Blood Sugar Control Limbo: How Low To Go?

New guidelines from the American College of Physicians recommend less stringent blood sugar targets for most people with diabetes. Other professional groups think that's a terrible idea.

By Sarah Kwon

Reasonable minds can differ, and interpreting clinical evidence is no exception to the rule. But the stakes are particularly high when interpretations differ on evidence for treating diabetes, a condition affecting 30 million Americans and costing $245 billion annually, the CDC estimates.

In March, the American College of Physicians (ACP) released a guideline recommending clinicians aim to achieve an HbA1c between 7% and 8% for most patients with type 2 diabetes. The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend HbA1c targets of less than 7% and less than 6.5%, respectively.

ACP, which represents internists, reviewed and ranked six national guidelines for treating type 2 diabetes on six criteria and concluded that its highest-ranked guidelines recommended less-aggressive targets than its lowest-ranked guidelines. The ADA and AACE/ACE guidelines scored the lowest, especially on editorial independence and scientific rigor. The ACP, in conjunction with the American Academy of Family Physicians, came out in favor of a less aggressive approach to blood pressure control last year after arriving at a similar conclusion about the blood pressure guidelines of specialty groups.

The ADA and AACE/ACE stand by their HbA1c recommendations. After the ACP published its guideline, the ADA issued a statement that said it is "deeply concerned" that the ACP guideline could increase complication rates for patients "who may safely benefit from lower evidence-based targets." The ADA said it reviewed the same evidence as the ACP did but decided that 7% is a "reasonable HbA1c goal for many nonpregnant adults with type 2 diabetes."

The ACP and ADA reviewed a similar crop of studies, including four that are among the most cited in the diabetes treatment literature: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), VADT (Veterans Affairs Diabetes Trial), and UKPDS (United Kingdom Prospective Diabetes Study), which technically is two studies. In those studies the average HbA1c attained for patients under intensive control ranged from 6.4% to 7.4%. "Standard control" ranged from 7.3% to 8.4%.

The ACP, ADA, and AACE/ACE don't disagree on everything. All three groups acknowledge intensive control carries the risk of causing hypoglycemia, which can lead to dizziness and fainting. But the ADA argues that research shows that intensive blood sugar control reduces microvascular complications (eye, kidney, and nerve diseases) over many years of treatment. The ACP says the results are more of a mixed bag and don't consistently support that conclusion. The ACP also contends that the studies don't show that intensive control reduces macrovascular complications (cardiac and vascular diseases). The ADA rates the evidence as mixed.

Another bone of contention is the two newer classes of diabetes medications, the SGLT2 inhibitors (Invokana [canagliflozin], Jardiance [empagliflozin], Farxiga [dapagliflozin]) and the GLP-1 receptor agonists (Victoza [liraglutide], Trulicity [dulaglutide],

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Bydureon [exenatide]). In the ADA's view, these achieve lower HbA1c levels and are less likely to cause hypoglycemia than other classes of diabetes medications. The ADA also sees evidence for the SGLT2 inhibitors and GLP-1 receptor agonists improving cardiovascular outcomes. When the ACP's guideline writers sifted through the evidence, they decided that the old standby, metformin, was still the best first-line medication for type 2 diabetes.

Adam Cifu, MD, a general internist at the University of Chicago who coauthors a *JAMA* clinical guidelines summary series, thinks different perspectives arising from treating different patient populations, rather than any kind of conflict of interest, drove the specialty society recommendations. "The endocrinologists are seeing the worst diabetes cases and thinking about diabetes 24/7," says Cifu. "Of course they're going to be more aggressive."

Pendulum swings

The notion of intensive glycemic control has been around for almost 100 years, beginning with the 1921 discovery that insulin injections reduced blood sugar in dogs. But it didn't become widely incorporated into clinical practice until 1993, when results from the NIH-funded Diabetes Control and Complications Trial (DCCT) found that intensive blood sugar control delayed the onset and slowed the progression of microvascular complications for patients with type 1 diabetes. Standard therapy involved one or two daily insulin injections, while patients in intensive therapy were administered insulin three times a day with a target HbA1c of 6.05%. Although the trial enrolled people with type 1 diabetes, many doctors were persuaded that the results were applicable to type 2 diabetes. But the optimum HbA1c level was far from a settled issue. The studies reviewed by the guideline writers for the ACP and the other professional groups were published over an 11-year period between 1998 and 2009 after the DCCT results came out.

In their 2015 book *Ending Medical Reversal*, Cifu and Vinay Prasad, MD, described a phenomenon of doctors jumping on the chance to use a new medication, procedure, or diagnostic test that doesn't have a lot of strong evidence behind it. Then, when persuasive evidence comes in that shows that the intervention doesn't help patients, or even harms them, they stop using it—or use it far less.

"I think medical reversal is like a pendulum, and originally, we maybe went too far in overtreating people [with diabetes]," says Cifu. "Then the data from [the ACCORD, ADVANCE, VADT, and UKPDS studies] pushed the pendulum back." But, Cifu adds, "The ACP guideline might swing the pendulum back too far to undertreating people." If an entire population of people with diabetes had an HbA1c of 8%, Cifu believes, complications would be more widespread.

As the guideline pendulum has swung, so have quality measures for diabetes. Minnesota Community Measurement (MNCM), a not-for-profit group funded in part by the Minnesota state government that convenes stakeholders and develops quality measures, has evolved its diabetes measures over time to reflect guideline changes. When MNCM first started measuring diabetes blood sugar control in 2007 as part of a diabetes measure bundle, it used an HbA1c level of less than 7% as a measure. Three years later, the organization changed it to less than 8%, taking its cue from the ACCORD results and the Institute for Clinical Systems Improvement guidelines.

Anne Snowden, director of performance measurement and reporting for MNCM, says the current evidence shows that an HbA1c target of less than 8% makes sense for diabetes patients. When it's appropriate, individual patients and clinicians can aim for more aggressive targets.

The ACP guideline recommends against quality measures that use HbA1c levels below 8% as a target and doing away with HbA1c targets altogether for adults older than age 80. CMS's star rating system for Medicare Advantage and prescription drug plans already uses a less-aggressive blood sugar control measure—HbA1c greater than 9%—and excludes enrollees over 75 years old.

Beyond MNCM, other prominent quality reporting

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TABLE Landmark type 2 diabetes studies evaluated in guidelines

	ADVANCE (2008)	ACCORD (2008)	
Baseline characteristics			
Sample	N=11,140, at least 55 years old, history of macrovascular or microvascular disease	N=10,251, between 40 and 79 years old with established CV disease or CV disease risk factors	
Mean or median baseline HbA1c	7.5%	8.1%	
Intervention	Gliclazide (modified release), plus other drugs as required to achieve target HbA1c (another part of the study, published separately, measured the effect of blood pressure interventions)	Varied; some patients received one medication or combination of medications. Metformin, rosiglitazone, and insulin were among the most common.	
Median follow-up	5 years	3.5 years; trial terminated early due to increase in all-cause mortality and CV-related deaths	
HbA1c target and level attained			
Standard therapy HbA1c	Target defined by local guidelines, 7.3% (attained)	7.0%–7.9% (target), 7.5% (attained)	
Intensive therapy HbA1c	≤6.5% (target), 6.5% (attained)	<6.0% (target), 6.4% (attained)	
Outcomes			
Microvascular	Reduced incidence of nephropathy (4.1% for intensive therapy group vs. 5.2% standard therapy group, *P*=.006)	Not reported	
Macrovascular	No significant effect	Lower rate of nonfatal myocardial infarction (3.6% for intensive therapy vs. 4.6% for standard therapy, *P*=.004)	
All-cause mortality	No significant effect	Increased rate of all-cause mortality (5.0% for intensive therapy vs. 4.0% for standard therapy, *P*=.04)	
CV-related death	No significant effect	Increased rate of CV-related death (2.6% for intensive therapy vs. 1.8% for standard therapy, *P*=.02)	
Risks	Severe hypoglycemia (2.7% for intensive therapy group vs.1.5% for standard therapy group, *P*<0.001) and minor hypoglycemia (120 events per 100 patients per year vs. 90 in standard therapy group)	3-fold risk of hypoglycemia, *P*<.001; 2-fold risk of >10-kg weight gain, *P*<.001	
Follow-up	A 6-year follow-up study found no difference in risk of death from any cause or major macrovascular events between the intensive and standard therapy groups.	One 9-year follow-up study found a neutral long-term effect from 3–4 years of intensive glycemic control on cardiovascular events and deaths and on all-cause mortality. Another follow-up study (5 years) found lower rates of myocardial infarction in the intensive therapy group compared with standard therapy.	

BMI=body-mass index, CV=cardiovascular.

	UKPDS 33 (1998)	UKPDS 34 (1998)	VADT (2009)
	N=3,867, newly diagnosed with type 2 diabetes, median age 54 years	N=1,704, subset of overweight patients from UKPDS 33 study	N=1,791, military veterans, mean age 60.4 years, suboptimal response to therapy for type 2 diabetes
	9.1%	Not reported	9.4%
	Sulphonylureas or insulin	Metformin. Study included another intervention group to test the effect of metformin against both conventional therapy and other medication therapies. The second intervention group received chlorpropamide, glibenclamide, or insulin.	Therapy varied based on patient BMI
	10 years	10.7 years	5.6 years
	7.9% (attained)	8.0% (attained)	<9.0% (target), 8.4% (attained)
	7.0% (attained)	7.4% (attained)	<6.0% (target), 6.9% (attained)
	12% lower risk among intensive therapy group compared with conventional therapy for any diabetes-related endpoint, *P*=.029, primarily due to 25% risk reduction in microvascular endpoints, including need for retinal photocoagulation, *P*=.0099	32% reduced risk among metformin group compared with conventional therapy for any diabetes-related endpoint, *P*=.002	No significant effect except on any increase in albuminuria: 9.1% for intensive therapy group vs. 13.8% for standard therapy, *P*=.01
	Not reported	Not reported	No significant effect
	No significant effect	36% reduced risk among metformin group compared with conventional therapy, *P*=.011	No significant effect
	No significant effect found for diabetes-related death	42% reduced risk for diabetes-related death among metformin group compared with conventional therapy, *P*=.017	No significant effect
	Hypoglycemia: 0.7% for standard therapy group vs. 1.0%–1.8% for intensive control group based on therapy, *P*<.0001; 2.9 kg mean weight gain for intensive therapy group compared with conventional therapy, *P*<.001	≥1 hypoglycemic attacks: 0% for metformin group vs. 0.7% for conventional therapy group vs. 0.3–2.5% for groups on other therapies	Adverse events (primarily hypoglycemia): 24.1% for intensive therapy group vs. 17.6% for standard therapy, *P*<.05
	A 10-year follow-up study found that relative reductions in risk persisted for any diabetes-related endpoint (9%, *P*=.04), microvascular disease (24%, *P*=.001), myocardial infarction (15%, *P*=.01), and death from any cause.	A 10-year follow-up study found significant risk reductions persisted for any diabetes-related endpoint (21%, *P*=.01), myocardial infarction (33%, *P*=.005), and death from any cause (27%, *P*=.002).	A 10-year follow-up study found a 17% relative reduction in major CV events compared with the standard therapy group (*P*=.04) but no significant improvement was seen in overall survival.

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programs also use an HbA1c standard of less than 8%. Examples include NCQA's health insurance plan ratings and the state of California's commercial health plan quality report card.

Looking beyond just HbA1c

Although, understandably, most of the attention has been on the differences between the ACP and specialty society guidelines, there are areas of agreement. The ACP, ADA, and AACE/ACE all recommend individualized HbA1c targets based on patient characteristics, such as hypoglycemia risk. Geisinger Health, an integrated health system in Pennsylvania, allows each provider to determine whether an individual patient's HbA1c goal should be less than 7% or between 7% and 8%.

While guidelines suggest using parameters such as age and comorbidities to determine patient-specific goals, finding the right HbA1c target for a patient means thinking about the individual person, says Brian Jameson, a Geisinger endocrinologist. "There are people with serious medical illnesses under 50 who might not be candidates for aggressive goals," he says. "You also don't want to say someone over 80 should never have an aggressive goal. There are sometimes people in that age group who are really active."

Nonclinical factors, such as a patient's financial status and willingness to partner on more challenging regimens, are other considerations, says Jameson, noting that Geisinger is looking into ways to audit patient-specific HbA1c goals to make sure they're being set appropriately.

"There are people with serious medical illnesses under 50 who might not be candidates for aggressive goals," says Brian Jameson, MD, of Geisinger. Others over 80 can be.

Patient empowerment, not just HbA1c levels achieved, have an influence on how well diabetes is ultimately managed, says Jennifer Schneider, MD, of Livongo Health.

Although setting an HbA1c goal requires careful consideration, Geisinger encourages a broader view, according to Jameson. It uses a nine-measure bundle to assess diabetes performance that, in addition to HbA1c measurement and control, includes such measures as blood pressure control, cholesterol management and control, and smoking status, he says.

Measurement is all-or-nothing, meaning care teams meet either all the measures or none of them. "There are nine things to pay attention to," says Jameson, "This allows you to be more aware of the entirety of the patient, and not just an A1c value."

Jennifer Schneider, MD, chief medical officer of Livongo Health, a digital health company that offers a chronic condition management platform, says successful diabetes management isn't determined by just clinical measurements but also by how empowered patients feel to manage their diabetes. The company, whose clients include six national health plans, invites all members to complete the diabetes-empowerment and diabetes-distress scales, which measure diabetes self-efficacy and diabetes-related emotional and social stress, respectively.

While the debate over optimal blood sugar levels likely won't end soon, Livongo and others will try to focus on the bigger picture. "A1c is a marker on a journey, not the destination," says Schneider. MC

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