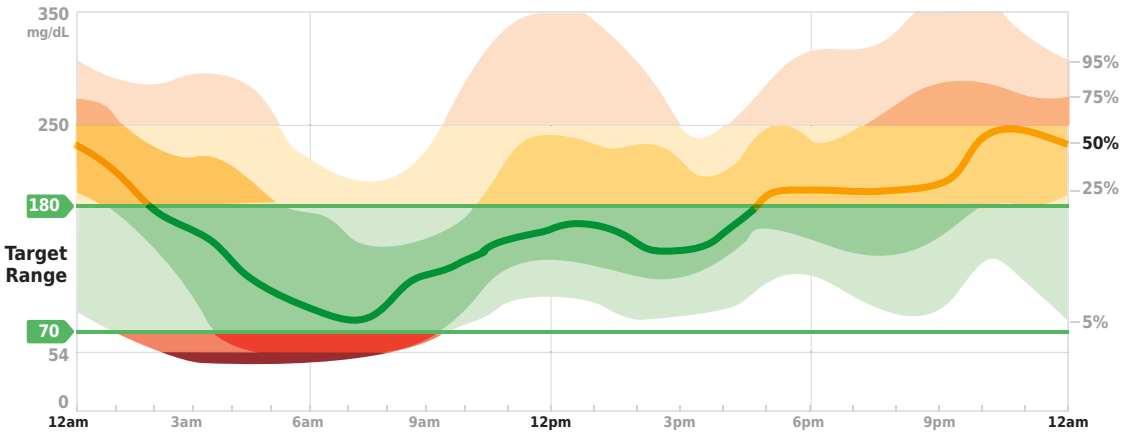
Average Glucose ..... **175 mg/dL**
Goal: <154 mg/dL

Glucose Management Indicator (GMI) **7.5%**
Goal: <7%

Glucose Variability **45.5%**
Defined as percent coefficient of variation
Goal: ≤36%

Ambulatory Glucose Profile (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if they occurred in a single day.



Daily Glucose Profiles

Each daily profile represents a midnight-to-midnight period.

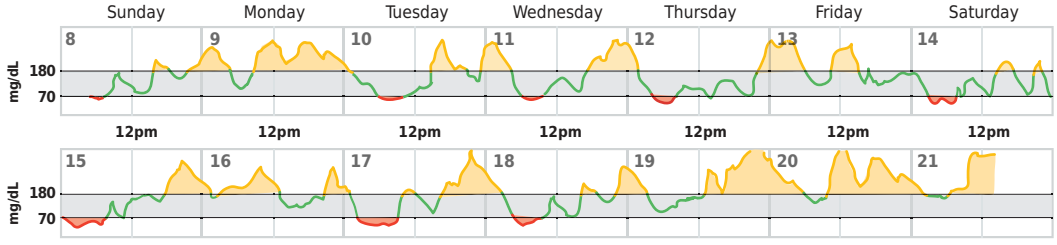


Figure 6.1—Key points included in a standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (21).

without significant hypoglycemia is appropriate. **A**

6.5b If using an ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is TIR >70% with time below range <4% and time <54 mg/dL (<3 mmol/L) <1%. For those with frailty or at high risk of hypoglycemia, a goal of >50% TIR with <1% time below range is recommended (**Fig. 6.1** and **Table 6.2**). **B**

6.6 On the basis of 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 significant hypoglycemia or other adverse effects of treatment. **B**

6.7 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**

6.8a 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**

6.8b 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**

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

6.10 Setting a glycemic goal during consultations is likely to improve patient outcomes. **E**

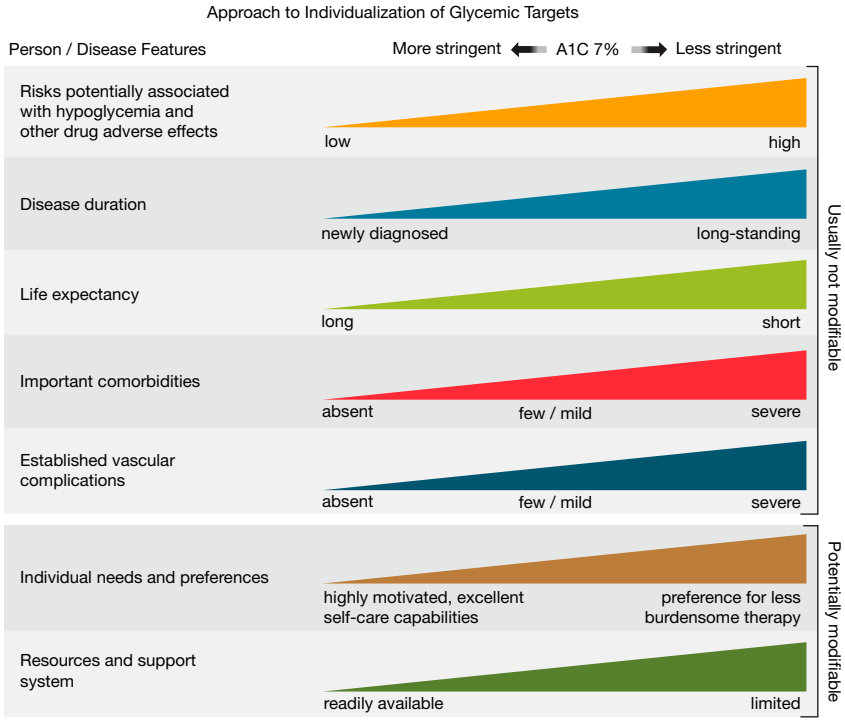


Figure 6.2—Person and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (36).

For all populations, it is critical that the glycemic goals be woven into the overall person-centered strategy (**Fig. 6.2**) (36). For example, less stringent A1C goals are appropriate for individuals with limited life expectancy and/or significant functional and cognitive impairments. In a very young child, safety and simplicity may outweigh the need for glycemic stability in the short run. Recommended glycemic goals for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with an A1C of <7% (<53 mmol/mol). For 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."

The health care professional needs to work 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 is likely to improve outcomes for individuals with diabetes (37).

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, these cells, when exposed 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.

Table 6.3—Summary of glycemic recommendations 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 individuals. †CGM may be used to assess glycemic status as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (per **Fig. 6.2**). ‡Postprandial glucose may be targeted 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, generally peak levels in people with diabetes.

The Diabetes Control and Complications Trial (DCCT) (38), a prospective randomized controlled trial of intensive (mean A1C ~7% [53 mmol/mol]) versus standard (mean A1C ~9% [75 mmol/mol]) glycemic control 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 (39,40) demonstrated persistence of these microvascular benefits over two decades even though the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (41) and UK Prospective Diabetes Study (UKPDS) (42,43) 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 the Kumamoto Study 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 (44). 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 (2,45). The DCCT (38) and UKPDS (46) studies demonstrated a curvilinear relationship between A1C 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 glycemic 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 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, which have been shown to improve glucose levels without increasing hypoglycemia.

Among individuals with type 2 diabetes, three landmark trials (Action to Control 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 control; ACCORD was stopped after a median of 3.5 years due to higher mortality in the intervention arm (47–51). Importantly, these landmark studies were conducted prior to the approval of glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, and intensive glycemic control 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 (52).

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 control reduced CVD events (38,47, 48,50). 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" (53).

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 ACCORD included the rapid escalation of therapies, the early use of large doses of insulin, massive 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, 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 control (54).

Longer-term epidemiological follow-up has been performed in these studies, and a clear pattern of CVD benefit has emerged (55–57). 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 (55). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (56) and to be associated with a modest reduction in all-cause mortality (58).

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 (44). 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 (57). 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 (59). 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 control, so that there was no difference in total mortality after a total of 9 years of follow-up and the increase in CVD deaths was obtunded (60). Collectively, the results of these studies confirm that long-term intensive glycemic control 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 receptor agonists and SGLT2 inhibitors were not yet in clinical use. These agents with established cardiovascular and renal benefits appear to be safe and beneficial in this group of individuals at high risk for cardiorenal 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 renal benefit (61). 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 (62). 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 targets cannot be safely and reasonably achieved. As discussed in Section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of specific SGLT2 inhibitors or GLP-1 receptor agonists 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 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (63):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or a GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists 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 (53,64).

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 patient 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 (36) 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 control, 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 receptor agonists 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 (65–68). 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 (69).

HYPOGLYCEMIA ASSESSMENT, PREVENTION, AND TREATMENT

Recommendations

6.11a History of hypoglycemia should be reviewed at every clinical encounter for all individuals at risk for hypoglycemia and evaluated as indicated. **C**

6.11b Clinicians should screen all individuals at risk for hypoglycemia for impaired hypoglycemia awareness. **E**

6.11c Clinicians should consider an individual's risk for hypoglycemia (see **Table 6.5**) when selecting diabetes medications and glycemic goals. **E**

6.11d Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia. **A**

6.12 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. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists. **B**

6.13 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. 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. **E**

6.14 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.

6.15 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**

6.16 Refer individuals with impaired hypoglycemia awareness to a trained health care professional to receive evidence-based intervention to help reestablish awareness of symptoms of hypoglycemia. **A**

6.17 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found. **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** (70). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (<3.9 mmol/L) but ≥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 neuroendocrine responses to falling glucose in people without diabetes. Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, sweating, and hunger (71). 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 hypoglycemia awareness (discussed further in HYPOGLYCENIMIA RISK ASSESSMENT, below). This clinical scenario warrants investigation and review of the treatment plan (72,73). 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 (74). 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 (75). An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial and in clinical practice (76,77). Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury (78). 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 (79–81). 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

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

Reprinted from Agiostratidou et al. (70).

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

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

Major risk factors are those that have a consistent, independent association with a high risk for level 2 or 3 hypoglycemia. Other risk factors are those with less consistent evidence or a weaker association. These risk factors are identified through observational analyses and are intended to be used for hypoglycemia risk stratification. Individuals considered at high risk for hypoglycemia are those with ≥1 major risk factor or who have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (87,88,92,94–97,113,146). 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 also 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 control 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 being underinsured or living in a socioeconomically deprived area.

self-management education and support, and use of technology to assist with hypoglycemia prevention and identification (73,82–85).

Studies of rates of hypoglycemia predominantly rely on claims data for hospitalizations and emergency department visits (86–89). 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 (86,90). Nevertheless, they reveal a substantial burden of hypoglycemia-related hospital utilization in the community (86–89). Level 1 and level 2 hypoglycemia can be ascertained from patient self-report (91) 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 6.11–6.17 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 (92,93). Individuals at high risk for hypoglycemia are the subset of individuals at risk for hypoglycemia who either have a major hypoglycemia 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 (87,88,92,94–97). Validated tools have been developed to estimate hypoglycemia risk using predominantly electronic health record data (98–100). 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 and severity (96,101–103). 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 (104), 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 (105). 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 (106). Impaired hypoglycemia awareness dramatically increases the risk for level 3 hypoglycemia (107). The Clark and Gold scores are validated questionnaires to assess impaired hypoglycemia awareness (108,109). However, these questionnaires may be impractical for routine clinical use. A recommended strategy is to screen for impaired hypoglycemia awareness by asking individuals whether they ever have low blood glucose without feeling symptoms, or by asking at what blood glucose levels they typically begin to feel symptoms (and what those symptoms

are), and follow up positive responses with a more detailed evaluation (105,110).

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 (92,93). 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 (92). 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 (111). 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 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 (112). In general, individuals with low annual household incomes (93), individuals who live in socioeconomically deprived areas (96), and individuals who are underinsured (97) or homeless (113) 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"), 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 (114).

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (115,116), 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, patient 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 (105). CGM with automated low-glucose suspend and automated insulin delivery systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (117). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental (118,119).

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 (120–122). 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 are recommended to ingest 5–10 g carbohydrates (except for hypoglycemia with exercise or with significant overestimation of carbohydrate/meal bolus) (123). The acute glycemic response to food correlates better with the glucose content than with the total carbohydrate content. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may slow and then prolong the acute glycemic response. Carbohydrate sources high in protein may increase insulin secretion and should not be used to treat hypoglycemia (124). 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 (125,126). 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 (127–130). Although physical and chemical stability of glucagon is improved with newer formulations, care should be taken to replace glucagon products when they reach their expiration date and 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 patient education for hypoglycemia prevention and treatment is critical and has been shown to improve hypoglycemia outcomes (131,132). Education should ideally be provided through a diabetes self-management education and support program or by a trained diabetes educator, although these services are not available in many areas (133,134). 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 (131).

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

Product	Form(s)	Median AWP* (min, max)	Median NADAC* (min, max)	Dosage(s)
Glucagon	Injection powder with diluent for reconstitution	$266 ($194, $369)	$249 ($225, $273)	1 mg
Glucagon	Nasal powder	$337	$270	3 mg
Glucagon	Prefilled pen, prefilled syringe	$368	$285	0.5 mg, 1 mg
Dasiglucagon	Prefilled pen, prefilled syringe	$371	NA	0.6 mg

AWP, average wholesale price; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP and NADAC prices are as of August 2023. *Calculated per unit (AWP [147] or NADAC [148]; median AWP or NADAC is listed alone when only one product and/or price is described).

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 (135,136). Real-time CGM can provide alarms that can warn individuals of falling glucose so that they can intervene (135,136). 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.

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 done 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.

Individuals with impaired awareness of hypoglycemia benefit from, and should be referred to, training programs that can reestablish awareness of hypoglycemia. Fear of hypoglycemia and hypoglycemia unawareness often cooccur, so interventions aimed at treating one often benefit both (137). Formal, evidence-based training programs that have been developed include the Blood Glucose Awareness Training Program, Dose Adjusted for Normal Eating (DAFNE), and DAFNEplus (138–140). Where these programs are not available, training can be provided through qualified behavioral health professionals, diabetes educators, 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 can improve counterregulation and hypoglycemia awareness in many people with diabetes (141). Hence, individuals with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic goals (142).

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, life-threatening 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 (143–145). Clinicians should consider temporarily decreasing or stopping sulfonylureas when these antimicrobials are prescribed.

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

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; 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. Jovanovic L, Savas H, Mehta M, Trujillo A, Pettitt DJ. Frequent monitoring of A1C during pregnancy as a treatment tool to guide therapy. Diabetes Care 2011;34:53–54
6. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98(4S):S1–S115
7. 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 August 2023. Available from https://ngsp.org/interf.asp
8. 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
9. 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
10. 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
11. 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
12. 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
13. Wheeler E, Leong A, Liu CT, 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
14. 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
15. 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
16. 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
17. 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
18. 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
19. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478
20. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. Diabetes Care 2014;37:1048–1051
21. 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
22. 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:e001045
23. 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
24. 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
25. 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
26. 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
27. Advani A. Positioning time in range in diabetes management. Diabetologia 2020;63:242–252
28. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21:81–85
29. 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
30. 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
31. 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
32. 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
33. Tchero H, Kangambega P, Briatte C, Brunet-Houdard S, Retali GR, 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
34. 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
35. 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
36. 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
37. 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
38. 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
39. Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA; 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
40. Lachin JM, Genuth S, Cleary P, Davis MD; 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
41. 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
42. 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
43. 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
44. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
45. Lind M, Pivodic A, Svensson AM, 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
46. 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
47. 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
48. 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
49. 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
50. 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
51. 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
52. 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
53. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; 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
54. 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
55. 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
56. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) 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
57. 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
58. Di Angelantonio E, Kaptoge S, Wormser D, et al.; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality. JAMA 2015;314:52–60
59. 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
60. ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39:701–708
61. 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
62. 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
63. 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
64. 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
65. 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
66. 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
67. 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
68. Sinclair AJ, Heller SR, Pratley RE, et al. Evaluating glucose-lowering treatment in older people with diabetes: lessons from the IMPERIUM trial. Diabetes Obes Metab 2020;22:1231–1242
69. 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
70. 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
71. 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
72. 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
73. 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
74. 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
75. 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
76. 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
77. 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
78. 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 8 August 2023. Available from https://www.ncbi.nlm.nih.gov/books/NBK114893/
79. Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycaemia on quality of life and related patient-reported outcomes in type 2 diabetes: a narrative review. Diabet Med 2012;29:293–302
80. 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
81. 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
82. 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
83. 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
84. Choudhary P, Amiel SA. Hypoglycaemia in type 1 diabetes: technological treatments, their limitations and the place of psychology. Diabetologia 2018;61:761–769
85. 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
86. 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
87. 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
88. 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(Suppl. 1):e002153
89. 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
90. 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
91. 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.e2
92. 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
93. 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
94. Yun JS, Ko SH, Ko SH, 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
95. 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
96. 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
97. 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
98. 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
99. 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
100. 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
101. 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
102. Davis TM, Brown SG, 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
103. 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
104. 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
105. 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
106. 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
107. 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
108. 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
109. 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
110. Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B. Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. Lancet 2001;357:1248–1253
111. 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
112. 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
113. 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
114. 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:e001248
115. 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
116. DuBose SN, Weinstock RS, Beck RW, et al. Hypoglycemia in older adults with type 1 diabetes. Diabetes Technol Ther 2016;18:765–771
117. 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
118. 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
119. Harlan DM. Islet transplantation for hypoglycemia unawareness/severe hypoglycemia: caveat emptor. Diabetes Care 2016;39:1072–1074
120. 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
121. 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
122. 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
123. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
124. 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
125. 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
126. 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

127. 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
128. 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
129. Pieber TR, Aronson R, Hövelmann U, et al. Dasiglucagon—a next-generation glucagon analog for rapid and effective treatment of severe hypoglycemia: results of phase 3 randomized double-blind clinical trial. Diabetes Care 2021;44:1361–1367
130. 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
131. 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
132. 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
133. 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
134. 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
135. 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
136. 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
137. 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
138. 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
139. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002;325:746
140. Stanton-Fay SH, Hamilton K, Chadwick PM, et al.; DAFNEplus study group. The DAFNEplus programme for sustained type 1 diabetes self management: intervention development using the Behaviour Change Wheel. Diabet Med 2021;38:e14548
141. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004;350:2272–2279
142. Mitchell BD, He X, Sturdy IM, Cagle AP, Settles JA. Glucagon prescription patterns in patients with either type 1 or 2 diabetes with newly prescribed insulin. Endocr Pract 2016;22:123–135
143. Parekh TM, Raji M, Lin YL, Tan A, Kuo YF, Goodwin JS. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. JAMA Intern Med 2014;174:1605–1612
144. Lee S, Ock M, Kim HS, 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
145. 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
146. 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
147. Merative. Micromedex RED BOOK (electronic version). Ann Arbor, MI, Merative. Accessed 22 August 2023. Available from https://www.merative.com/clinical-decision-support
148. U.S. Centers for Medicare & Medicaid Services. NADAC (National Average Drug Acquisition Cost) 2023. Accessed 22 Aug 2023. Available from https://data.medicaid.gov/dataset/4a00010a-132b-4e4d-a611-543c9521280f