



# Is HbA<sub>1c</sub> <7% a Marker of Poor Performance in Individuals >65 Years Old?

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In this issue of *Diabetes Care*, Pogach et al. (1) raise reasonable concepts of the dangers of hypoglycemia as a criterion for assessing glycemic control, but the authors suggest a performance measure pertaining to glycemic control of persons with diabetes with which we disagree. They propose an out-of-range measure of having either HbA<sub>1c</sub> <7.0% or HbA<sub>1c</sub> >9.0%, “for patients aged ≥65 years with diabetes and significant comorbid conditions taking antihyperglycemic agents other than metformin alone.” The presence of a “significant comorbid condition” was primarily driven by cardiovascular disease but also included persons with serum creatinine >1.7 mg/dL, cognitive impairment, diabetic retinopathy, major depression, and/or substance abuse. This out-of-range concept certainly merits discussion. Indeed, the notion has recently been put forward that HbA<sub>1c</sub> <7% is comparable to overuse of anticoagulation for atrial fibrillation, to inappropriate testosterone supplementation, and to opiate use after overdose (2). The strength of the suggested approach might be said to be its appearance of symmetry, given our recognition that excessive glucose lowering may be associated with adverse outcomes. We assert, however, that it is a fundamental

error to confound good control with hypoglycemia; the reality, we suggest, is that while hypoglycemia should certainly be considered an adverse outcome, it is not the achievement of glycemic control that is undesirable but rather the excessive use of hypoglycemia-causing treatments. Interestingly, the out-of-range measure showed inverse correlation with what Pogach et al. term the standard measure of HbA<sub>1c</sub> <8%. A total of 11.7% of the studied population had HbA<sub>1c</sub> >9%, but 35.7% had HbA<sub>1c</sub> <7.0%; those deemed by Pogach et al. to be out of range are, primarily, persons at an HbA<sub>1c</sub> level currently considered evidence of appropriate treatment.

Is there evidence that better glycemic control is undesirable for older persons with other medical conditions? Are those individuals with HbA<sub>1c</sub> <7.0% more likely than those with higher HbA<sub>1c</sub> levels to experience hypoglycemia and adverse outcomes? This idea appears to stem from an interpretation of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Veterans Affairs Diabetes Trial (VADT) studies, in which therapies were carried out to improve glycemic control without explicit efforts to avoid hypoglycemia. Although neither trial was restricted to

persons ≥65 years of age, in both trials the preponderance of enrollees had cardiovascular disease or were at high risk, with mean ages 62.2 and 60.4 years, respectively. Progression of diabetic retinopathy, explicitly mentioned by Pogach et al. (1) as a significant comorbid condition, was reduced by more than half among participants in ACCORD undergoing intensive rather than standard glycemic treatment (3). Furthermore, allocation to intensive rather than standard glycemic treatment in ACCORD significantly reduced myocardial infarction, coronary revascularization, and unstable angina, an effect explained by the reduction in HbA<sub>1c</sub> (4). It is noteworthy that a significant increase in mortality was seen only in the intensive intervention arm of ACCORD among persons with baseline HbA<sub>1c</sub> >8.5% (5); such individuals were less likely to have on-trial mean HbA<sub>1c</sub> <7%. Those randomized to intensive treatment who achieved lower HbA<sub>1c</sub> levels actually had lower mortality rates than the control group, while those whose on-trial HbA<sub>1c</sub> levels were higher were the ones whose mortality rates increased (6). Indeed, epidemiologic evidence suggests that hypoglycemia frequency only increases at relatively low HbA<sub>1c</sub> (below 6%), and there is

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also a trend to increased hypoglycemia frequency at HbA<sub>1c</sub> >9% (7), a pattern similar to that seen in ACCORD (8). The view proposed by Pogach et al. is further contradicted by the findings of recent cardiovascular outcome trials for empagliflozin (9), liraglutide (10), semaglutide (11), and (in an insulin-resistant nondiabetic population) pioglitazone (12). These trials included participants with mean ages 63.1, 64.3, 64.7, and 63.5, respectively, rather than being restricted to those ≥65 years of age. All showed evidence of improvement in coronary disease and/or stroke outcome with glucose-lowering agents having low intrinsic association with hypoglycemia, in persons with or at high risk of cardiovascular disease, for whom the proposed out-of-range measure would lead to less use of glucose-lowering treatments.

Of further importance is the recognition that HbA<sub>1c</sub> varies with erythrocyte kinetics (13). Conditions that artifactually lower HbA<sub>1c</sub> levels, such as the more rapid erythrocyte turnover seen in anemia (14), were not taken into account in the analysis reported by Pogach et al. (1). Renal insufficiency, even below the authors' creatinine cutoff of 1.7 mg/dL, also results in HbA<sub>1c</sub> levels below those typical of the prevailing blood glucose concentrations (15). By selecting only those persons with diabetes with "high-risk" conditions, the authors may have overselected those who would be expected to have such nonglycemic HbA<sub>1c</sub> lowering, increasing their inclusion in the "overtreatment" category. Such individuals would also be expected to have increased likelihood of adverse outcomes, leading to the conceptual error that appears to underlie the proposed out-of-range measure. In contrast, HbA<sub>1c</sub> increases with age for a given level of glycemia (16). We question the supposition by Pogach et al. that age per se represents a suitable marker of risk, given the evidence of increasing population life expectancy (17), even into the ninth decade (18). Comorbidities appear to us to be better predictors for both the risk of and the risk from hypoglycemia for a given individual (19) and should remind us to avoid agents likely to cause hypoglycemia.

The notion that hypoglycemia avoidance should be included in diabetes

treatment performance measure initiatives has been advanced (20), and we agree. However, we recommend more nuance and different cutoffs. Based on our reading of the literature, an HbA<sub>1c</sub> >8% is associated with poorer outcomes, even in populations at high cardiovascular risk such as those participating in the ACCORD (5) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (21) trials, so that would be our upper limit. For the lower limit, the real issue is hypoglycemia. Since ≤6.5% is considered the target in some guidelines (22) and <7% the target for most guidelines, we suggest that a lower cutoff of 6.5% only be used if the individual is taking medication likely to cause hypoglycemia. We do recognize that, in effect, Pogach et al. (1) are arguing that sulfonylureas have an undesirable association with hypoglycemia. This position has been firmly taken in the Comprehensive Type 2 Diabetes Management Algorithm of the American Association of Clinical Endocrinologists and American College of Endocrinology (22), and we would not be averse to considering the use of nonsulfonylurea hypoglycemic treatments as a "good performance" measure. As it stands, however, although it appears superficially attractive to have a "balanced" approach rejecting both low and high HbA<sub>1c</sub>, we would respectfully suggest that better control using specific approaches to avoid hypoglycemia is indeed better for the vast majority of persons with diabetes, including populations with cardiovascular disease and diabetic retinopathy such as those analyzed by Pogach et al.

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