

Should A1C Targets Be Individualized for All People With Diabetes?

Arguments for and against

HWEE TEOH, PHD¹
 PHILIP HOME, DM, DPHIL²
 LAWRENCE A. LEITER, MD³

Diabetes guidelines and organizations typically advocate a target glycated hemoglobin (A1C) value of 6.5–7.0% but highlight that glycemic management must be individualized. Whereas individualization of both glycemic targets and management is appealing to the clinician as a way of potentially maximizing benefit while minimizing risk, there is little evidence that such an approach will bring more patients to target. It may be argued that this approach could contribute to fewer patients attaining optimal glycemic targets. Nonetheless, the results of recent large outcome trials clearly highlight the fact that individual glycemic target achievement varied markedly, with some patients apparently deriving more clinical benefit and others deriving more harm. At the same time, there is ongoing evidence of a treatment gap in many surveys of clinical practice and a suggestion that algorithm-driven protocols may be more effective. Collectively, therefore, the currently available evidence suggests that algorithm-driven protocols that incorporate individualized targets based on patient characteristics designed to preserve a sound balance between the benefits and risk of good glycemic control may be an appropriate way of getting more patients to target in a safe and effective manner.

Over 280 million people worldwide are known to have diabetes (1), and this number is projected to grow to 438 million by 2030 (2). Current diabetes treatment guidelines (3–9) encourage a multifaceted therapeutic approach (10,11). Central to these recommendations is early diagnosis and active intervention to realize and maintain glycemic control, with the aim of stopping the development of microvascular complications, reducing the risk of macrovascular events, and ameliorating the symptoms of acute hyperglycemia (7,10–17).

The prognostic significance of A1C in regard to the incidence of diabetes complications, and the risk reductions associated with improvements in A1C, have been documented in both type 1 (12,18) and type 2 (14–16,19) diabetes. These have led to the underscoring of the importance of A1C target achievement. Many organizations around the world including the American Association of Clinical Endocrinologists, the American Diabetes Association (ADA), the Canadian Diabetes Association, the European Association for the Study of Diabetes, the International Diabetes Federation, and the U.K. National Institute for Clinical Excellence currently advocate a general target level for A1C of 6.5–7.0% (3–9). They also all say that the targets of therapy must be

individualized. Recently, a joint position statement from the American College of Cardiology, ADA, and the American Heart Association released in response to the premature discontinuation of the glycemic intervention in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (20) recommended that although an appropriate A1C target is generally <7.0%, individualized glycemic targets may be appropriate for some patients. For example, they stated that higher A1C targets may be more appropriate for those patients who are older, have longer duration of diabetes, have a history of severe hypoglycemia, exhibit advanced microvascular or macrovascular complications, or present with extensive comorbidities. Others have noted that where glucose control closer to normal, or in the normal range, is easily attained, the care necessary to achieve it should be offered to the individual concerned (8).

The purpose of this article is to summarize the arguments made for and against target A1C individualization during a formal debate at the 3rd World Congress on Controversies to Consensus in Diabetes, Obesity, and Hypertension (CODHy). Given the significance of the topic, this document highlights the salient features of the opposing views while providing unified guidance on this important issue.

Individualization of glycemic targets appears to be logical, since it allows the vast majority of patients to derive the benefits of improved glycemic control while minimizing the potential harm. It should be recognized, however, that there is not much evidence that such an approach will bring more patients to target. In fact, it can be argued that in allowing for individualization of A1C goals in a real-world setting, it is possible that paradoxically fewer people overall may achieve their optimal glycemic targets. It may even be contended that the overall evidence for the potential benefits of improved glycemia are similar for most patient groups and that the potential “harm” of improved glycemia can be minimized by appropriate drug choices in

From the ¹Division of Cardiac Surgery, Keenan Research Center in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; the ²Newcastle Diabetes Center and Newcastle University, Newcastle upon Tyne, U.K.; and the ³Division of Endocrinology and Metabolism, Keenan Research Center in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

Corresponding author: Lawrence A. Leiter, leiterl@smh.ca.

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protocol-driven algorithms. Thus, removing the “flexibility” of individualized targets may increase the likelihood of getting people to target by removing the physicians’ excuse of not treating to target because of perceived “individual” patient needs.

INDIVIDUALIZATION OF A1C TARGETS

The argument for individualization can be traced to a number of observations. At its simplest, all clinicians in diabetes are aware of people (some on lifestyle alone, but some even on insulin therapy) who have A1C levels in the normal range, and certainly below target levels, without any special effort or lifestyle restriction and without overt or covert hypoglycemia. These patients are of course to be distinguished from patients who have lower levels as a result of obsession with tighter glucose levels or unusual fear of microvascular complications. Some of the former group with A1C levels in the normal or near-normal range may have abnormalities of A1C formation, but anyone in this category without problems should seemingly be allowed to so continue, provided the issue of covert hypoglycemia has been considered.

Naturally, blood glucose control is very tight, with short blood glucose excursions to a mean maximum of ~7.0 mmol/L (126 mg/dL) (21). This result is achieved by storing glucose as muscle glycogen, subsequently recycled to glucose through two-carbon intermediates and gluconeogenesis in the liver, losing ~30% of energy value in the process. That nature chooses to “waste” energy in achieving tight blood glucose control emphasizes the importance of that and provides a strong argument for emulating it clinically. Updated average A1C is linearly related to myocardial infarction well below normal target levels, and indeed such a relationship has been described within the normal range in a diabetic population (Fig. 1) (15,22,23). Although randomized controlled trial evidence does not exist, and probably cannot in the current state of glucose-lowering technologies, it is not unreasonable to presume on this epidemiological evidence that glucose lowering into the normal range may be beneficial in the absence of acute problems.

At the other end of the scale, clinicians are equally familiar with individuals who, for lifestyle reasons or problems with insulin therapy, find it difficult to achieve conventional target levels. Incidence of hypoglycemia or fear of hypoglycemia is

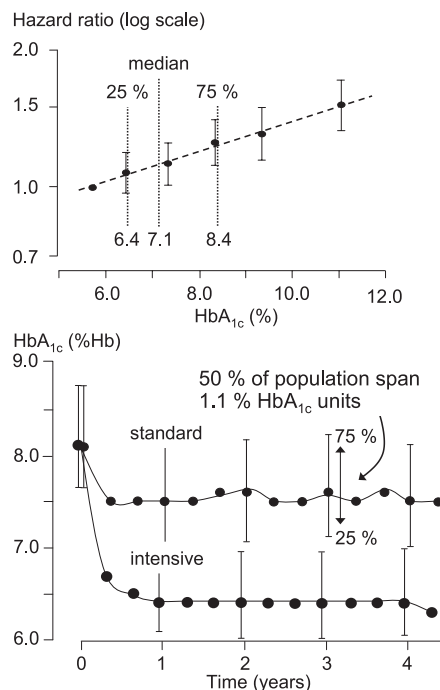


Figure 1—Data supporting individualization of targets. A: In nearly 50,000 people with diabetes in regular care in New Zealand, 50% were already achieving A1C <7.1% and 25% were achieving A1C <6.4%, suggesting that even current target levels are easily achieved in a high percentage of the treated population without special effort. B: In both arms of the ACCORD study, the range of A1C achieved around the mean was large, with over 50% of people outside an interquartile range of 1.1%. Because these study participants were under active management, this suggests that individuals can only achieve very different personal targets.

often a factor here, although other factors such as fear of weight gain are a factor for some. This reason for individualization has recently gained further attention because of the concerns arising from the results of the glycemetic intervention in ACCORD (24). This large study was of people at high risk for cardiovascular (CV) disease, being a mean of 62 years old, duration of diabetes of 10 years, and 35% known CV disease at baseline. The intensive strategy aiming for an A1C of <6.0% caused the study to be stopped prematurely after a median duration of 3.5 years because of a 22% higher mortality in this group, although the primary composite end point of CV death, nonfatal myocardial infarction, and nonfatal stroke was a nonsignificant 10% lower. It was feared by many that the increased mortality was a result of A1C levels being driven “too low” or “too quickly” and/or the result

of an about threefold increase in the risk for major hypoglycemia. The risk for mortality appeared to be greater with a prior history of CV event(s) or baseline A1C >8.0% (both not statistically significant), whereas a significantly reduced primary CV outcome was found in individuals with no history of a CV event and baseline A1C ≤8.0% (uncorrected $P = 0.04$ and 0.03).

Further analysis of ACCORD data has supported individualization of A1C targets. Thus, it appears that contrary to expectation, whereas hypoglycemia was higher in the intensively managed group, in both groups, more hypoglycemia was found at higher rather than at lower A1C levels (25). Hypoglycemia could not be found to be associated with risk of mortality (26). Furthermore, the death risk was associated with higher A1C and failure of the A1C to improve in the intensive group, with patients achieving lower A1C and falling to target levels faster doing better (27). This suggests that pursuing tight glucose control targets in those in whom it proves difficult to improve A1C is associated with higher death risk, even if insulin and oral agents are used appropriately.

This need for individualization according to what can be achieved is underlined by the actual A1C results in ACCORD (Fig. 1). In the standard therapy group, for example, <50% of participants were within the target range of 7.0–7.9% at any one time, with some below and some above (24).

Further support for this notion comes from the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release and Controlled Evaluation (ADVANCE) trial (28), which compared intensive management (target A1C ≤6.5%) versus standard control (local guidelines) in patients at baseline ≥55 years of age with mean A1C of 7.5% who were diagnosed with type 2 diabetes at ≥30 years of age and had a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease. Better mean A1C levels were noted at the end of the median 5-year follow-up in the intensive control (6.5%) versus the standard control (7.3%) group. However, whereas all-cause and CV mortality appeared to be relatively reduced by 22 and 25%, respectively, for every 1% reduction in A1C (29), patients in the intensive care group also demonstrated more severe hypoglycemic episodes (2.7 vs. 1.5%, hazard ratio 1.86, 95% CI 1.42–2.40, $P < 0.001$),

significantly more weight gain (0.7 kg difference, $P < 0.0001$), and higher incidences of any-cause hospitalizations (44.9 vs. 42.8%, $P = 0.03$) (28).

Similarly, in the Veterans Affairs Diabetes Trial (VADT) that monitored CV events after intensive glycemic control (A1C goal $\leq 6.0\%$) or standard glycemic control (A1C goal 8.0–9.0%) in subjects with suboptimal response to therapy for type 2 diabetes (30), median A1C achieved after a mean follow-up of 5 years was 8.4% for the standard control group and 6.9% for the intensive glycemic control group, with no difference in mortality and marginal significant differences only in renal outcome. However, improvements in the intensively managed group were accompanied by approximately three to four times more hypoglycemic episodes ($P < 0.001$), significant weight (4 kg) and BMI (1.5 kg/m^2) gain ($P = 0.01$), and more patients having at least one serious adverse event (24.1 vs. 17.6%, $P = 0.05$) (30,31).

Collectively, the results of the UK Prospective Diabetes Study, ACCORD, ADVANCE, and VADT have shown benefits of intensive glycemic therapy (14,16). At the same time, even within a research trial, individual glycemic target achievement varied markedly, with some patients apparently deriving more benefit and others deriving more harm. Whatever the drivers of this heterogeneity of clinical benefit/risk, attempting to shoe-horn individuals to a single target level seems to be neither wise nor efficient practice.

CONFORMITY OF A1C TARGETS

—Meta-analyses that include the results from ADVANCE, the UK Prospective Diabetes Study, VADT, and ACCORD have shown that, overall, intensive therapy is not associated with increased (or decreased) risk for mortality (16). Furthermore, there was a statistically significant 9% reduced risk for major CV events. Although this benefit was observed in subjects who lacked a history of macrovascular disease but not in subjects who had it, there was no heterogeneity in response to therapy based on other subgroups, including age, baseline A1C, and duration of diabetes. In addition, as noted above, achieving a low A1C was not associated with increased mortality, and there was no evidence that hypoglycemia accounted for the higher mortality in the intensive group. This should be taken to suggest that, for the majority of people with diabetes, tighter blood

glucose targets are desirable. The suggestion that the increased mortality observed in ACCORD is a reason to avoid good glycemic control in some patients is likely to be wrong.

Type 2 diabetes typically culminates in β -cell deterioration and dysfunction. Inasmuch as most of the current oral glucose-lowering agents do not prevent the progressive degeneration of β -cell function and that their efficacy depends on the integrity of some endogenous insulin secretion, most are unable to provide prolonged glycemic control, especially as the disease advances. As a result, periodic review together with timely adjustments and appropriate escalation of antihyperglycemic regimens to achieve target levels is imperative to meet therapeutic goals. Nonetheless, there is a body of evidence demonstrating that a persistent treatment gap is not uncommon when it comes to the glycemic management of people with diabetes. Indeed, many people continue to have A1C levels well above target, with unacceptable delays in titration and addition of antihyperglycemic agents, a phenomenon reiterating that the translation of clinical evidence to everyday practice continues to be challenging.

Today's guidelines not only generally have the proviso that patients who do not meet the A1C goal be followed every 2–3 months to enable adjustment of the ongoing treatment regimen, but also indicate that clinical judgment should be individually tailored (3–8). However, this case-by-case approach may not be the best practice tactic for the vast majority of patients, since the progressive nature of diabetes demands prompt and consistent therapeutic attention.

A well-controlled A1C of $< 7.0\%$ with oral monotherapy for up to 3 years is typically achieved by ~50% of type 2 diabetic patients (32–37). It has been suggested that this unsatisfactory outcome is partly the consequence of first-line therapy being begun only after A1C reaches levels higher than those at which the expected glucose-lowering from monotherapy could be expected to return glucose control to target levels (38). This result has been attributed in part to physicians—both specialists and those in primary care (39,40)—not being well prepared for early interventions and therefore often missing the critical window to launch effective management (35). Despite poor and worsening A1C, many people are kept on the same medications, thus aggravating their glycemic burden and risking worsening health

problems. Interestingly, a recent survey of awareness and attitudes in eight countries found that 51% of patients had never heard of A1C and that $>10\%$ of physicians measured it less than once a year (41).

Before the recent enhanced focus on more structured guidelines with specific recommended A1C targets, diabetes management with antihyperglycemic pharmacotherapy was often inadequate, with appropriate changes in medical regimens implemented only when A1C levels were $>9.0\%$ and/or several months to years after ascertaining that A1C readings were higher than acceptable (32–34,42). As a result of incremental treatment not keeping abreast with degenerating glycemic status (Fig. 2) and most individuals who managed to successfully achieve recommended A1C targets demonstrating an inability to maintain glycemic status, glycemic burden was unnecessarily extended in parallel with a substantial increase in CV risk (43). For example, Alvarez Guisasola et al. (44) reported that 26% of the 2,025 people that they monitored from seven European countries had an average A1C of 7.2% after 2.6 years of metformin-sulfonylurea or metformin-thiazolidinedione combinations. After 5 years, 20% of the 176 patients with A1C assessments were under control (mean A1C 7.4%), with 30% of this subgroup on insulin, resonating the often-observed temporal decline in glycemic management.

Poor glycemic management and the ensuing departure from A1C target levels are often attributed in part to clinical inertia and perhaps inappropriate individualization of glycemic targets. Although most people with type 2 diabetes will need insulin therapy to maintain A1C $< 7.0\%$ 9 years after diagnosis (37), there is substantial resistance to its introduction, both from patients (45) and physicians (46). In many cases, the lag in insulin initiation can present a challenging hurdle, especially when insulin becomes the next treatment option (44,47,48). Choice of treatment is also often influenced by patient characteristics. In a cohort of 253,238 subjects, physicians were more likely to initiate therapy modifications in response to poor control if the patient had higher baseline risk factor values and a history of coronary artery disease or end organ damage and were less likely to do so if the patient was of a minority group (49). Both appear to be inappropriate individualization. Similarly, hypertension (50), patient adherence (51), age (48), weight, sex (female), and

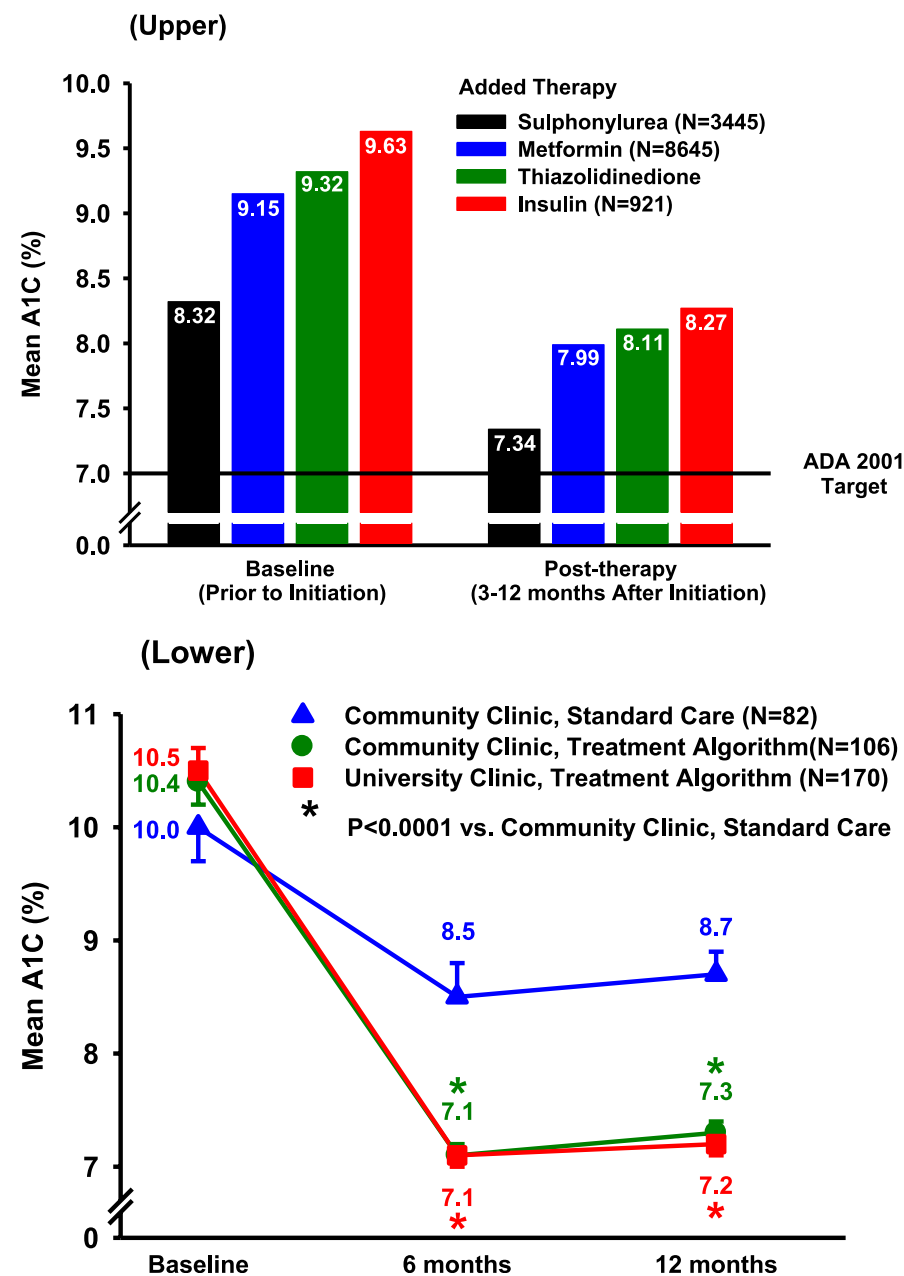


Figure 2—A: Change in A1C levels in adults with type 2 diabetes within 3–12 months after initiation of a new diabetes therapy. Of the 15,125 patients starting a new regimen, 81% (12,215) maintained their new therapy regimen without further change throughout the 3- to 12-month postinitiation observation window, without achieving target levels. Adapted from Karter et al. (38). B: Effect of community care vs. university care and standard “usual care” vs. treatment algorithm-driven therapy on A1C. Adapted from Fanning et al. (52).

duration of diabetes (13) increased the odds of therapy intensification.

In contrast to the ongoing treatment gaps in reaching glycemic targets, several, albeit nonrandomized and observational, studies suggest that the consistent use of treatment algorithms by both physicians and other health care workers may assist in bringing more patients to target. In comparing type 2 diabetes management

in three settings, Fanning et al. (52) reported that A1C goal realization (Fig. 2), fasting plasma glucose levels, and lipid profiles improved appreciably in nurse manager-directed algorithm-managed groups when compared with the usual care group. Lending further credence to this school of thought are results from another nurse-led diabetes management care program that was supervised by an endocrinologist

and that relied on detailed treatment algorithms based on current guidelines. Mean A1C fell to 8.7 from 9.3% in the year before entry into the program and to 7.0% by the end of the first management year ($P < 0.001$), at which point 60% fulfilled the ADA A1C target of $<7.0\%$ versus 28% at entry (53). Whereas this somewhat “non-individualized” algorithm-based approach appears to go against most physicians’ desire to provide individualized care to their patients, it seems plausible that an appropriate algorithm-driven approach coupled with tangible A1C targets may be quite effective in getting more patients to target.

PROS AND CONS—In summary, there is excellent clinical evidence that good glycemic control significantly reduces the risk of diabetes complications and particularly the microvascular complications. At the same time, stringent pharmacotherapeutic management to reach an A1C $<6.5\%$ or even 7.0% may be inadvisable or impractical in some patients. Treatment must therefore be individualized over time to maintain an appropriate balance between the benefits and risk of good glycemic control, taking into account the specific features of the patient (e.g., presence or absence of prior CV disease, duration of diabetes, etc.) and the agents used (e.g., risk of hypoglycemia).

It is also evident from the available data that a major problem in achieving targets continues to be persistent delays in appropriate use of oral agents and insulin. To ensure across the board attainment and maintenance of guidelines-recommended A1C levels, it would appear that physicians and other members of the health care team at all levels need to be presented with well-structured directives, with feedback and audit mechanisms that outline safe therapy intensification processes and do not allow them the excuse of “individualized” therapy.

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