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VA-DoD Update of Diabetes Guidelines: What Clinicians Need to Know About Absolute Risk of Benefits and Harms and A_{1c} Laboratory Accuracy

In 2010, the VA and the DoD provided health care to more than 5 million veterans and more than 10 million active-duty personnel, dependents, and health care beneficiaries, respectively. It is estimated that 20% to 25% of veterans and 15% to 20% of active-duty military, dependents, and annuitants have diabetes. In 2000, the VA and the DoD agreed on a joint approach to the development of clinical practice guidelines (CPGs), including those for the care of patients with diabetes, with the goals of reducing practice variation; promoting use of best practices; and avoiding non–evidence-based metrics for self-assessment, performance measurement, and benchmarking. The VA-DoD CPG for the Management of Diabetes provides uniform medical practice recommendations for the 2 largest agencies that provide direct care in the federal health care system.

An independent review of diabetes guidelines published prior to 2006 in the United States, Canada, and the United Kingdom, using the "GRADE" instrument (based on grades of recommendation assessment, development, and evaluation) scored the guidelines of the VA-DoD and generalist professional societies higher than the guidelines of subspecialty professional societies.[1] The 2003 VA-DoD CPG for the Management of Diabetes[2] was noted for having an extensive discussion of comorbid conditions in setting glycemic targets.

The 2010 VA-DoD CPG for the Management of Diabetes, available online, is the product of a comprehensive review and update of the 2003 CPG conducted by subject matter experts in the VA and DoD.[3] There was an interdisciplinary (dieticians, nurses, pharmacists, and physicians) approach to identifying key questions and issues for potential revision, as well as to grading the evidence. In addition, the final draft guidelines were widely distributed to the clinicians and managers in the field, resulting in broad-based interactive review.

In this article, we review some of the key new or revised topic areas from the 2010 CPG and compare the recommendations with those from the 2011 American Diabetes Association (ADA) Clinical Practice Recommendations.[4] These topic areas include an emphasis on the understanding of the methodologic variability in A_{1c} tests to inform clinical interpretation of A_{1c} results; the use of A_{1c} values for diagnosis; the use of estimated average glucose (eAG) values to guide clinical practice; and the use of explicit risk-stratified A_{1c} target ranges rather than a single target applicable to many patients.

INTERPRETATION OF A_{1c} RESULTS

The correlation between glucose-based tests of glycemic control (such as, fasting blood glucose and oral glucose tolerance) and A_{1c} level is influenced by comorbid conditions as well as by age and race. For example, A_{1c} measurements are unreliable in the presence of hemolytic anemia, iron deficiency anemia, and severe chronic kidney disease. A_{1c} level is higher compared

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Table 1. VA-DoD diagnostic criteria for diabetes and prediabetes

A diagnosis of diabetes is made if the:

- A_{1c} level is ≥ 7% on 2 occasions using a clinical laboratory (not a point-of-care) methodology standardized to the NGSP; or
- A_{1c} level is ≥ 6.5% and the FPG level is ≥ 126 mg/dL. These tests can be done on the same day or on different days; or
- RPG level is ≥ 200 mg/dL on 2 occasions, or on 1 occasion if there are symptoms of hyperglycemia. However, RPG is not recommended as a routine screening test.

A diagnosis of prediabetes is made if the:

- FPG level is between 100 mg/dL and 126 mg/dL on 2 occasions; or
- A_{1c} level is between 5.7% and 6.4% and is confirmed with an FPG level between 100 mg/dL and 126 mg/dL. The FPG level can be obtained at the same time as the A_{1c} level.

FPG = fasting plasma glucose; NGSP = National Glycohemoglobin Standardization Program; RPG = random plasma glucose.

to glucose-based test results in older individuals without diabetes,[5] minority patients compared with white patients (as demonstrated in the Diabetes Prevention Program), and those with treated diabetes.[6]

In addition to these biological sources of non–glucose-dependent A_{1c} variation, A_{1c} values from any clinical laboratory have intrinsic variation among the available methods of measurement. Although this issue of variation is not addressed in the ADA Clinical Practice Recommendations, the VA/DoD Diabetes Guideline Working Group highlights it because of the influence it had on their consensus recommendations.

Variability of A_{1c} results among testing methods and laboratories has been monitored by the National Glycohemoglobin Standardization Program (NGSP) since the early 1990s. In 2007, the College of American Pathologists (CAP) began accuracy-based grading for A_{1c} using NGSP-assigned target values, and lowered the acceptable upper limit for proficiency testing to ± 7% for 2011 and 2012.[7] The variability in the performance of the A_{1c} test (intrinsic test methodology) includes both the accuracy—also referred to as bias—and precision—also referred to as the coefficient of variation (CV) (Figure). Based on the most recent CAP survey data, most NGSP-standardized A_{1c} testing methods have an inter-laboratory CV of < 5% (many are < 3%) and a bias of < 0.3% from NGSP target values.[7]

Because of measurement error, an individual result might be better understood as being within a range around the reported result. Therefore, if the patient is not at their target goal, the clinician should consider the likelihood that this is due to measurement error. These considerations also are critical in interpretation of change over time. It has been posed by laboratory experts that a change in A_{1c} of ≥ 0.5% should be deemed clinically significant.[8] This requires an assay CV of < 2%. Many, but not all current testing methods, meet this criterion. In particular, since point-of-care A_{1c} tests are Clinical Laboratory Improvement Amendments waived, the accuracy and precision at a site should be verified with the operator.

In summary, this information highlights the difficulty in comparing test results obtained from different laboratories, even within a single system of care. Therefore, the Working Group believes it is essential for clinicians to have knowledge of the accuracy and precision of the A_{1c} tests used at their own sites of practice, as well as any external laboratories that are utilized by their patients, in order to inform clinical treatment decisions

USE OF eAG

A_{1c} reflects average blood glucose over a period of time. The A_{1c} Derived Average Glucose study demonstrated a linear relationship between A_{1c} level and mean plasma glucose (MPG) level in patients with stable type 1 and type 2 diabetes.[9] For an A_{1c} level of 7%, the MPG level was 154 mg/dL, with a 95% confidence interval of 123 mg/dL to 185 mg/dL. Additionally, there was a trend toward racial differences that did not reach significance; the sample size of minority patients was small, however.

A subsequent study, using less rigorous methodology, demonstrated differences in MPG between white and nonwhite groups.[10] The ADA acknowledges a trend toward such differences but concludes that the overall linear correlation remains strong enough to justify reporting eAG results along with A_{1c} value.

After reviewing the same evidence, the Working Group does not recommend the use of eAG because of concerns that the wide confidence interval of the MPG values for a given A_{1c} level would limit its use in counseling individual patients. In addition, the Working Group is concerned that, given the still evolving evidence base on racial and ethnic differences between A_{1c} and glucose-based testing, the clinical significance of these findings requires more careful consideration.

Table 2. A_{1c} target recommendations, %

Major comorbidity[a] or physiologic age	Microvascular complications		
	Absent or mild[b]	Moderate[c]	Advanced[d]
Absent > 10 years of life expectancy	< 7	< 8	8-9[e]
Present[f] 5-10 years of life expectancy	< 8	< 8	8-9[e]
Marked[g] < 5 years of life expectancy	8-9[e]	8-9[e]	8-9[e]

[a]Major comorbidity includes, but is not limited to, any or several of the following active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.

[b]Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.

[c]Moderate microvascular disease is defined by preproliferative (without severe hemorrhage, intraretinal microvascular anomalies [IRMA], or venous bleeding) retinopathy, or persistent, fixed proteinuria (macroalbuminuria), and/or demonstrable peripheral neuropathy (sensory loss).

[d]Advanced microvascular disease is defined by severe nonproliferative (with severe hemorrhage, IRMA, or venous bleeding) or proliferative retinopathy, and/or renal insufficiency (serum creatinine level, > 2.0 mg/dL), and/or insensate extremities or autonomic neuropathy (for example, gastroparesis, impaired sweating, or orthostatic hypotension).

[e]Further reductions may be appropriate, balancing safety and tolerability of therapy.

[f]Major comorbidity is present, but is not end-stage and management is achievable.

[g]Major comorbidity is present and either is end-stage or management is significantly challenging.

DIAGNOSIS OF DIABETES AND PREDIABETES

The Working Group recommends that A_{1c} testing can be used to screen patients for prediabetes and diabetes, but, generally, does not recommend its use for diagnosis unless the A_{1c} level is ≥ 7% on 2 occasions (Table 1). This differs from the ADA recommendations, which state that an A_{1c} level between 5.7% and 6.4% may be used to diagnose prediabetes, and an A_{1c} level ≥ 6.5% on 2 occasions may be used to diagnose diabetes. Of concern is that, in the Diabetes Prevention Program, A_{1c} levels were higher among minority racial and ethnic groups compared with whites with impaired glucose tolerance.[3,4]

In weighing the implications of misdiagnosing diabetes from A_{1c} results alone (based on variability in clinical practice and racial–ethnic differences) vs the convenience of A_{1c} testing, the Working Group accepts A_{1c} as a screening tool but not as a diagnostic tool. Thus, they recommend using fasting blood glucose measurements to confirm a diagnosis of diabetes or prediabetes. One exception is when the A_{1c} level is ≥ 7% on 2 occasions, using a clinical laboratory test with acceptable precision and accuracy (not a point-of-care test), a diagnosis of diabetes may be made.

GLYCEMIC CONTROL TARGETS AND SHARED DECISION MAKING

The Working Group recommends a risk-stratified approach to setting A_{1c} targets based on shared decision making between clinicians and patients that focuses on life expectancy, comorbid conditions, complications, medications, and the absolute benefits and potential harms of treatment. Specific recommendations for A_{1c} target ranges—ranging from < 7% to < 9%—are offered, based on physiologic age or the presence/severity of major comorbidities and microvascular complications (Table 2).

This approach differs significantly from that of the ADA, especially up through 2010. In 2011, the ADA Clinical Practice Recommendations for glycemic control was revised to state that "a reasonable A_{1c} goal for many nonpregnant adults is < 7%" and notes that "less stringent A_{1c} goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions, and those with long-standing diabetes, in whom, the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin)."[4] However, the ADA does not provide an explicit definition of "less stringent" A_{1c} goals.

All groups developing guidelines must deal with the shortcomings of available evidence. In considering A_{1c} guidelines, there are no long-term studies of glycemic control in patients

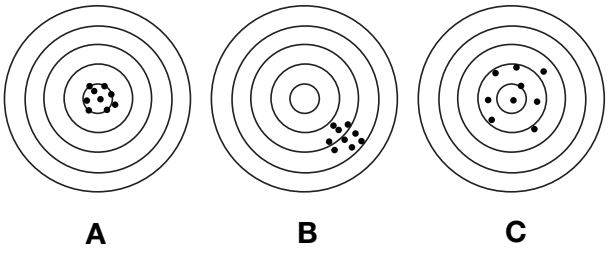
Clinical interpretation of single or sequential A_{1c} test results requires an understanding of the following terms:

Precision (coefficient of variation [CV])

This is a metric derived from quality monitoring. It is a measure of the amount of variation you might expect due to the measurement process in general (for example, if a patient's sample is run many times on the same day or if that specific sample is run on each of many different days). The CV is calculated as the SD expressed as a percentage of the average value of the quality control sample. Because the performance of the assay may not be uniform at all sample values, there may be different CVs for different measurement ranges (high, average, low).

Accuracy (analytic bias)

In clinical practice, a specific A_{1c} laboratory methodology may result in values that are consistently higher or lower than the A_{1c} "gold standard" (the National Glycohemoglobin Standardization Program-Diabetes Control and Complications Trial [NGSP-DCCT] standard). This laboratory reference standard is used for key clinical trials, upon which, guideline recommendations are made. Compared to the NGSP-DCCT standard, test results obtained from immunoassays tend to have a negative (results lower) bias, whereas, test results from high-performance liquid chromatography tend to have a positive (results higher) bias. As with precision, bias may vary across the different measurement ranges.



The concepts of accuracy and precision are illustrated in targets A-C. Target A is both precise and accurate (closely clustered and evenly distributed to the mark). Target B is precise but inaccurate (results are clustered but are off-center). Target C is both imprecise and inaccurate.

Total error

The total error combines both accuracy and precision, and is closely related to the probable error of a single A_{1c} laboratory test. The NGSP certification criteria for the 95% confidence interval of the differences between a method and the NGSP is ± 0.70%, based on quarterly monitoring of 10 samples from the highest quality laboratories. The acceptable limit for total error in the College of American Pathologists (CAP) GH2 Survey for 2011 and 2012 is ± 7%. It is difficult to directly compare the CAP and NGSP criteria. The most recent CAP GH2 Survey results for the evaluated laboratory methods are available on the NGSP Web site (http://www.ngsp.org/CAPdata.asp).

Figure. What clinicians need to know about A_{1c} laboratory measurement for clinical decision making.

who are elderly or who have multiple comorbid conditions. Thus, all such groups rely on consensus to some degree regarding the benefits and potential harms of a given recommendation.

While the ADA and VA-DoD considered the same studies, the Working Group explicitly considered the impact of A_{1c} reduction on the absolute risk reduction over the time course of the clinical studies to develop a tiered risk-stratification approach to A_{1c} target ranges and detailed life expectancies.

The United Kingdom Prospective Diabetes Study (UKPDS) showed clear benefit of glycemic control on microvascular complications over 10 years for patients with new onset type 2 diabetes treated with sulfonylurea or insulin, but not metformin, as initial therapy.[11] Patients receiving intensive treatment maintained an average A_{1c} level of 7.0% over the course of the study, with an A_{1c} level of approximately 7.3% in the final year; whereas, conventionally treated patients ended the study with an average A_{1c} level of 7.9%, and an A_{1c} level of approximately 8.3% in the final year. Most of the risk reduction achieved during the study was related to microvascular disease, primarily in the reduced need for retinal photocoagulation. The absolute risk reduction in microvascular events was approximately 3 per 100 persons treated over 10 years. The benefit on myocardial infarction over 10 years was of borderline significance (P = .052) for the sulfonylurea group.

A subgroup study of obese patients who received metformin as initial therapy demonstrated a 42% rela-

tive risk reduction in diabetes-related death and a 36% reduction in all-cause mortality, with an absolute risk reduction of 8 per 100 persons treated over 10 years.[12]

After the UKPDS ended, between-group differences in A_{1c} levels were lost in the first year following the study. Many of these patients were followed for up to another 10 years. The intensively treated patients continued to accrue mortality benefits even though their A_{1c} levels now were comparable to those in the original control group. There were 3.5 deaths per 1,000 patient-years (relative risk reduction, 13%; P = .007) and 7.2 deaths per 1,000 patient-years (relative risk reduction, 27%; P = .002) for the sulfonylurea and metformin groups, respectively. The absolute risk reduction in microvascular events was 3.5 per 1,000 patient-years in the sulfonylurea/insulin group and 1 per 1,000 patient-years in the metformin group.[13] Both the initial and follow-up UKPDS also indicate that metformin appears to be superior to sulfonylurea or insulin therapy in reducing cardiovascular mortality.

Based on the UKPDS,[11,12] the Working Group recommends aggressive treatment of diabetes early in its course for patients with a life expectancy of > 10 years. Patients with longer duration of diabetes (> 10 years) or comorbid conditions, and those who require combination medications (including insulin), should have an A_{1c} target of < 8%. In making this recommendation, the Working Group considered the fact that no study has maintained average A_{1c} values of < 7% for more than 9 to 10 years.[11] Therefore, the marginal benefit and risk of sustaining tighter control for longer periods of time is unknown.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD),[14] the VA Diabetes Trial (VADT),[15] and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[16] studies did not demonstrate a benefit of tighter glycemic control on cardiovascular disease. Intermediate outcomes, such as progression of albuminuria and retinopathy, were improved. The ADVANCE, ACCORD, and VADT results, while not directly applicable to the issue of further intensifying treatment to maintain tight glycemic control, raise concerns of possible harms if more intensive control is instituted in this population.

The Working Group's recommendation of maintaining A_{1c} values of < 8% in patients with longer duration of disease does not preclude A_{1c} targets close to or < 7% for patients who do not have significant comorbid conditions and have a longer life expectancy. Rather, it highlights that the target range for glycemic control should be individualized, based on the clinician's appraisal of the risk–benefit ratio, and should be incorporated into shared decision-making with each patient. The risk factors for the association of serious hypoglycemia and mortality, particularly in patients who also are receiving insulin, remain poorly understood. The Working Group's cautious approach has been supported by newer data demonstrating an association between serious hypoglycemia and morbidity and mortality in both the intensive and control arms of the ACCORD[17] and ADVANCE studies.[18]

Based on the lack of a clinically significant benefit in the VADT[15] (lowering A_{1c} from 8.4% to 6.9% over 5.6 years), the Working Group reasons that patients with advanced microvascular complications, major comorbidities, or shortened life expectancy (< 5 years) could maintain a target A_{1c} between 8% and 9%, especially if serious hypoglycemia is a concern. Finally, glycemic targets need not be whole numbers, since A_{1c} is a continuous risk factor. Indeed, given the variation in A_{1c} tests within and between laboratories, a target range is more appropriate. In addition, achieving A_{1c} goals should not occur at the expense of safety. Modest differences between a patient's achieved A_{1c} level and his/her target range may not have a significant impact on the long-term absolute risk reduction of complications, but may have a profound effect on the short-term risks for hypoglycemia. Goals can and should be modified (upward or downward) as clinical circumstances or patient preferences warrant.

The target range for glycemic control should be individualized, based on the clinician's appraisal of the risk–benefit ratio, and should be incorporated into shared decision making with each patient.

CONCLUSION

We have described some highlights from the evidence-based VA-DoD CPG for the Management of Diabetes—a comprehensive document de-

veloped as a guide for primary care providers regarding the diagnosis and management of patients with diabetes. Three areas of the CPG that we discussed here relate to the accuracy of laboratory tests, the absolute benefits and harms of treatment for different groups of patients, and the need for shared decision making in setting A_{1c} targets. We strongly encourage clinicians to join with their patients to consider their unique circumstances, events, and preferences within the context of available evidence when developing and implementing strategies to manage their diabetes. ●

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