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2018 Clinical Practice Guidelines

Targets for Glycemic Control

Diabetes Canada Clinical Practice Guidelines Expert Committee

S. Ali Imran MBBS, FRCP (Edin), FRCPC, Gina Agarwal MBBS, PhD, MRCGP, CCFP, FCFP, Harpreet S. Bajaj MD, MPH, ECNU, FACE, Stuart Ross MB, ChB, FRACP, FRCPC



KEY MESSAGES

- Optimal glycemic control is fundamental to the management of diabetes.
- Both fasting and postprandial plasma glucose levels correlate with the risk of complications and contribute to the measured glycated hemoglobin (A1C) value.
- Glycemic targets should be individualized based on the individual's frailty or functional dependence and life expectancy.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Try to keep your blood glucose as close to your target range as possible. This will help to delay or prevent complications of diabetes.
- Target ranges for blood glucose and A1C can vary and depend on a person's medical conditions and other risk factors. Work with your diabetes health-care team to determine your target A1C and blood glucose target range (fasting and after meals).

Introduction

Optimal glycemic control is fundamental to the management of diabetes. Regardless of the underlying treatment, glycated hemoglobin (A1C) levels $>7.0\%$ are associated with a significantly increased risk of both microvascular and cardiovascular (CV) complications (1–3). The initial data from the Diabetes Control and Complications Trial (DCCT; type 1 diabetes) (2) and the United Kingdom Prospective Diabetes Study (UKPDS; type 2 diabetes) (3) demonstrated a curvilinear relationship between A1C and diabetes complications, with no apparent threshold of benefit, although the absolute reduction in risk was substantially less at lower A1C levels. Similarly, both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) are directly correlated to the risk of complications, with some evidence that PPG might constitute a stronger independent risk factor for CV complications (4–10).

Evidence indicates that improved glycemic control reduces the risk of both microvascular and CV complications. The initial prospective randomized controlled trials were conducted in people with

recently diagnosed diabetes. These trials—the DCCT in type 1 diabetes (11), the Kumamoto trial (12) and the UKPDS (1,13) in type 2 diabetes—confirmed that improved glycemic control significantly reduced the risk of microvascular complications, but had no significant effect on CV outcomes. Subsequent observational data from long-term follow up after termination of randomization periods of both the DCCT and UKPDS cohorts showed a persistence of significant microvascular benefits and also demonstrated an emergence of beneficial effect on CV outcomes attributed to intensive glycemic control. This has been termed as “metabolic memory” or “legacy effect” (14–16). In the DCCT cohort, there was a significant reduction in CV outcomes (42%), nonfatal myocardial infarct (MI), stroke and CV death (57%), as well as all-cause mortality (33%) in previously intensively treated participants compared with those who were previously in the standard arm (17–19). Similarly, there was a significant reduction in MI (15% to 33%) and all-cause mortality (13% to 27%) in the UKPDS cohort in participants who had been originally randomized to intensive treatment (16).

Whereas the UKPDS trial enrolled people with recently diagnosed type 2 diabetes, 3 major subsequent trials—the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT)—examined the effect of intensive glycemic control on people with long-standing type 2 diabetes. The ACCORD trial randomly assigned 10,251 participants who had either a previous history of cardiovascular disease (CVD) or multiple risk factors for CVD, and a baseline A1C level $\geq 7.5\%$ to intensive therapy targeting an A1C $<6.0\%$ or standard therapy targeting an A1C level of 7.0% to 7.9% (20,21). The mean age of participants was 62 years and the mean duration of diabetes was 10 years. A difference in A1C was rapidly obtained and maintained throughout the trial at 6.4% and 7.5% in the intensive and standard therapy groups, respectively. The primary composite major CV outcomes (nonfatal MI, nonfatal stroke or death from CV causes) were not reduced significantly in ACCORD (hazard ratio [HR] 0.90, $p=0.16$). The glycemic control portion of the trial was prematurely terminated after 3.5 years due to higher mortality (1.41% vs. 1.14% per year, HR 1.22) associated with assignment to the intensive-treatment arm (19,20). However, an observational follow up of the surviving ACCORD participants over a median of 8.8 years showed a neutral long-term effect of intensive glucose control on the composite outcome and all-cause mortality (HR 1.01, confidence interval [CI] 0.92–1.10) (22).

Conflict of interest statements can be found on page S44.

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A1C%	Targets for Glycemic Control
≤ 6.5	Adults with type 2 diabetes to reduce the risk of CKD and retinopathy if at low risk of hypoglycemia*
≤ 7.0	MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES
7.1 ↓ 8.5	Functionally dependent*: 7.1-8.0% Recurrent severe hypoglycemia and/or hypoglycemia unawareness: 7.1-8.5% Limited life expectancy: 7.1-8.5% Frail elderly and/or with dementia†: 7.1-8.5%
	Avoid higher A1C to minimize risk of symptomatic hyperglycemia and acute and chronic complications
End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia. * based on class of antihyperglycemic medication(s) utilized and the person's characteristics † see Diabetes in Older People chapter, p. S283	

Figure 1. Recommended targets for glycemic control.
A1C, glycated hemoglobin; CKD, chronic kidney disease.

The ADVANCE trial randomly assigned 11,140 participants to standard (targeting A1C based on local guidelines) or intensive glucose control therapy aimed at reducing A1C ≤6.5% (23). Participants were ≥55 years of age with a history of major CV or microvascular disease or at least 1 other risk factor for CVD. The mean duration of diabetes was 8 years. After a 5-year follow up, mean A1C was 6.5% in the intensive group and 7.3% in the standard group. The primary outcome was a composite of microvascular events (nephropathy and retinopathy) and CV disease defined by major adverse CV events. There was significant reduction in the incidence of major microvascular events in the intensive control group, mainly through a 21% relative reduction in nephropathy (23); however, no beneficial effect of intensive glucose lowering was found on major CV events or all-cause mortality either during the trial or the subsequent median observational follow up of 5.4 years (24).

The VADT randomly assigned 1,791 United States military veterans with a mean duration of diabetes being 12 years and with poor glycemic control (≥7.5%) to either standard or intensive glucose therapy, which aimed for an overall reduction in A1C levels by 1.5% (25,26). The mean duration of diabetes was 12 years and the A1C levels achieved in the standard and intensive therapy groups were 8.4% and 6.9%, respectively. During a median follow up of 5.6 years, there was a nonsignificant reduction in the primary outcome (first occurrence of a major CV event), but the progression to albuminuria was significantly reduced in the intensive-treatment participants, with 9.1% of participants having significantly reduced progression compared to 13.8% in the standard therapy group. However, during an observational median follow up of 9.8 years, the intensive-therapy group had a significantly lower risk of the primary outcome (MI, stroke, new or worsening congestive heart failure [CHF], amputation for ischemic gangrene, or CV-related death) than did the standard therapy group (HR 0.83, p=0.04), with an absolute reduction in risk of 8.6 major CV events per 1,000 person-years (27).

Data from a meta-analysis suggest that people with type 2 diabetes who receive intensive glucose lowering therapy have a reduced risk of the composite major adverse CV events (MACE) and MI, with

no significant effect on the risk of total mortality, cardiac death, stroke and CHF (28). Although an explanation for the unexpected higher mortality rates associated with intensive-treatment in the ACCORD study remains elusive (29), the frequency of severe hypoglycemia in these trials was 2 to 3 times higher in the intensive therapy groups and a higher mortality was reported in participants with 1 or more episodes of severe hypoglycemia in the ACCORD (30), ADVANCE (31) and VADT trials (25), irrespective of the different treatment arms in which individual participants were allocated. Therefore, it has been suggested that a tight glycemic control with a target A1C of 6.0% may not be ideal for older/frail individuals, those with longer duration of diabetes, advanced coronary artery disease (CAD) and a known history of severe hypoglycemia (32,33) (see Diabetes in Older People chapter, p. S283; Hypoglycemia chapter, p. S104). Higher glycemic targets are also appropriate for functionally dependent adults of any age or individuals with limited life expectancy and little likelihood of benefit from intensive therapy.

Evidence also supports the use of multifactorial risk-reduction strategies in addition to A1C control for CV prevention, including blood pressure (BP) and lipid targets; CV prevention medications; physical activity and other healthy behaviours; as well as smoking cessation (see Cardiovascular Protection in People with Diabetes chapter, p. S162). Such multifactorial interventions have recently been suggested to lead to not only significant microvascular and CV benefits but also mortality reduction in the 21-year follow up of the Steno-2 study (34). The salient results of this study include: increased survival for a median of 7.9 years; 8.1 years longer median time before first CV event; and reduction in all microvascular complications, except for peripheral neuropathy, for participants in the intensive-therapy group compared to the conventional therapy group.

A1C measurement encompasses a component of both the FPG and postprandial PG. In addition, mean glucose values also correlate with A1C in both type 1 and type 2 diabetes as shown in Figure 1 (35,36). When A1C values are higher, the major contribution is the FPG levels, but as the A1C value approaches the target value of ≤7.0%, there is a greater contribution from PPG values (37–39). Another

Table 1
Correlation between A1C and estimated mean glucose values

A1C values (%)	5.5–6.5	6.5–6.9	7.0–7.4	7.5–7.9	8.0–8.5
Estimated mean glucose (mmol/L)	6.2–7.7	7.8–8.5	8.6–9.3	9.4–10.1	10.2–10.9

A1C, glycated hemoglobin.

study using continuous glucose monitoring (CGM) demonstrated that a 2-hour PPG <8.0 mmol/L correlates best with an A1C <7.0% (40). In 1 study of forced intensified antihyperglycemic treatment in 164 participants with type 2 diabetes with A1C not at target ($\geq 7.5\%$), achievement of a target A1C <7.0% was associated with a FPG target of <5.5 mmol/L in 64% of participants, and a PPG target of <7.8 mmol/L in 94% of participants (38). In addition, several insulin treat-to-target trials have safely used dose titration protocols in individuals not at target A1C to reach lower than “traditional” FPG and PPG targets, including: FPG levels of 4.5 to 5.5 mmol/L in participants with type 2 diabetes (41,42); FPG levels of 4.0 to 5.5 mmol/L in participants with type 2 diabetes (43–46); FPG levels of 3.9 to 5.0 mmol/L in participants with type 1 diabetes (47), as well as protocols targeting both FPG levels of 4.5 to 5.5 mmol/L and 2-hour PG levels of 5.0 to 7.0 mmol/L in participants with type 2 diabetes (48).

However, a major challenge in attempting to use evidence-based observations to determine the value of tighter PPG control has been the lack of well-designed, long-term outcome studies where assessing PPG values is the major objective of the study. Most of the large outcome trials conducted so far have been mostly based on preprandial glucose and A1C targets, with limited evidence of a long-term benefit of targeting PPG alone (49,50).

Although, nontraditional glycemic targets, such as fructosamine and glycated albumin, have also been associated with CV outcomes and mortality in a cohort study (51), the broader utility of such targets and their correlation with A1C has not yet been established.

Finally, glucose variability (GV) as an additional therapeutic goal has recently been gaining support. Limited data support the possibility that GV is involved in the pathogenesis of vascular complications of diabetes by inducing inflammatory activation and oxidative stress (52,53). Key components of GV (variability in FPG and PPG, as well as hypoglycemia) have received some prominence in clinical literature recently, linking these components to diabetes complications. In a cohort of >5,000 people with type 2 diabetes, time-dependent variation of fasting glycemia was a strong predictor of all-cause and CV mortality (53). Specific clinical targets suggested in the literature for people monitored via CGM include minimizing daily glucose standard deviation (SD) (to less than 3 times the mean BG), maximizing time in range (3.9 to 10 mmol/L) and minimizing hypoglycemia duration, severity and frequency. However, management strategies that would minimize glucose variability and their impact on hard clinical outcomes remain to be determined before these novel measurement targets of glucose quality can systematically be incorporated into clinical practice guidelines.

Conclusions

Intensive glucose control with lowering A1C values to $\leq 7.0\%$ in both type 1 and type 2 diabetes provides strong benefits for microvascular complications and, if achieved early in the disease with avoidance of hypoglycemia and glucose variability as part of a multifactorial treatment approach, likely provide a significant CV benefit. More intensive glucose control, A1C $\leq 6.5\%$, may be sought in people with a shorter duration of diabetes and longer life expectancy, especially in those people who are on treatment with antihyperglycemic

agents with a low risk of hypoglycemia. An A1C target $\leq 8.5\%$ may be more appropriate in people with type 1 and type 2 diabetes with limited life expectancy, higher level of functional dependency and a history of repeated severe hypoglycemia with hypoglycemia unawareness.

RECOMMENDATIONS

- Glycemic targets should be individualized [Grade D, Consensus].
- In most people with type 1 or type 2 diabetes, an A1C $\leq 7.0\%$ should be targeted to reduce the risk of microvascular [Grade A, Level 1A (1,2,22,23)] and, if implemented early in the course of disease, CV complications [Grade B, Level 3 (23)].
- In people with type 2 diabetes, an A1C $\leq 6.5\%$ may be targeted to reduce the risk of CKD [Grade A, Level 1A (23)] and retinopathy [Grade A, Level 1A (21)], if they are assessed to be at low risk of hypoglycemia based on class of antihyperglycemic medication(s) utilized and the person's characteristics [Grade D, Consensus].
- A higher A1C target may be considered in people with diabetes with the goals of avoiding hypoglycemia and over-treatment related to antihyperglycemic therapy, with any of the following [Grade D, Consensus for all]:
 - Functionally dependent: 7.1%–8.0%
 - History of recurrent severe hypoglycemia, especially if accompanied by hypoglycemia unawareness: 7.1%–8.5%
 - Limited life expectancy: 7.1%–8.5%
 - Frail elderly and/or with dementia: 7.1%–8.5%
 - End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia.
- In order to achieve an A1C $\leq 7.0\%$, people with diabetes should aim for:
 - FPG or preprandial PG target of 4.0 to 7.0 mmol/L and a 2-hour PPG target of 5.0–10.0 mmol/L [Grade B, Level 2 (2) for type 1; Grade B, Level 2 (1) for type 2 diabetes]
 - If an A1C target $\leq 7.0\%$ cannot be achieved with a FPG target of 4.0–7.0 mmol/L and PPG target of 5.0–10.0 mmol/L, further FPG lowering to 4.0 to 5.5 mmol/L and/or PPG lowering to 5.0–8.0 mmol/L may be considered, but must be balanced against the risk of hypoglycemia [Grade D, Level 4 (38) for FPG target for type 2 diabetes; Grade D, Consensus for FPG target for type 1 diabetes; Grade D, Level 4 (38,40) for PPG target for type 2 diabetes; Grade D, Consensus for PPG target for type 1 diabetes].

Abbreviations:

A1C, glycated hemoglobin; BG, blood glucose; CGM, continuous glucose monitoring; CHF, congestive heart failure, CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; FPG, fasting plasma glucose; GV, glucose variability HR, hazard ratio; MI, myocardial infarct; PG, plasma glucose; PPG, postprandial plasma glucose.

Author Disclosures

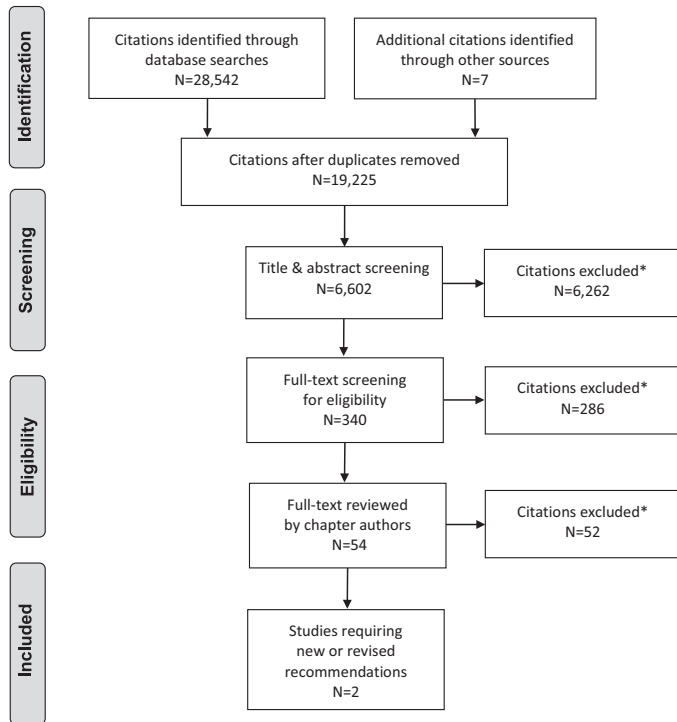
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Literature Review Flow Diagram for Chapter 8: Targets for Glycemic Control



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (54).

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