6. Glycemic Targets

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ASSESSMENT OF GLYCEMIC CONTROL

Patient self-monitoring of blood glucose (SMBG) and A1C are available to health care providers and patients to assess the effectiveness and safety of the management plan on glycemic control. Continuous glucose monitoring (CGM) also has an important role in assessing the effectiveness and safety of treatment in subgroups of patients with type 1 diabetes and in selected patients with type 2 diabetes.

Recommendations

- Most patients using intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should perform self-monitoring of blood glucose (SMBG) prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. **B**
- When prescribed as part of a broad educational program, SMBG may help to guide treatment decisions and/or self-management for patients taking less frequent insulin injections **B** or noninsulin therapies. **E**
- When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique, SMBG results, and their ability to use SMBG data to adjust therapy. **E**
- When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥25 years) with type 1 diabetes. **A**
- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. **B**
- CGM may be a useful tool in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. **C**
- Given the variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing. **E**
- When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use. **E**
- People who have been successfully using CGM should have continued access after they turn 65 years of age. **E**

Self-monitoring of Blood Glucose

Major clinical trials of insulin-treated patients have included SMBG as part of the multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications. SMBG is thus an integral component of effective therapy (1). SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Integrating SMBG results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, and adjusting medications (particularly prandial insulin doses). Among patients with type 1 diabetes, there is a correlation between greater SMBG frequency and lower A1C (2). The patient's specific needs and goals should dictate SMBG frequency and timing.

Optimization

SMBG accuracy is dependent on the instrument and user, so it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper review and interpretation of the data, by both the patient and the provider. Among patients who check their blood

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glucose at least once daily, many report taking no action when results are high or low. In a yearlong study of insulin-naive patients with suboptimal initial glycemic control, a group trained in structured SMBG (a paper tool was used at least quarterly to collect and interpret 7-point SMBG profiles taken on 3 consecutive days) reduced their A1C by 0.3 percentage points more than the control group (3). Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. The ongoing need for and frequency of SMBG should be reevaluated at each routine visit to avoid overuse (4–6). SMBG is especially important for insulin-treated patients to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia.

For Patients on Intensive Insulin Regimens

Most patients using intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should perform SMBG prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. For many patients, this will require testing 6–10 (or more) times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjustment for multiple confounders, increased daily frequency of SMBG was significantly associated with lower A1C (–0.2% per additional test per day) and with fewer acute complications.

For Patients Using Basal Insulin or Oral Agents

The evidence is insufficient regarding when to prescribe SMBG and how often testing is needed for patients who do not use intensive insulin regimens, such as those with type 2 diabetes using oral agents or basal insulin. For patients using basal insulin, lowering of A1C has been demonstrated for those who adjust their dose to attain a fasting glucose as determined by SMBG within a targeted range (7,8).

For individuals with type 2 diabetes on less intensive insulin therapy, more frequent SMBG (e.g., fasting, before/after meals) may be helpful, as increased frequency is associated with meeting A1C targets (9).

Several randomized trials have called into question the clinical utility and cost-effectiveness of routine SMBG in noninsulin-treated patients (10–12). Meta-analyses have suggested that SMBG can reduce A1C by 0.25–0.3% at 6 months (10,13), but the effect was attenuated at 12 months in one analysis (13). A key consideration is that performing SMBG alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Continuous Glucose Monitoring

CGM measures interstitial glucose (which correlates well with plasma glucose) and includes sophisticated alarms for hypo- and hyperglycemic excursions. The U.S. Food and Drug Administration (FDA) has not yet approved these devices as a sole device to monitor glucose. CGMs require calibration with SMBG, and SMBG is still required to make treatment decisions. An FDA advisory panel recently recommended approval for use of one CGM device alone (without SMBG) to make treatment decisions, but the final FDA decision is still pending.

A 26-week randomized trial of 322 patients with type 1 diabetes showed that adults aged ≥25 years using intensive insulin therapy and CGM experienced a 0.5% reduction in A1C (from ~7.6% to 7.1% [~60 mmol/mol to 54 mmol/mol]) compared with those using intensive insulin therapy with SMBG (14). CGM use in those aged <25 years (children, teens, and adults) did not result in significant A1C lowering, and there was no significant difference in hypoglycemia in any group. The greatest predictor of A1C lowering for all age-groups was frequency of sensor use, which was highest in those aged ≥25 years and lower in younger age-groups. Other small, short-term studies have demonstrated similar A1C reductions using CGM compared with SMBG in adults with A1C levels ≥7% (53 mmol/mol) (15,16).

A registry study of 17,317 participants confirmed that more frequent CGM use is associated with lower A1C (17), whereas another study showed that children with >70% sensor use (i.e., ≥5 days per week) missed fewer school days (18). Small randomized controlled trials in adults and children with baseline A1C <7.0–7.5% (53–58 mmol/mol) have confirmed favorable outcomes including a reduced frequency of hypoglycemia (defined as a blood glucose level <70 mg/dL [3.9 mmol/L]) and maintaining A1C <7% (53 mmol/mol) during the study period in groups using CGM, suggesting that CGM may provide further benefit for individuals with type 1 diabetes who already have good glycemic control (19–21).

A meta-analysis suggests that compared with SMBG, CGM is associated with short-term A1C lowering of ~0.26% in insulin-treated patients (22). The long-term effectiveness of CGM needs to be determined. This technology may be particularly useful in insulin-treated patients with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not shown consistent reductions in severe hypoglycemia (22–24). A CGM device equipped with an automatic low glucose suspend feature has been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 patients with type 1 diabetes and documented nocturnal hypoglycemia showed that sensor-augmented insulin pump therapy with a low glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (25). These devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. In September 2016, the FDA approved the first hybrid closed-loop system, which may be considered as an option in those already on an insulin pump when it is available on the market. The safety of hybrid closed-loop systems has been supported in the literature (26).

Due to variable adherence, optimal CGM use requires an assessment of individual readiness for the technology as well as initial and ongoing education and support (17,27). Additionally, providers need to provide robust diabetes education, training, and support for optimal CGM implementation and ongoing use. As people with type 1 or type 2 diabetes are living longer healthier lives, individuals who have been successfully using CGM should have continued access to these devices after they turn 65 years of age (28).

A1C TESTING

Recommendations

- Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. **E**
- Point-of-care testing for A1C provides the opportunity for more timely treatment changes. **E**

A1C reflects average glycemia over approximately 3 months and has strong predictive value for diabetes complications (29,30). 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 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 (e.g., pregnant women with type 1 diabetes) may require testing more frequently than every 3 months (31).

A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. Conditions that affect red blood cell turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's SMBG levels. For patients in whom A1C/estimated average glucose (eAG) and measured blood glucose appear discrepant, clinicians should consider the possibilities of altered red blood cell turnover. Options for monitoring include more frequent and/or different timing of SMBG or CGM use. Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol (1,5-AG) are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C (see Section 2 "Classification and Diagnosis of Diabetes").

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 and A1C. A1C may also confirm the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

A1C and Mean Glucose

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on two studies: 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 (32), 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 (27). 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 eAG result when a clinician orders the A1C test (**Table 6.1**). Clinicians should note that the mean plasma glucose numbers in the table are based on ~2,700 readings per A1C in the ADAG trial.

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 values observed in Africans/African Americans compared with non-Hispanic whites. Other studies have also demonstrated higher A1C levels in African Amercans than in whites (33). 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 (34). Whether there are clinically meaningful differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (35,36). For the time being, the question has not led to different recommendations about testing A1C or to different interpretations of the clinical meaning of given levels of A1C in those populations. Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of both individualized SMBG and A1C results.

A1C GOALS

For glycemic goals in children, please refer to Section 12 "Children and Adolescents." For glycemic goals in pregnant women, please refer to Section 13 "Management of Diabetes in Pregnancy."

Recommendations

- A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). **A**
- Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. **C**
- 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 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**

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (1), a prospective randomized controlled trial of intensive versus standard glycemic control in patients with type 1 diabetes, showed definitively that better glycemic control is associated with significantly decreased rates of development and progression of microvascular (retinopathy [37] and diabetic kidney disease) and neuropathic complications. Follow-up of the

Table 6.1—Mean glucose levels for specified A1C levels (27,32)

A1C	Mean plasma glucose*		Mean fasting glucose		Mean premeal glucose		Mean postmeal glucose		Mean bedtime glucose	
% (mmol/mol)	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L
6 (42)	126 (100–152)	7.0 (5.5–8.5)								
5.5–6.49 (37–47)			122 (117–127)	6.8 (6.5–7.0)	118 (115–121)	6.5 (6.4–6.7)	144 (139–148)	8.0 (7.7–8.2)	136 (131–141)	7.5 (7.3–7.8)
6.5–6.99 (47–53)			142 (135–150)	7.9 (7.5–8.3)	139 (134–144)	7.7 (7.4–8.0)	164 (159–169)	9.1 (8.8–9.4)	153 (145–161)	8.5 (8.0–8.9)
7 (53)	154 (123–185)	8.6 (6.8–10.3)								
7.0–7.49 (53–58)			152 (143–162)	8.4 (7.9–9.0)	152 (147–157)	8.4 (8.2–8.7)	176 (170–183)	9.8 (9.4–10.2)	177 (166–188)	9.8 (9.2–10.4)
7.5–7.99 (58–64)			167 (157–177)	9.3 (8.7–9.8)	155 (148–161)	8.6 (8.2–8.9)	189 (180–197)	10.5 (10.0–10.9)	175 (163–188)	9.7 (9.0–10.4)
8 (64)	183 (147–217)	10.2 (8.1–12.1)								
8.0–8.5 (64–69)			178 (164–192)	9.9 (9.1–10.7)	179 (167–191)	9.9 (9.3–10.6)	206 (195–217)	11.4 (10.8–12.0)	222 (197–248)	12.3 (10.9–13.8)
9 (75)	212 (170–249)	11.8 (9.4–13.9)								
10 (86)	240 (193–282)	13.4 (10.7–15.7)								
11 (97)	269 (217–314)	14.9 (12.0–17.5)								
12 (108)	298 (240–347)	16.5 (13.3–19.3)								

Data in parentheses represent 95% CI, unless otherwise noted. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at http://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, and no diabetes. The correlation between A1C and average glucose was 0.92 (32).

DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (38) demonstrated persistence of these microvascular benefits despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (39) and UK Prospective Diabetes Study (UKPDS) (40,41) confirmed that intensive glycemic control significantly decreased rates of microvascular and neuropathic complications in patients with type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (42).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of diabetes. Epidemiological analyses of the DCCT (1) and UKPDS (43) 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. Given the substantially increased risk of hypoglycemia in type 1 diabetes trials and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets outweigh the potential benefits on microvascular complications.

ACCORD, ADVANCE, and VADT

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]) showed that lower A1C levels were associated with reduced onset or progression of microvascular complications (44–46).

The concerning mortality findings in the ACCORD trial (47), discussed below, and the relatively intense efforts required to achieve near-euglycemia should also be considered when setting glycemic targets. 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 (e.g., A1C target <6.5% [48 mmol/mol]) as long as significant hypoglycemia does not become a barrier.

A1C and Cardiovascular Disease Outcomes

Cardiovascular Disease and Type 1 Diabetes

Cardiovascular disease (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 and type 2 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 (48). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (49) and to be associated with a modest reduction in all-cause mortality (50).

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. 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) (42).

The ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for 3.5–5.6 years 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% versus 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% versus 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% versus 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in the ADA position statement "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" (51).

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 (47).

Longer-term follow-up has shown no evidence of cardiovascular benefit or harm in the ADVANCE trial (52). 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 (53) 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 (54).

Mortality findings in ACCORD (47) and subgroup analyses of VADT (55) 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 (56,57).

Providers should be vigilant in preventing hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such targets cannot be safely and reasonably achieved. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals. Many factors, including patient preferences, should be taken into account when developing a patient's individualized goals (**Table 6.2**)

A1C and Glycemic Targets

Numerous aspects must be considered when setting glycemic targets. The ADA proposes optimal targets, but each target must be individualized to the needs of each patient and his or her disease factors.

When possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. **Figure 6.1** is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making (58), both in type 1 and type 2 diabetes.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.2**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7% (53 mmol/mol). The issue of preprandial versus postprandial SMBG targets is complex (59). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiological 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

Table 6.2—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.

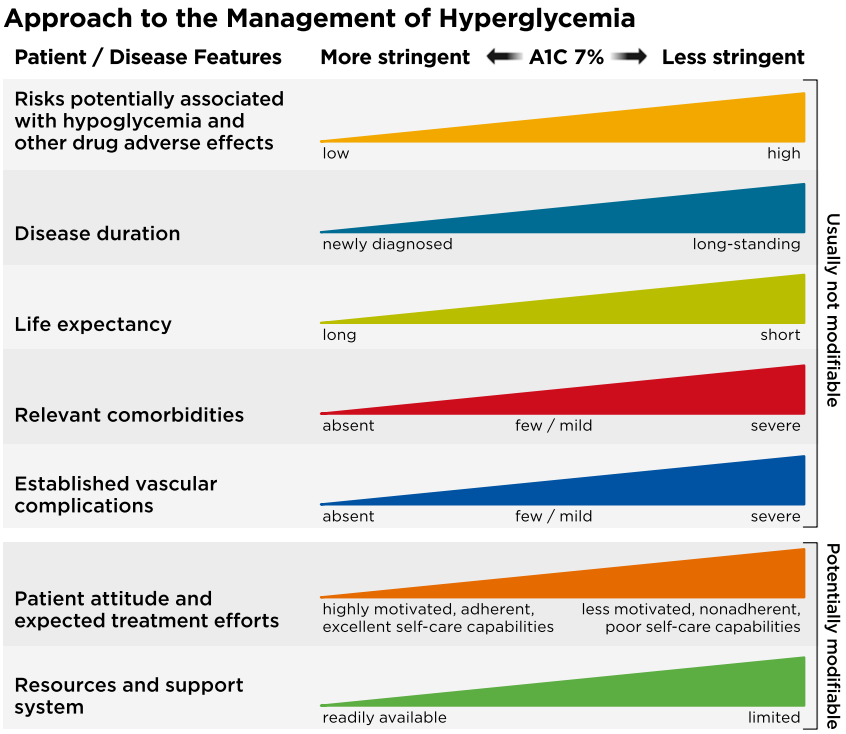

Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (58).

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 (60). 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 actual average glucose levels associated with conventional A1C targets were higher than older DCCT and ADA targets (**Table 6.1**) (27,29). 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

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**
- Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia (glucose alert value of ≤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. **E**
- Glucagon should be prescribed for all individuals at increased risk of clinically significant 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. **E**
- Hypoglycemia unawareness or one or more episodes of severe hypoglycemia should trigger reevaluation of the treatment regimen. **E**
- Insulin-treated patients with hypoglycemia unawareness or an episode of clinically significant 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**
- 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**

Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations from the International Hypoglycaemia Study Group regarding the classification of hypoglycemia are outlined in **Table 6.3** (61). Of note, this classification scheme considers a blood glucose <54 mg/dL (3.0 mmol/L) detected by SMBG, CGM (for at least 20 min), or laboratory measurement of plasma glucose as sufficiently low to indicate serious, clinically significant hypoglycemia that should be included in reports of clinical trials of glucose-lowering drugs for the treatment of diabetes (61). However, a glucose alert value of ≤70 mg/dL (3.9 mmol/L) can be important for therapeutic dose adjustment of glucose-lowering drugs in clinical care and is often related to symptomatic hypoglycemia. Severe hypoglycemia is defined as severe cognitive impairment requiring assistance from another person for recovery (62).

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. Severe 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. Clinically significant hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle

Table 6.3—Classification of hypoglycemia (61)

Level	Glycemic criteria	Description
Glucose alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

accidents, or other injury. A large cohort study suggested that among older adults with type 2 diabetes, a history of severe hypoglycemia was associated with greater risk of dementia (63). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of severe hypoglycemia (64). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of severe hypoglycemia and cognitive decline (65), as discussed in Section 12 "Children and Adolescents."

Severe 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 severe hypoglycemia with mortality was also found in the ADVANCE trial (66). An association between self-reported severe hypoglycemia and 5-year mortality has also been reported in clinical practice (67).

Young children with type 1 diabetes and the elderly are noted as particularly vulnerable to clinically significant 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), exercise management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (62).

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 (27). 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 blood glucose alert value of 70 mg/dL (3.9 mmol/L) or less. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods. 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. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless further 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, child care providers, correctional institution staff, or coworkers) should be instructed on the use of glucagon kits including where the kit is and when and how to administer glucagon. An individual does not need to be a health care professional to safely administer glucagon. Care should be taken to ensure that glucagon kits 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 fasting for tests or procedures, delayed meals, during or 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 both are 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 (68). Hence, patients with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets.

INTERCURRENT ILLNESS

For further information on management of patients with hyperglycemia in the hospital, please refer to Section 14 "Diabetes Care in the Hospital."

Stressful events (e.g., illness, trauma, surgery, etc.) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic 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 temporarily 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 hyperglycemic nonketotic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (69).

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