Is HbA_{1c} <7% a Marker of Poor Performance in Individuals >65 Years Old?

Zachary T. Bloomgarden,[1] Daniel Einhorn,[2,3] and Yehuda Handelsman[4]

Diabetes Care 2017;40:526–528 | DOI: 10.2337/dci16-0043

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_{1c} <7.0% or HbA_{1c} >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_{1c} <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_{1c}, <8%. A total of 11.7% of the studied population had HbA_{1c} >9%, but 35.7% had HbA_{1c} <7.0%; those deemed by Pogach et al. to be out of range are, primarily, persons at an HbA_{1c} 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_{1c} <7.0% more likely than those with higher HbA_{1c} 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_{1c} (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_{1c} >8.5% (5); such individuals were less likely to have on-trial mean HbA_{1c} <7%. Those randomized to intensive treatment who achieved lower HbA_{1c} levels actually had lower mortality rates than the control group, while those whose on-trial HbA_{1c} levels were higher were the ones whose mortality rates increased (6). Indeed, epidemiologic evidence suggests that hypoglycemia frequency only increases at relatively low HbA_{1c} (below 6%), and there is

[1]*Icahn School of Medicine at Mount Sinai, New York, NY*
[2]*University of California, San Diego, San Diego, CA*
[3]*Scripps Whittier Diabetes Institute, San Diego, CA*
[4]*Metabolic Institute of America, Tarzana, CA*

Corresponding author: Zachary T. Bloomgarden, zbloom@gmail.com.

See accompanying articles, pp. 440, 444, 453, 461, 468, 476, 485, 494, 502, 509, and 518.

also a trend to increased hypoglycemia frequency at HbA_{1c} >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_{1c} varies with erythrocyte kinetics (13). Conditions that artifactually lower HbA_{1c} 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_{1c} 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_{1c} 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_{1c} 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_{1c} >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_{1c}, 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.

Duality of Interest. Z.T.B. has been a consultant/advisor for AstraZeneca, Johnson & Johnson, Merck, Intarcia, and Novartis; a speaker for Merck, AstraZeneca, and Johnson & Johnson; and is a stockholder in Allergan, Pfizer, Zimmer Biomet, and Novartis. D.E. has been a consultant for Eli Lilly, Novo Nordisk, Sanofi, Janssen, Adocia, Medtronic, Takeda, Halozyme, Freedom Meditech, Epitracker, Nexus BioPharma, Intarcia, and GlySens; has been involved with research for Eli Lilly, Novo Nordisk, Sanofi, MannKind, Janssen, AstraZeneca, Freedom Meditech, and Adocia; and is a shareholder in Halozyme, GlySens, Epitracker, Nexus BioPharma, and Freedom Meditech. Y.H. has received research grants and consultant and speaker honoraria from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Boehringer Ingelheim–Eli Lilly, Esperion, Grifols, GlaxoSmithKline-Hanmi, Intarcia, Janssen, Lexicon, Eli Lilly, Merck, Novo Nordisk, Pfizer, Regeneron, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

References

1. Pogach L, Tseng C-L, Soroka O, Maney M, Aron D. A proposal for an out-of-range glycemic population health safety measure for older adults with diabetes. Diabetes Care 2017;40:518–525
2. Morgan DJ, Dhruva SS, Wright SM, Korenstein D. 2016 update on medical overuse: a systematic review. JAMA Intern Med 2016;176:1687–1692
3. Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group; Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent effects of intensive glycemic control on retinopathy in type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On study. Diabetes Care 2016;39:1089–1100
4. Gerstein HC, Miller ME, Ismail-Beigi F, et al.; ACCORD Study Group. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet 2014;384:1936–1941
5. Calles-Escandón J, Lovato LC, Simons-Morton DG, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:721–727
6. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983–990
7. Lipska KJ, Warton EM, Huang ES, et al. HbA_{1c} and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes Care 2013;36:3535–3542
8. Miller ME, Bonds DE, Gerstein HC, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444
9. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
10. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
11. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
12. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic

stroke or transient ischemic attack. N Engl J Med 2016;374:1321–1331
13. Malka R, Nathan DM, Higgins JM. Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. Sci Transl Med 2016;8:359ra130
14. Ford ES, Cowie CC, Li C, Handelsman Y, Bloomgarden ZT. Iron-deficiency anemia, non-iron-deficiency anemia and HbA1c among adults in the US. J Diabetes 2011;3:67–73
15. Lo C, Lui M, Ranasinha S, et al. Defining the relationship between average glucose and HbA1c in patients with type 2 diabetes and chronic kidney disease. Diabetes Res Clin Pract 2014;104:84–91
16. Pani LN, Korenda L, Meigs JB, et al. Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. Diabetes Care 2008;31:1991–1996
17. Cao B. Future healthy life expectancy among older adults in the US: a forecast based on cohort smoking and obesity history. Popul Health Metr 2016;14:23
18. Broad JB, Dunstan K, Claridge A, Harris R. Am I too old for this, Doctor? Using population life expectancy to guide clinical decision-making. Australas J Ageing. 27 October 2016 [Epub ahead of print]. DOI: 10.1111/ajag.12355
19. Eldor R, Raz I. The individualized target HbA1c: a new method for improving macrovascular risk and glycemia without hypoglycemia and weight gain. Rev Diabet Stud 2009;6:6–12
20. Rodriguez-Gutierrez R, Ospina NS, McCoy RG, Lipska KJ, Shah ND, Montori VM; Hypoglycemia as a Quality Measure in Diabetes Study Group. Inclusion of hypoglycemia in clinical practice guidelines and performance measures in the care of patients with diabetes. JAMA Intern Med 2016;176:1714–1716
21. Zoungas S, Chalmers J, Ninomiya T, et al.; ADVANCE Collaborative Group. Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia 2012;55:636–643
22. Garber AJ, Abrahamson MJ, Barzilay JI, et al.; American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE). Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm–2016 Executive Summary. Endocr Pract 2016;22:84–113