

## JAMA Clinical Guidelines Synopsis

## Glycemic Control in Nonpregnant Adults With Type 2 Diabetes

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**GUIDELINE TITLE** Hemoglobin A<sub>1c</sub> Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

**DEVELOPER/FUNDING SOURCE** American College of Physicians (ACP)

**RELEASE DATE** March 2018

**PRIOR VERSION** September 2007

**TARGET POPULATION** Nonpregnant adults with type 2 diabetes

**MAJOR RECOMMENDATIONS**

- Personalize hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) goals for patients with type 2 diabetes based on discussions of benefits and harms of pharmacotherapy; patient preferences, health, and life expectancy; treatment burden; and costs of care.
- Aim for an HbA<sub>1c</sub> level between 7% and 8% in most patients with type 2 diabetes.
- Consider deintensifying pharmacologic therapy in patients with type 2 diabetes and HbA<sub>1c</sub> levels less than 6.5%.
- Treat patients with type 2 diabetes to minimize hyperglycemia symptoms and avoid targeting an HbA<sub>1c</sub> level in patients with a life expectancy of less than 10 years due to advanced age, nursing home residence, or end-stage chronic conditions.

**Summary of the Clinical Problem**

In the United States, type 2 diabetes affects 30 million people and is a major cause of morbidity and mortality.<sup>1</sup> Glycemic control has been shown to reduce diabetes complications, particularly for microvascular disease.<sup>2,3</sup> However, increasing recognition of adverse events due to intensive diabetes treatments has prompted major disagreements about optimal glycemic targets.

**Characteristics of the Guideline Source**

The updated guidance statement (Table) was funded by the ACP and developed by the ACP Clinical Guidelines Committee, composed of 12 clinicians and 2 nonclinician representatives with expertise in primary care, health care administration, and health services research.<sup>4,5</sup>

Potential conflicts of interest were disclosed and resolved prior to each meeting. The final guideline was revised based on peer review and online comments.

**Evidence Base**

The committee searched the National Guideline Clearinghouse and the Guidelines International Network library to identify English-language guidelines on HbA<sub>1c</sub> targets for the treatment of type 2 diabetes. Two guidelines were identified from the [National Institute for Health and Care Excellence \(NICE\)](#) and the [Institute for Clinical Systems Improvement](#). Committee members included 4 additional guidelines from the [American Association of Clinical Endocrinologists and American College of Endocrinology \(AAACE/ACE\)](#), the [American Diabetes Association \(ADA\)](#), the [Scottish Intercollegiate Guidelines Network \(SIGN\)](#), and the [Department of Veterans Affairs/US Department of Defense](#). Guidelines were rated on scope and purpose, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence.<sup>6</sup>

The committee also reviewed major studies that examined “treat-to-target” glycemic control strategies, including ACCORD,<sup>7</sup> ADVANCE,<sup>8</sup> UKPDS,<sup>2</sup> and VADT.<sup>3</sup> Recommendations were not graded on their strength or by level of supporting evidence.

**Benefits and Harms**

The ACP guidance statement recommends that clinicians personalize HbA<sub>1c</sub> goals by weighing the long-term benefits of more intensive HbA<sub>1c</sub> control (eg, fewer microvascular complications) against potential harms (eg, hypoglycemia, medication burden, and cost), patient preferences, life expectancy, comorbidities, and functional status.<sup>5</sup>

For most patients with type 2 diabetes, the ACP recommends an HbA<sub>1c</sub> target range between 7% and 8%.<sup>5</sup> Although the major trials found that more intensive glycemic control led to reductions in microvascular events, the ACP emphasizes that these reductions were in surrogate microvascular outcomes (eg, albuminuria) and that evidence of reductions in clinically significant microvascular outcomes (eg, end-stage renal disease) remains unclear.<sup>3,7,8</sup>

The ACP also recommends deintensifying pharmacologic therapy in patients with type 2 diabetes who have HbA<sub>1c</sub> levels less

Table. Guideline Rating

Rating Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline-systematic review intersection	Fair
Establishing evidence foundations and rating strength for each guideline recommendation	Poor
Articulation of recommendations	Good
External review	Fair
Updating	Poor
Implementation issues	Fair

than 6.5%, based on increased mortality among patients randomized to intensive treatments in ACCORD<sup>7</sup> and a greater risk of severe hypoglycemia without mortality benefit among patients randomized to intensive treatments in ADVANCE.<sup>8</sup>

For older patients with limited life expectancy, the ACP recommends that care be guided by symptoms rather than HbA<sub>1c</sub> goals.<sup>5</sup> The committee justified this recommendation by noting that intensive glycemic control in clinical trials did not demonstrate cardiovascular or mortality benefits until at least 10 years of follow-up.<sup>2,3</sup>

## Discussion

The 2018 ACP guidance statement is oriented to the potential harms and uncertain benefits of intensive HbA<sub>1c</sub> control.<sup>5</sup> These recommendations, with the exception of personalizing glycemic goals, are a substantial departure from existing clinical guidelines.

One major distinction is the recommendation to aim for HbA<sub>1c</sub> targets between 7% and 8% for most patients with type 2 diabetes. In contrast, 4 of the 6 evaluated guidelines recommend a general HbA<sub>1c</sub> goal of less than 6.5% or less than 7%. This disagreement potentially reflects differing perspectives of the guideline writers. Nationally representative data suggest that up to 70% of US adults have characteristics (eg, high comorbidity, preexisting diabetes complications, longer duration of diabetes) that limit the benefits of achieving HbA<sub>1c</sub> levels less than 7%.<sup>9</sup> Thus, the ACP guideline appears to take a population-based approach attuned to potential harm in the general US population with diabetes. In contrast, the ADA, AACE/ACE, SIGN, and NICE take more of an individual patient perspective and seek to minimize diabetes-related complications if possible (eg, the AACE/ACE guidelines advise that an HbA<sub>1c</sub> level less than 6.5% is considered optimal "if it can be achieved safely").

The ACP guidance statement adds to an important conversation about balancing the benefits and harms of intensive therapy. However, these recommendations could have unintended consequences. In the United States, younger adults with diabetes have the highest HbA<sub>1c</sub> levels and have the most to gain from intensive HbA<sub>1c</sub> control because of their long remaining life expectancy and the long-term benefits ("legacy effects") of lower HbA<sub>1c</sub> values.<sup>2,3,7</sup> A serious

concern is that clinicians may apply ACP recommendations to this group, which could lead to systematic undertreatment and worse outcomes for younger adults. Moreover, clinicians have little current guidance on maintaining HbA<sub>1c</sub> levels within a narrow range or safely deintensifying diabetes medications as patients age and develop comorbidities. It is likely that effectively communicating such medication changes to patients will be difficult because patients may be accustomed to tracking HbA<sub>1c</sub> levels and may prefer a proactive approach to diabetes management. More relaxed targets may also reduce the impetus to identify and treat adults with currently undiagnosed type 2 diabetes that is relatively early in its course.

In this era of individualized care, the ACP guidance statement reorients the tradition of glycemic goal setting by establishing higher HbA<sub>1c</sub> target ranges and explicitly recommending deintensification. It recognizes the importance of reducing adverse events in populations for whom there is unclear benefit and potential harm from intensive glycemic control; however, its recommendations may have unintended consequences for patients who are newly diagnosed, relatively young, and less likely to have major adverse effects from medications.

## Areas in Need of Future Study or Ongoing Research

High-quality, long-term randomized trials have improved knowledge of glycemic control in type 2 diabetes, but important gaps remain. Despite consensus that personalizing goals for glycemic control is important, little evidence exists for how to personalize goals consistently. Similarly, while protocols for deintensification are being developed, the long-term safety and benefits of deintensification are largely unknown. The intensity of glycemic and blood pressure control may be too narrow a focus for diabetes care, given the newer medications (ie, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists) that may have independent cardioprotective effects. A broader risk-benefit calculation based on clinical factors (glycemic control, blood pressure, dyslipidemia, tobacco use, renal function, duration of diabetes, medications) as well patient preferences regarding various risks and therapies may better determine personalized goals in the future.

## ARTICLE INFORMATION

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**Note:** Links to additional resources are available through embedded hyperlinks in the article text online.

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