# 6. Glycemic Targets: *Standards of Medical Care in Diabetes—2020*

*American Diabetes Association*

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## ASSESSMENT OF GLYCEMIC CONTROL

Glycemic management is primarily assessed with the A1C test, which was the measure studied in clinical trials demonstrating the benefits of improved glycemic control. Patient self-monitoring of blood glucose (SMBG) may help with self-management and medication adjustment, particularly in individuals taking insulin. Continuous glucose monitoring (CGM) also has an important role in assessing the effectiveness and safety of treatment in many patients with type 1 diabetes, and limited data suggest it may also be helpful in selected patients with type 2 diabetes, such as those on intensive insulin regimens (1).

### A1C Testing

***Recommendations***

**6.1** Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**

**6.2** Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. **E**

**6.3** Point-of-care testing for A1C provides the opportunity for more timely treatment changes. **E**

A1C reflects average glycemia over approximately 3 months. The performance of the test is generally excellent for National Glycohemoglobin Standardization Program (NGSP)-certified assays (see www.ngsp.org). The test is the major tool for assessing glycemic control and has strong predictive value for diabetes complications (1–3). Thus, A1C testing should be performed routinely in all patients with diabetes—at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained. The frequency of A1C testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment. The

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use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters between patients and providers. Patients with type 2 diabetes with stable glycemia well within target may do well with A1C testing only twice per year. Unstable or intensively managed patients or people not at goal with treatment adjustments may require testing more frequently (every 3 months) (4).

### A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. As with any laboratory test, there is variability in the measurement of A1C. Although such variability is less on an intraindividual basis than that of blood glucose measurements, clinicians should exercise judgment when using A1C as the sole basis for assessing glycemic control, particularly if the result is close to the threshold that might prompt a change in medication therapy. Conditions that affect red blood cell turnover (hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoesis, end-stage kidney disease, and pregnancy) may result in discrepancies between the A1C result and the patient's true mean glycemia. Hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's SMBG levels. However, most assays in use in the U.S. are accurate in individuals heterozygous for the most common variants (see www.ngsp.org/interf.asp). Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C. Though some variability in the relationship between average glucose levels and A1C exists among different individuals, generally the association between mean glucose and A1C within an individual correlates over time (5).

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially patients with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from SMBG or CGM and A1C. A1C may also inform the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

### Correlation Between SMBG and A1C

**Table 6.1** shows the correlation between A1C levels and mean glucose levels based on the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between A1C and frequent SMBG and CGM in 507 adults (83% non-Hispanic whites) with type 1, type 2, and no diabetes (6), and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial (7). 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 in the ADAG trial. In a recent report, mean glucose measured with CGM versus central laboratory–measured A1C in 387 participants in three randomized trials demonstrated that A1C may underestimate or overestimate mean glucose (5). Thus, as suggested, a patient's CGM profile has considerable potential for optimizing his or her glycemic management (5).

### A1C Differences in Ethnic Populations and Children

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although the study was underpowered to detect a difference and there was a trend toward a difference between the African/African American and non-Hispanic white cohorts, with higher A1C values observed in Africans/African Americans compared with non-Hispanic whites for a given mean glucose. Other studies have also demonstrated higher A1C levels in African Americans than in whites at a given mean glucose concentration (8,9).

A1C assays are available that do not demonstrate a statistically significant difference in individuals with hemoglobin variants. Other assays have statistically significant interference, but the difference is not clinically significant. Use of an assay with such statistically significant interference may explain a report that for any level of mean glycemia, African Americans heterozygous for the common hemoglobin variant HbS had lower A1C by about 0.3 percentage points when compared with those without the trait (10,11). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African Americans, was associated with a decrease in A1C of about 0.8% in hemizygous men and 0.7% in homozygous women compared with those without the trait (12).

A small study comparing A1C to CGM data in children with type 1 diabetes found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation ($r = 0.7$) was significantly lower than in the ADAG trial (13). Whether there are clinically meaningful differences in how

**Table 6.1—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 (6,7). Adapted from Nathan et al. (6).

A1C relates to average glucose in children or in different ethnicities is an area for further study (8,14,15). Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of both individualized SMBG and A1C results.

### Glucose Assessment

*Recommendations*

**6.4** Standardized, single-page glucose reports with visual cues such as the Ambulatory Glucose Profile (AGP) should be considered as a standard printout for all CGM devices. **E**

**6.5** Time in range (TIR) is associated with the risk of microvascular complications and should be an acceptable end point for clinical trials and can be used for assessment of glycemic control. Additionally, time below target (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above target (>180 mg/dL [10.0 mmol/L]) are useful parameters for reevaluation of the treatment regimen. **E**

For many people with diabetes, glucose monitoring is key for the achievement of glycemic targets. Major clinical trials of insulin-treated patients have included SMBG as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (16). SMBG is thus an integral component of effective therapy of patients taking insulin. In recent years, CGM has emerged as a complementary method for the assessment of glucose levels. Glucose monitoring allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. The international consensus on time in range provides guidance on standardized CGM metrics (see **Table 6.2**) and considerations for clinical interpretation and care (17). To make these metrics more actionable, standardized reports with visual cues such as the Ambulatory Glucose Profile (see **Fig. 6.1**) are recommended (17) and may help the patient and the provider interpret the data and use it to guide treatment decisions. Integrating SMBG and CGM results into diabetes management can be useful for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, and adjusting medications. As recently reviewed, while A1C is currently the primary measure guiding glucose management and a valuable marker of the risk of developing diabetes complications, the Glucose Management Indicator (GMI) along with the other CGM metrics are suggested to provide for a much more personalized diabetes management plan. The incorporation of these metrics into clinical practice is in evolution, and optimization of CGM terminology will evolve to suit patient and provider needs. The patient's specific needs and goals should dictate SMBG frequency and timing or the consideration of CGM use. Please refer to Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc20-S007) for a fuller discussion of the use of SMBG and CGM.

### Glucose Assessment Using Continuous Glucose Monitoring

With the advent of new technology, CGM has evolved rapidly in both accuracy and affordability. As such, many patients have these data available to assist with both self-management and assessment by providers. Reports can be generated from CGM that will allow the provider to determine time in range (TIR) and to assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a recent consensus document, a report formatted as shown in **Fig. 6.1** can be generated (17). Published data suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% in two prospective studies (18,19).

## A1C GOALS

For glycemic goals in older adults, please refer to Section 12 "Older Adults" (https://doi.org/10.2337/dc20-S012). For glycemic goals in children, please refer to Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-S013). For glycemic goals in pregnant women, please refer to Section 14 "Management of Diabetes in Pregnancy" (https://doi.org/10.2337/dc20-S014).

*Recommendations*

**6.6** An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) is appropriate. **A**

**6.7** On the basis of provider judgement and patient preference, achievement of lower A1C levels (such as <6.5%) may be acceptable if this can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **C**

**6.8** Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular

**Table 6.2—Standardized continuous glucose monitoring (CGM) metrics for clinical care**

| | |
|---|---|
| 1. Number of days CGM device is worn (recommend 14 days) | |
| 2. Percentage of time CGM device is active (recommend 70% of data from 14 days) | |
| 3. Mean glucose | |
| 4. Glucose management indicator (GMI) | |
| 5. Glycemic variability (%CV) target ≤36%* | |
| 6. Time above range (TAR): % of readings and time >250 mg/dL (>13.9 mmol/L) | Level 2 |
| 7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L) | Level 1 |
| 8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L) | In range |
| 9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L) | Level 1 |
| 10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L) | Level 2 |

CGM, continuous glucose monitoring; CV, coefficient of variation. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (17).

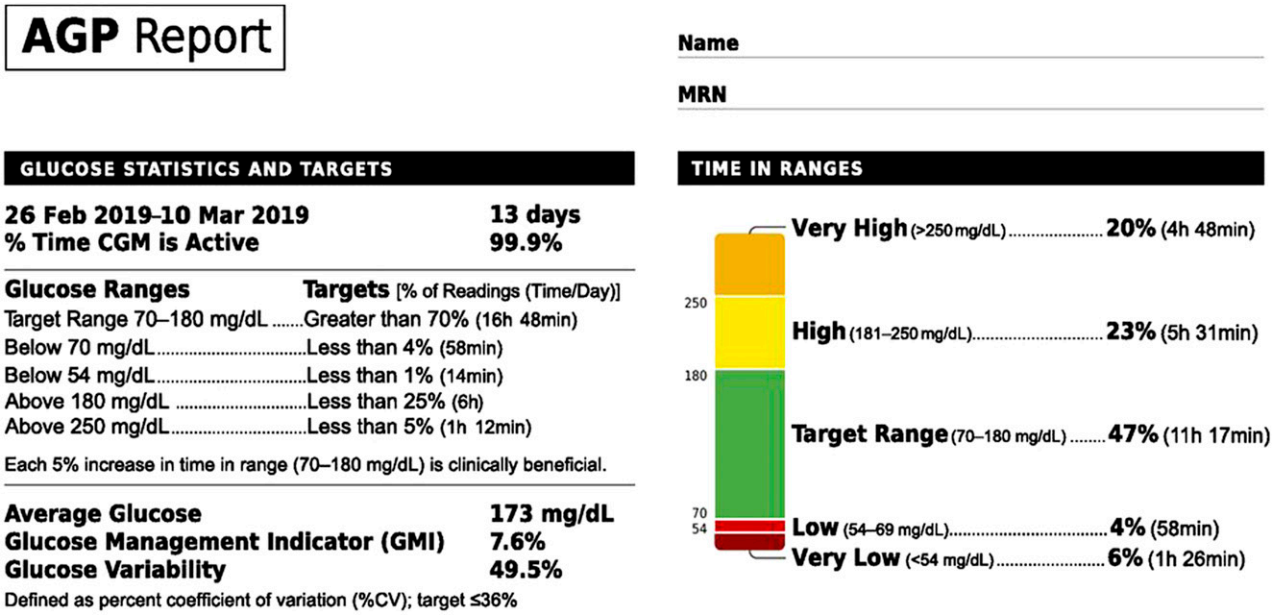


**Figure 6.1**—Sample Ambulatory Glucose Profile (AGP) report. Adapted from Battelino et al. (17).

complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B

**6.9** Reassess glycemic targets over time based on the criteria in **Fig. 6.2** or, in older adults, **Table 12.1.** E

### A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (16), a prospective randomized controlled trial of intensive (mean A1C about 7% [53 mmol/mol]) versus standard (mean A1C about 9% [75 mmol/mol]) glycemic control in patients with type 1 diabetes, showed definitively that better glycemic control is associated with 50–76% reductions in rates of development and progression of microvascular (retinopathy, neuropathy, and diabetic kidney disease) complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (20,21) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (22) and UK Prospective Diabetes Study (UKPDS) (23,24) confirmed that intensive glycemic control significantly decreased rates of microvascular complications in patients with short-duration type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (25).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (26). Epidemiologic analyses of the DCCT (16) and UKPDS (27) demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. 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% and low hypoglycemia risk with a long life expectancy.

Given the substantially increased risk of hypoglycemia in type 1 diabetes and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications. 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 in individuals with long-standing type 2 diabetes and either known cardiovascular disease (CVD) or high cardiovascular risk. These trials showed that lower A1C levels were associated with reduced onset or progression of some microvascular complications (28–30).

The concerning mortality findings in the ACCORD trial (31), discussed below, and the relatively intense efforts required to achieve near euglycemia should also be considered when setting glycemic targets for individuals with long-standing diabetes such as those studied in ACCORD, ADVANCE, and VADT. Findings from these studies suggest caution is needed in treating diabetes aggressively to near-normal A1C goals in people with long-standing type 2 diabetes with or at significant risk of CVD. However, on the

basis of physician judgment and patient preferences, select patients, especially those with little comorbidity and long life expectancy, may benefit from adopting more intensive glycemic targets if they can achieve it safely without hypoglycemia or significant therapeutic burden.

## A1C and Cardiovascular Disease Outcomes

### *Cardiovascular Disease and Type 1 Diabetes*

CVD is a more common cause of death than microvascular complications in populations with diabetes. There is evidence for a cardiovascular benefit of intensive glycemic control after long-term follow-up of cohorts treated early in the course of type 1 diabetes. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year 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 (MI), stroke, or cardiovascular death compared with those previously randomized to the standard arm (32). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (33) and to be associated with a modest reduction in all-cause mortality (34).

### *Cardiovascular Disease and Type 2 Diabetes*

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. In addition, data from the Swedish National Diabetes Registry and Joint Asia Diabetes Evaluation (JADE) demonstrate greater proportions of people with diabetes being diagnosed at <40 years of age and a demonstrably increased burden of heart disease and years of life lost in people diagnosed at a younger age (35–37). Thus, for prevention of both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to target for an individual patient (37). During the UKPDS, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance ($P = 0.052$), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). However, after 10 years of observational follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (25).

ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for shorter durations (3.5–5.6 years) and who had more advanced type 2 diabetes than UKPDS participants. All three trials were conducted in relatively older participants with longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. The target A1C among intensive-control subjects was <6% (42 mmol/mol) in ACCORD, <6.5% (48 mmol/mol) in ADVANCE, and a 1.5% reduction in A1C compared with control subjects in VADT, with achieved A1C of 6.4% vs. 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% vs. 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% vs. 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (38).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]), with a similar increase in cardiovascular deaths. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive treatment arm (31).

Longer-term follow-up has shown no evidence of cardiovascular benefit or harm in the ADVANCE trial (39). The end-stage renal disease rate was lower in the intensive treatment group over follow-up. However, 10-year follow-up of the VADT cohort (40) showed a reduction in the risk of cardiovascular events (52.7 [control group] vs. 44.1 [intervention group] events per 1,000 person-years) with no benefit in cardiovascular or overall mortality. Heterogeneity of mortality effects across studies was noted, which may reflect differences in glycemic targets, therapeutic approaches, and population characteristics (41).

Mortality findings in ACCORD (31) and subgroup analyses of VADT (42) suggest that the potential risks of intensive glycemic control may outweigh its benefits in higher-risk patients. In all three trials, severe hypoglycemia was significantly more likely in participants who were randomly assigned to the intensive glycemic control arm. Those patients with long duration of diabetes, a known history of hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (43,44).

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (45). Providers should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such targets cannot be safely and reasonably achieved. As discussed in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc20-S009), addition of specific sodium–glucose cotransporter 2 inhibitors (SGLT2i) or glucagon-like peptide 1 receptor agonists (GLP-1 RA) that have demonstrated CVD benefit are recommended for use in patients with established CVD or indicators of high risk. As outlined in more detail in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc20-S009) and Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc20-S010), the cardiovascular benefits of SGLT2i or GLP-1 RA are not dependent upon A1C lowering, so initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal. Based on these considerations, the following two strategies are offered (46):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2i or GLP-1 RA in patients with CVD at A1C goal for cardiovascular benefit.

### *Setting and Modifying A1C Goals*

Numerous factors must be considered when setting glycemic targets. The ADA proposes general targets appropriate for many patients but emphasizes the

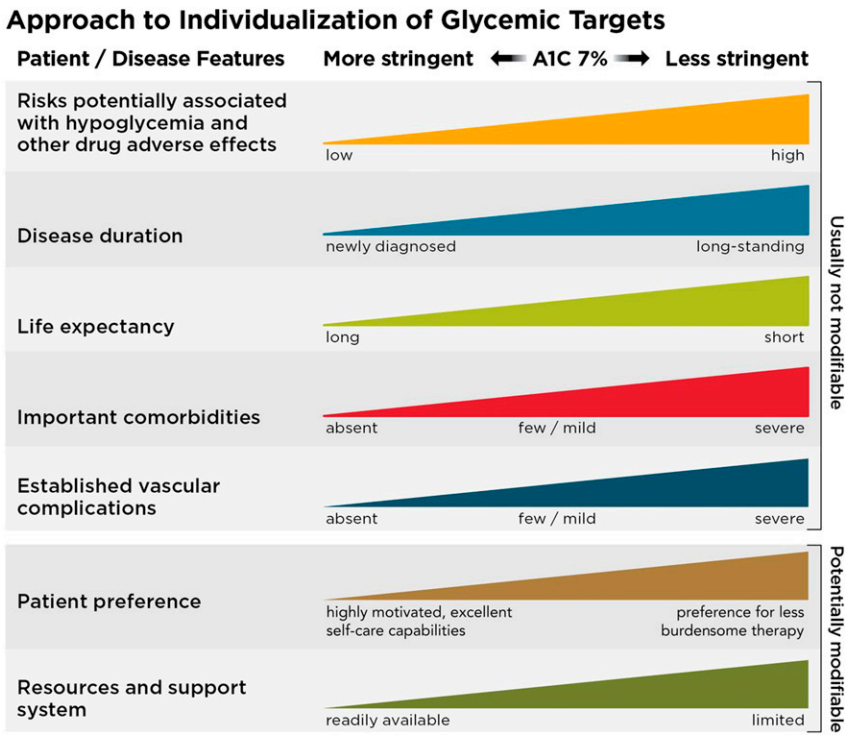


**Figure 6.2**—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (47).

importance of individualization based on key patient characteristics. Glycemic targets must be individualized in the context of shared decision-making to address the needs and preferences of each patient and the individual characteristics that influence risks and benefits of therapy for each patient.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. **Figure 6.2** is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making (47) and engage in shared decision-making in both type 1 and type 2 diabetes. More stringent targets may be recommended if they can be achieved safely and with acceptable burden of therapy and if life expectancy is sufficient to reap benefits of stringent targets. Less stringent targets (A1C up to 8% [64 mmol/mol]) may be recommended if the life expectancy of the patient 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 regimens, 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 the disease may change over time. Newly diagnosed patients and/or those without comorbidities that limit life expectancy may benefit from intensive control proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS demonstrated metabolic memory, or a legacy effect, in which a finite period of intensive control yielded benefits that extended for decades after that control ended. Thus, a finite period of intensive control to near-normal A1C may yield enduring benefits even if control is subsequently deintensified as patient characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby potential to reap benefits from intensive control. Also, with longer duration of disease, diabetes may become more difficult to control, with increasing risks and burdens of therapy. Thus, A1C targets should be reevaluated over time to balance the risks and benefits as patient factors change.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7% (53 mmol/mol). Pregnancy recommendations are discussed in more detail in Section 14 "Management of Diabetes in Pregnancy" (https://doi.org/10.2337/dc20-S014).

The issue of preprandial versus postprandial SMBG targets is complex (48). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiologic studies, but intervention trials have not shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In subjects with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7% (53 mmol/mol). However, outcome studies have clearly shown A1C to be the primary predictor of complications, and landmark trials of glycemic control such as the DCCT and UKPDS relied overwhelmingly on preprandial SMBG. Additionally, a randomized controlled trial in patients with known CVD found no CVD benefit of insulin regimens targeting postprandial glucose compared with those targeting preprandial glucose (49). Therefore, it is reasonable for postprandial testing to be recommended for individuals who have premeal glucose values within target but have A1C values above target. Measuring postprandial plasma glucose 1–2 h after the start of a meal and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10.0 mmol/L) may help to lower A1C.

An analysis of data from 470 participants in the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that the glucose ranges highlighted in **Table 6.1** are adequate to meet targets and decrease hypoglycemia (7,50). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data prompted the revision in the ADA-recommended premeal glucose target to 80–130 mg/dL (4.4–7.2 mmol/L)

but did not affect the definition of hypoglycemia.

## HYPOGLYCEMIA

***Recommendations***

**6.10** Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**

**6.11** In patients taking medication that can lead to hypoglycemia, investigate, screen, and assess risk for or occurrence of unrecognized hypoglycemia, considering that patients may have hypoglycemia unawareness. **C**

**6.12** Glucose (15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL [3.9 mmol/L]), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**

**6.13** Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals, particularly with the availability of intranasal and stable soluble glucagon available in autoinjector pens. **E**

**6.14** Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation of the treatment regimen. **E**

**6.15** Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**

**6.16** Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. **B**

**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 individual patients. 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. †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 patients with diabetes.

Hypoglycemia is 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** (51–56). 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. Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important, independent of the severity of acute hypoglycemic 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 a patient has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have hypoglycemia unawareness (discussed further below). This clinical scenario warrants investigation and review of the medical regimen. 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.

Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, and hunger. Hypoglycemia may be inconvenient or frightening to patients with diabetes. Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. It is reversed by administration of rapid-acting glucose or glucagon. Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical regimen adjustment, behavioral intervention, and, in some cases, use of technology to assist with hypoglycemia prevention and identification (52,57–60). A large cohort study suggested that among older adults with type 2 diabetes, a history of level 3 hypoglycemia was associated with greater risk of dementia (61). Conversely, in a substudy of the ACCORD trial, cognitive impairment at

**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 |

Reprinted from Agiostratidou et al. (51).

baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of level 3 hypoglycemia (62). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of level 3 hypoglycemia and cognitive decline (63), as discussed in Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-S013).

Studies of rates of level 3 hypoglycemia that rely on claims data for hospitalization, emergency department visits, and ambulance use substantially underestimate rates of level 3 hypoglycemia (64) yet find high burden of hypoglycemia in adults over 60 years of age in the community (65). African Americans are at substantially increased risk of level 3 hypoglycemia (65,66). In addition to age and race, other important risk factors found in a community-based epidemiologic cohort of older black and white adults with type 2 diabetes include insulin use, poor or moderate versus good glycemic control, albuminuria, and poor cognitive function (65). Level 3 hypoglycemia was associated with mortality in participants 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. An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial (67). An association between self-reported level 3 hypoglycemia and 5-year mortality has also been reported in clinical practice (68)

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (61,69), are noted as particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glucose targets, patient education, dietary intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), exercise management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (70). CGM with automated low glucose suspend has been shown to be effective in reducing hypoglycemia in type 1 diabetes (71). For patients 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 (72,73).

In 2015, the ADA changed its preprandial glycemic target from 70–130 mg/dL (3.9–7.2 mmol/L) to 80–130 mg/dL (4.4–7.2 mmol/L). This change reflects the results of the ADAG study, which demonstrated that higher glycemic targets corresponded to A1C goals (7). An additional goal of raising the lower range of the glycemic target was to limit overtreatment and provide a safety margin in patients titrating glucose-lowering drugs such as insulin to glycemic targets.

### Hypoglycemia Treatment

Providers should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less. This should be reviewed at each patient visit. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods (74–76). The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. In type 2 diabetes, ingested protein may increase insulin response without increasing plasma glucose concentrations (77). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery. Once the glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia.

#### *Glucagon*

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, childcare providers, 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. An individual does not need to be a health care professional to safely administer glucagon. In addition to traditional glucagon injection powder that requires reconstitution prior to injection, intranasal glucagon and glucagon solution for subcutaneous injection recently received U.S. Food and Drug Administration approval. Care should be taken to ensure that glucagon products are not expired.

### Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management. SMBG and, for some patients, CGM are essential tools to assess therapy and detect incipient hypoglycemia. Patients should understand situations that increase their risk of hypoglycemia, such as when fasting for tests or procedures, when meals are delayed, during and after the consumption of alcohol, during and after intense exercise, and during sleep. Hypoglycemia may increase the risk of harm to self or others, such as with driving. Teaching people with diabetes to balance insulin use and carbohydrate intake and exercise are necessary, but these strategies are not always sufficient for prevention.

In type 1 diabetes and severely insulin deficient type 2 diabetes, hypoglycemia unawareness (or hypoglycemia-associated autonomic failure) can severely compromise stringent diabetes control and quality of life. This syndrome is characterized by deficient counterregulatory hormone release, especially in older adults, and a diminished autonomic response, which are both risk factors for, and caused by, hypoglycemia. A corollary to this "vicious cycle" is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counterregulation and hypoglycemia awareness in many patients (78). Hence, patients with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets and availability of glucagon (79).

### Use of CGM Technology in Hypoglycemia Prevention

With the advent of CGM and CGM-assisted pump therapy, there has been a

promise of alarm-based prevention of hypoglycemia (80,81). To date, there have been six randomized controlled trials in adults with type 1 diabetes and seven in adults and children with type 1 diabetes using real-time CGM. These studies had differing A1C at entry and differing primary end points and thus must be interpreted carefully. Real-time CGM studies can be divided into studies with elevated A1C with the primary end point of A1C reduction and studies with A1C near target with the primary end point of reduction in hypoglycemia (81–97). In people with type 1 and type 2 diabetes with A1C above target, CGM improved A1C between 0.3% and 0.6%. For studies targeting hypoglycemia, most studies demonstrated a significant reduction in time spent between 54 and 70 mg/dL. No study to date has reported a decrease in level 3 hypoglycemia. In a single study using intermittently scanned CGM, adults with type 1 diabetes with A1C near goal and impaired awareness of hypoglycemia demonstrated no change in A1C and decreased level 2 hypoglycemia (88). For people with type 2 diabetes, studies examining the impact of CGM on hypoglycemic events are limited; a recent meta-analysis does not reflect a significant impact on hypoglycemic events in type 2 diabetes (98), whereas improvements in A1C were observed in most studies (98–104). Overall, real-time CGM appears to be a useful tool for decreasing time spent in hypoglycemia range in people with impaired awareness.

## INTERCURRENT ILLNESS

For further information on management of patients with hyperglycemia in the hospital, please refer to Section 15 "Diabetes Care in the Hospital" (https://doi.org/10.2337/dc20-S015).

Stressful events (e.g., illness, trauma, surgery, etc.) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or alteration in the level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment regimen and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or medical nutrition therapy alone may require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration is more likely to necessitate hospitalization of the person with diabetes than the person without diabetes.

A physician with expertise in diabetes management should treat the hospitalized patient. For further information on the management of diabetic ketoacidosis and the nonketotic hyperglycemic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (105).

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