HbA1c in CVD treatment: farewell to one size fits all

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March 2017—Anchor. Central pillar. Cornerstone. It would be hard to find a weighty synonym for "linchpin" that hasn't been used to describe HbA_{1c}'s role in diabetes diagnosis and management since 2010, when the assay was recognized by key standard-setting organizations as the equal of fasting glucose and oral glucose tolerance testing in diabetes and prediabetes testing.

But recognition of the complex nature of the relationship between HbA_{1c} and diabetes-related complications has influenced and modified HbA_{1c}'s clinical use as the test evolves. A new review article by experts in the field outlines how use of the HbA_{1c} test in cardiovascular disease treatment and prevention is trending toward a more patient-centered approach as the assay's intricacies are explored.

"Three decades after measurement of HbA_{1c} was introduced for clinical purposes, we are moving beyond one-size-fits-all A1c therapeutic targets in people with diabetes," M. Odette Gore, MD, tells CAP TODAY. She is coauthor of "A test in context: hemoglobin A1c and cardiovascular disease" in the Dec. 6 issue of the *Journal of the American College of Cardiology* (2016;68[22]:2479–2486). As the article notes, type 1 and type 2 diabetes are major independent risk factors for CVD.

In writing this article, Dr. Gore and her coauthor, Darren K. McGuire, MD (of the Department of Internal Medicine, UT Southwestern Medical Center, Dallas), sought to distill the most important aspects of the HbA_{1c} assay from the standpoint of cardiovascular disease. Dr. Gore, an assistant professor of medicine at the University of Colorado Anschutz Medical Campus and Denver Health Medical Center, sees room for clinicians to improve their understanding of HbA_{1c} assays. "Not all clinicians can afford the luxury of reading and digesting the vast amount of primary research published in this field, and this is where review articles can help," she explains.

By covering HbA_{1c}'s historical context and basic biology as well as the assay's limitations and its growing clinical evidence base, the authors hoped to shed light on the ways in which the interpretation of the assay has become increasingly complex. Their core subject is the importance of a patient-centered approach to HbA_{1c} and the clinical trials that have justified such an approach.

"We like to think that all clinicians who deal with A1c understand it very well, and no doubt they do when it comes to diagnosis. The issue of prognosis—and implicitly the issue of the most appropriate A1c therapeutic goals—is much more delicate," Dr. Gore says.

As she and Dr. McGuire point out, the 2012 position statement of the American Diabetes Association and European Association for the Study of Diabetes—reiterated in a 2015 update—represented a major shift from target-based recommendations to more nuanced, patient-centered treatment.

While the latest ADA guidelines still recommend an HbA_{1c} treatment target of less than seven percent for type 2 diabetes mellitus in non-pregnant adults, the authors note, it is now recognized that less stringent targets, such as HbA_{1c} of less than eight percent or even higher, may be more appropriate for some patients, such as those with a history of severe hypoglycemia and long duration of diabetes, extensive complications or multiple comorbidities, and moderate to severe cardiovascular disease.

Three major trials—ACCORD (Action to Control CVD Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease), and VADT (Veterans Affairs Diabetes Trial)—unequivocally support the statement that HbA_{1c} lowering per se is a poor marker of a therapeutic regimen's impact on cardiovascular risk and survival in type 2 diabetes, Drs. Gore and McGuire say. The most recent professional guidelines issued by the American Diabetes Association and

European Association for the Study of Diabetes reflect this position, Dr. Gore tells CAP TODAY, and should guide how clinicians use HbA_{1c}.

Clinicians should take into account several important patient differences in treating type 2 diabetes, Dr. Gore advises. “In no particular order, the most important are duration of diabetes, the presence of advanced microvascular or macrovascular complications, comorbid conditions, and the patient’s individual response to diabetes management and therapy, both in terms of glucose lowering and in terms of adverse effects such as hypoglycemia. And, of course, we always have to consider the patient’s own goals, preferences, and social support system.”

Drs. Gore and McGuire also note in their article that interference is a key issue for laboratories as well as clinicians to keep in mind. “A number of factors interfere with specific A1c assays and are very important to consider,” Dr. Gore says. “In particular, some assays may yield inaccurate results in patients with hemoglobin variants such as HbC, HbS, HbE, and HbD, as well as in those with elevated fetal hemoglobin. This should dictate the choice of assays in individual patients with known A1c variants, as well as in specific populations at higher risk of assay interference based on higher prevalence of hemoglobin variants.”

Those cautions aside, she says, the adoption of HbA_{1c} criteria to complement plasma glucose and the glucose tolerance test was a major step forward in the clinical space. The public health domain has also benefited, she says, “because it opens up new avenues for population-based research and community screening, without the need for fasting blood or OGTT.” HbA_{1c} assay standardization, which began in 1996 with the National Glycohemoglobin Standardization Program (officially renamed NGSP), was a key contributor to these advances. Without standardization of the assay, “we would not be talking about HbA_{1c} criteria and clinical recommendations,” Dr. Gore says, noting that standardization has probably made more of a difference for HbA_{1c} than for some other tests. Before standardization, “A1c assays had particularly low intra-assay and interassay reproducibility, resulting in significant disparities between the results reported by different laboratories or even by the same laboratory at different times.”

The ongoing research aimed at understanding the race-based differences in HbA_{1c} could have implications for differentiating diabetes management, Dr. Gore says. Particularly with cardiovascular outcome trials, “It would certainly be good to have more data from clinical trials adequately designed and powered to allow for analyses by race, since A1c lowering alone is a poor surrogate for macrovascular risk reduction.”

Could the field eventually unite around race-specific recommended HbA_{1c} cutoffs? That’s a move that would require wide consensus that cohort-specific cutoffs are biologically warranted and that their potential clinical benefits outweigh the risk, Dr. Gore says. “As of 2017, these matters are still quite controversial. I don’t have a crystal ball, but I would say it is entirely possible that we may move not to cohort-specific but to patient-specific cutoffs at some point this century.”
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