A1C Targets Should Be Personalized to Maximize Benefits While Limiting Risks

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A set of guidance statements recently published by the American College of Physicians (ACP) advocates relaxation of goals for control of glycated hemoglobin (A1C) by people with type 2 diabetes (T2D) (1). This publication advises that "clinicians should reevaluate HbA_{1c} levels and revise treatment strategies on the basis of changes in the balance of benefits and harms." Specifically, it proposes reducing pharmacotherapy for any person when A1C is <6.5%, seeking a level between 7 and 8% for "most patients," and aiming only to minimize symptoms without any specific A1C goal for those over age 80 years or with chronic medical conditions likely to limit life expectancy. These recommendations are at odds with those of other professional organizations, including the American Diabetes Association (ADA) (2–5). We believe the ACP recommendations fail to consider several important bodies of scientific evidence, and if they are widely adopted in clinical practice, the recent progress in management of diabetes may be threatened. Each of the ACP's recommendations requires specific comments. These will be followed by a more general discussion of our concerns.

The ACP's main justification for decreasing therapy whenever A1C is <6.5% is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial's finding of ~20% increased mortality—mostly from cardiovascular (CV) events—when the median A1C attained by intensive treatment was 6.4% (6). However, this generalized advice does not acknowledge experience in other trials. In contrast to ACCORD, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (7) and the Veterans Affairs Diabetes Trial (VADT) (8), which similarly enrolled high-risk patients and sought A1C levels <7%, did not show increased short-term CV risk or mortality. Importantly, the newly diagnosed, low-risk participants in the UK Prospective Diabetes Study (UKPDS) also showed no tendency toward increased early mortality accompanying intensive therapy (9). Also, the participants in ACCORD who accounted for the increased risk with intensive therapy were not those who attained A1C <6.5% but rather those unable to reduce A1C even to 7% from an originally higher level (10). The CV harms of seeking A1C levels <7% in ACCORD were therefore neither replicated nor supported by epidemiologic evidence. They are also not relevant to management of the large numbers of patients with shorter-duration diabetes and low CV risk who already have attained A1C levels <6.5%.

Furthermore, the ACP guidance fails to appreciate the "legacy" effect of achieving good glycemic control early in the time course of T2D. Long-term observation of UKPDS participants with T2D shows that seeking near-normal glucose levels soon after diagnosis, when attainment of goals is easier, has beneficial effects on microvascular outcomes (retinopathy and nephropathy) that persist long after cessation of intensive therapy (11) and also CV benefits that can emerge 10 years later (11).

Keeping A1C <6.5% is a goal that can be attained with little risk of hypoglycemia or weight gain by many patients. Even without the use of recently developed glucose-lowering agents, which do not cause hypoglycemia and weight gain, participants with early T2D and high CV risk in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial were able to maintain near-normal A1C levels without harm (12,13). The T2D participants in ORIGIN, whose mean duration of diabetes was ~5 years, entered the trial with mean A1C ~6.5% while treated with lifestyle alone or supplemented by

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one oral agent. This level of control was maintained during 6 years of treatment with either conventional oral step-therapy or an insulin-based regimen. Hypoglycemia did occur more frequently in the insulin arm. As this is the most worrisome adverse effect of targeting near-normal glucose levels, the relationship between hypoglycemia and adverse outcomes was analyzed rigorously in this and other trials (14–17). None of these analyses provided convincing evidence that severe hypoglycemia is a cause as opposed to a marker of mortality risk in T2D. Finally, the therapy most widely used in early T2D is metformin, which not only does not induce hypoglycemia but in the UKPDS was associated with 39% lower risk of myocardial infarction and 36% lower risk of total mortality during randomized therapy (18). After 10 years of follow-up, reductions of risk for these end points were still significant at 33 and 27%, respectively (11).

In support of guidance to use 7 to 8% as a default target range, the ACP document cites the lack of CV benefit from 5–10 years of treatment in ACCORD, ADVANCE, and the VADT trials, all of which enrolled high–CV risk patients and sought A1C targets <7%. This emphasis on short-term, secondary intervention disregards the favorable long-term evidence from treatment of early T2D, described above.

Also, the harm postulated from seeking A1C levels <7% is based on concern about high-risk patients with long duration of T2D and other significant medical conditions. This concern seems most appropriate for those with serious CV disease, for whom the likelihood of future hypoglycemia may be increased (17). However, while high-risk patients are common in clinical practice, they are not "most patients." More than half (~60%) of the ~23 million adults in the U.S. with diagnosed diabetes in 2015 were younger than 65 years old and therefore likely to be relatively healthy (19). Another U.S. study found at least half (51%) of patients age 65 years or older to be relatively healthy (20). Thus, although setting a target range higher than 7% A1C—especially to avoid hypoglycemia—may be appropriate for many patients, there are large numbers of patients to whom this conservatism need not apply.

Another issue is whether the entire range between 7 and 8% proposed for most patients by the ACP's guidance is equally acceptable. In an epidemiologic analysis from the UKPDS, a person with an A1C averaging 7% was estimated to have 21% lower risk of any diabetes-related end point, compared with a person with an 8% average A1C, and crucially a 37% lower risk for microvascular complications (21). These and other analyses support the view that the lower the A1C attained by treatment of T2D, the lower the long-term risks of microvascular and CV events over a wide range of values (21).

For patients >80 years old or with limited life expectancy, a primary focus on avoiding symptoms due to hyperglycemia is appropriate. Nonetheless, there are other reasons to consider A1C levels in guiding therapy. Of greatest concern is the risk of worsening hyperglycemia progressing to life-threatening ketoacidosis or hyperosmolarity (22). In addition, marked hyperglycemia consistent with A1C >9% may be associated with lower self-reported quality of life (23), increased risk of painful neuropathy (24), and susceptibility to bacterial and fungal infections (25). Relaxing expectations for control of A1C in the patients with reduced life expectancy should not require dispensing with individualized glycemic goals.

The preceding comments on each of the ACP recommendations address the specific points raised by the authors of these guidelines. However, they must be placed in the context of a much larger body of evidence. The ACP statement focuses selectively on CV events versus other diabetes-related outcomes and highlights findings from the ACCORD trial while discounting those from many other glucose-lowering trials and their subsequent meta-analyses. It also does not consider the improved understanding of mechanisms underlying the complications from diabetes and the recently published large-scale outcome trials of specific glucose-lowering therapies. The ACCORD trial's finding that participants allocated to seek A1C <6% had higher mortality than those assigned to seek A1C between 7 and 8% has not been replicated in any other trial. A meta-analysis of the major glucose-lowering trials performed in low- and high-risk patients showed a neutral effect on mortality, a 9% reduction of CV outcomes, a 20% reduction of renal events, and 13% reduction in eye events (26). A second meta-analysis using slightly different methods obtained similar results (27). Somewhat longer follow-up of the VADT and ADVANCE confirmed reductions of CV events (28) and end-stage kidney disease (29), respectively. The only trial in T2D with follow-up extending beyond 10 years, the UKPDS, showed clear reductions of both microvascular and CV events long after intensive therapy was discontinued (11).

The short- and long-term benefits of seeking A1C <7% in the T2D trials are supported by the findings in type 1 diabetes (T1D) in the Diabetes Control and Complications Trial (DCCT) and its long-term follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Participants in DCCT had markedly reduced rates of microvascular complications during 6 years of intensive treatment (30), which persisted for many years in EDIC (31). Although no short-term CV effect was seen in the relatively healthy participants enrolled at a mean age of 26 years, long-term follow-up in DCCT/EDIC found reductions of 42% in CV events (32) and 33% in all-cause mortality (33) in the former intensive therapy arm. The "legacy effect" or "metabolic memory" from early improvement of glycemic control in both the UKPDS and DCCT/EDIC has been linked to the formation in tissues of advanced glycation end products (AGEs) that correlate with CV risk (34–36).

Taken together, these findings present a coherent picture linking hyperglycemia from the initial stages of diabetes to later complications, all of which can be reduced or prevented by effective glycemic control. Debate about the glucose hypothesis is essentially over: hyperglycemia is a modifiable risk factor (37–39). The isolated finding of increased short-term risk during intensive treatment in ACCORD is not the only relevant part of this body of evidence. Rather, all available information should be considered to assess the balance of risks to benefits (40).

Beyond the incompleteness of evidence from which the ACP recommendations were derived, there are more general limitations to the process used. The ACP's central aim appears to be the development of standardized guidelines for practice to simplify decisions for providers and allow assessment of guideline adherence in health systems. This approach has value, but it diverts attention from population-based efforts toward early

detection, early and effective intervention, and limitation of preventable sequelae of diabetes. Widespread use of A1C has greatly improved both our understanding of the need for population-based management and our ability to accomplish it. Relaxing the A1C targets for T2D could reinforce clinical inertia in diagnosis and timely advancement of therapy. Systematic undertreatment meant to limit risks may have unintended harmful consequences.

Everyone agrees that therapeutic goals and tactics should consider the needs and preferences of each patient. The ADA, along with other professional groups concerned with diabetes, has long advocated personalized therapy. The ACP's guidance, in contrast, describes individualization based on statistical risks implied by a few clinical and demographic factors. This is not a truly personalized approach, which should include an overall assessment of each patient's disease duration, life expectancy, comorbidities, capacities for self-care, and preferences regarding treatment options.

Withdrawing metformin treatment from a healthy, symptom-free, 30-year-old woman with T2D following prior gestational diabetes mellitus just because her A1C is <6.4% is not personalized therapy. Her hyperglycemic exposure over time could lead to serious consequences, including risks during future pregnancies and also long-term complications. With patients enjoying longer lifetimes thanks to improved overall care, even modest elevations of glucose over extended periods of time will substantially increase risks of vision-threatening retinopathy, kidney failure, neuropathy and amputations, and CV events. She herself should determine whether preventive treatment is unnecessarily burdensome and costly. For a vigorous gentleman with recently diagnosed T2D whose A1C is 8.5%, deciding not to repeat an A1C measurement because he is 80 years old is also not a personalized approach. In this setting, the risk of harm from ignoring possible progression to severe hyperglycemia is likely greater than that from seeking a conservative A1C goal. Adaptation of goals and therapeutic methods to individual patients' characteristics and wishes should go beyond one-size-fits-all guidelines.

A balanced assessment of both short- and long-term risks and benefits is needed. As emphasized in the ACP statement, the potential for harm by unnecessarily intensive treatment of vulnerable patients is a real concern. However, the statement does not fully address potential benefits in the short and especially the longer term. A standardized approach that denies early and effective treatment to patients whose risks are low is not supported by existing data and may increase rather than decrease overall risks versus benefits. Also, there is growing evidence that newer therapies such as the long-acting glucagon-like peptide 1 (GLP-1) receptor agonists (41,42) and the sodium–glucose linked transporter 2 (SGLT2) blockers (43,44), which were not available at the time of earlier trials, can reduce CV events and progression of kidney disease in high-risk patients within 5 years. The characteristics of patients who will benefit most from treatment with these new classes of drugs are still being evaluated, along with the potential risks of these agents. From what is known already about their CV effects, together with favorable effects on weight and lack of tendency to cause hypoglycemia, it is likely they will improve the risk-to-benefit ratio for many patients at high CV risk. Thus, the ACP proposal may encourage a step backward at a time when accumulating evidence from randomized controlled trials calls for movement forward in the treatment of diabetes.

Longer-term testing of established and newer therapeutic options may show how to optimize individualization of both goals and methods of therapy. For the present, we believe the ADA's current statement provides appropriately balanced guidance (2), which is generally consistent with that of other professional organizations (3–6). It suggests that "a reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol)," that "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," and that "less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate" for higher risk individuals.

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