Published in final edited form as:

JAMA. 2017 March 14; 317(10): 1017–1018. doi:10.1001/jama.2017.0029.

Is Hemoglobin A1C the right outcome for studies of diabetes?

Kasia J. Lipska, MD, MHS* and Harlan M. Krumholz, MD, SM†

*Section of Endocrinology and Metabolism, Department of Internal Medicine, Yale School of Medicine, New Haven, CT

†Section of Cardiovascular Medicine and the Robert Wood Johnson Foundation Clinical Scholars Program, Department of Internal Medicine, Yale School of Medicine, Department of Health Policy and Management, Yale School of Public Health, and the Center for Outcomes Research and Evaluation, Yale–New Haven Hospital, New Haven, CT

The goals of treatment of type 2 diabetes are to reduce the risk of diabetic complications and, as a result, improve the quality and, possibly, quantity of life. For several decades, authoritative guidelines instructed clinicians to strictly control glucose levels of patients with diabetes to accomplish these goals. In addition, in the 1990s, the FDA began to approve drugs for the treatment of diabetes based upon hemoglobin A1c (HbA1c) as the outcome. The prevailing belief was that risk reduction could be achieved by a clinical focus on reaching target values of HbA1c, agnostic to the strategies employed. This belief, analogous to early notions about lipid lowering, persisted despite the failure of trials evaluating tight glycemic targets to reduce the risk of heart disease or improve survival.¹

Results from recent cardiovascular outcomes trials of patients with type 2 diabetes are shifting this approach. In these trials, drugs that lowered HbA1c to similar levels had different effects on patient outcomes.^{2–6} For example, empagliflozin compared with placebo decreased cardiovascular events and mortality.⁵ Levels of HbA1c were similar between the groups because investigators were encouraged to adjust background therapies to achieve glycemic control according to local guidelines. Similarly, semaglutide compared with placebo lowered the risk of major cardiovascular events, despite minimal differences in HbA1c between the groups.⁴ The results imply that the type of drug used to achieve glycemic control matters, because the total effect of a drug is not entirely conveyed by its effect on glucose levels. As a result, the diabetes field is moving away from its historic reliance on surrogate markers and toward outcome studies to identify drugs that actually achieve the goals of diabetes care.

Evolving approaches

For many decades, glycemic control was a well-established primary objective in diabetes care, supported by basic clinical research and the results from the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS). Both of these key trials showed that more intensive glycemic control (HbA1c levels around 7%)

Corresponding Author Harlan M. Krumholz, MD, SM, 1 Church Street, Suite 200, New Haven, CT 06510, 203-764-5885; harlan.krumholz@yale.edu.

compared with standard treatment was associated with some improvements in outcomes for people with type 1 diabetes (DCCT) and newly diagnosed type 2 diabetes (UKPDS). At that time, prominent investigators wrote: “These studies have ended the argument about the benefits of lowering glucose levels in diabetes.”⁷ The question was simply how far to go with glucose lowering. However, these studies were conducted prior to the widespread use of cardioprotective therapies, such as statins and renin-angiotensin system inhibitors. Subsequently, three major clinical trials demonstrated that lowering HbA1c levels to below 7% was not associated with cardiovascular benefits compared with less intensive glycemic control.¹ Moreover, intensive glucose control had minimal, if any, effects on hard microvascular complications, such as vision loss or renal failure.¹ Around the same time, a meta-analysis indicated the possibility that a certain glucose-lowering drug (i.e., rosiglitazone) was paradoxically associated with increased cardiovascular risk. As a result, in 2008, the Food and Drug Administration (FDA) began to require post-approval trials that could reasonably exclude cardiovascular risk associated with new glucose-lowering agents.

The FDA guidance led to multiple large clinical trials designed to evaluate the effect of new drugs on major cardiovascular events. In contrast to studies designed to assess the effects of glycemic control on cardiovascular outcomes, these trials evaluated the effects of different strategies to achieve similar levels of glycemic control on cardiovascular outcomes. In order to do so, these trials compared a new agent versus placebo, but allowed adjustment of background glucose-lowering therapies according to local guidelines. Several of these studies revealed cardiovascular benefits for some of the new agents. For example, treatment with empagliflozin (an SGLT-2 inhibitor) and treatment with liraglutide (GLP-1 agonist) both significantly reduced the risk of major cardiovascular events, mortality from cardiovascular causes, and mortality from any cause when compared with placebo.^{4,5} Treatment with semaglutide, another GLP-1 agonist, conferred a lower risk of major cardiovascular events, but did not reduce cardiovascular or all-cause mortality.⁶ In contrast to these studies, several large trials of DPP-4 inhibitors showed non-inferiority in the rate of cardiovascular events with the use of these agents compared with placebo.^{2,3} One of the trials found a significantly increased risk of heart failure hospitalization with the use of saxagliptin.² In all of the trials, the effects of treatment on outcomes were out of proportion to the small differences in glycemic control levels. Therefore, the effects are likely unrelated to differences in the drugs’ glucose-lowering efficacy.

These trials reinforce the evolving approach in diabetes care: the need to assess outcomes other than HbA1c to understand the effect of glucose-lowering drugs. Based on these trials, the way in which glucose levels are reduced matters for the ultimate outcome on patients. Reliance on data with respect to glycemic control efficacy is not sufficient.

Asymmetry of the Evidence

The trials conducted as a result of the FDA guidance provide important evidence for treatment decisions in type 2 diabetes. However, similar evidence is lacking with respect to many other newer drugs, as well as older drugs approved before 2008.

Metformin is a widely recommended first-line treatment for type 2 diabetes, but the evidence about the cardiovascular effects of metformin is primarily based on a small subgroup of patients (n=342) in the UKPDS trial, conducted more than 2 decades ago. This level of evidence does not compare with the modern cardiovascular outcomes trials, which randomized thousands of patients with diabetes. Similarly, there are no cardiovascular outcomes trials for sulfonylureas, which along with metformin are the most common oral agents used by patients with type 2 diabetes.

There are similarly few data on the outcomes associated with the use of insulin in type 2 diabetes, despite multiple approved branded options. The exception is the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which reported no increase in cardiovascular events with the use of insulin glargine compared with placebo in patients with newly diagnosed type 2 diabetes or prediabetes, all of whom had mild elevations in HbA1c.⁸

As a result, evidence about cardiovascular safety of older and less expensive drugs is limited compared with the evidence about some of the newer and often branded options. One limitation of these trials is that the evaluation of complications of diabetes is focused on cardiovascular outcomes and little is known about the effect of the various drugs on microvascular outcomes, such as visual acuity, painful neuropathy, or renal failure.

Implications for Clinical Guidelines

Major clinical guidelines for treatment of type 2 diabetes still recommend therapy with a primary objective of reaching set glycemic targets. Although guidelines promote individualized glycemic targets for patients based on their comorbidities, propensity for hypoglycemia, and capacity to carry out the treatment plan, a more profound shift is needed.

Based on the recent trials, treatment should be selected to target specific complications and inherent risks, not solely glucose levels. Patients at high risk for cardiovascular disease may benefit from treatment with drugs that lower this risk. Setting an individualized glycemic target without accounting for the types and number of drugs needed to achieve it is no longer congruent with current evidence.

Similarly, quality measures based on reaching specific targets ignore the fact that the means of reaching an HbA1c level matter. The optimal glycemic control target will depend on patients' risk for complications, their preferences, and the strategy used to lower glucose.

Implications for Design of Trials

The FDA does not require post-marketing studies to ensure that drugs used for the treatment of type 2 diabetes do not increase (and hopefully reduce) microvascular events. In fact, the FDA advises that drugs that lower HbA1c levels can be “reasonably expected to reduce the long-term risk of microvascular complications” and, therefore “reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus.”⁹

Recent evidence suggests that this assumption may also not be valid. Any drug that lowers glucose levels may not predictably reduce the risk of microvascular complications. For example, empagliflozin reduced the risk of several kidney outcomes despite minimal differences in glycemic control between study groups. Semaglutide also improved nephropathy endpoints, but increased the risk of retinopathy. In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial (NCT01032629), the independent data monitoring committee identified an increased risk of leg and foot amputations associated with canagliflozin use, which is currently under investigation.

Trials that use outcomes based solely on glycemic parameters are no longer acceptable for clinical decision-making. Clinicians and patients need evidence about outcomes associated with different drug classes and likely with different agents within a class. Investments in pragmatic studies of existing agents are needed to understand the value of all treatment options.

Acknowledgments

Disclosures

Drs. Lipska and Krumholz work under contract to the Centers of Medicare & Medicaid Services to develop and maintain performance measures that are used for public reporting. Dr. Krumholz receives research support from Medtronic, Inc. and Johnson and Johnson (Janssen), through Yale University, to develop methods of clinical trial data sharing, and from the Food and Drug Administration and Medtronic, through Yale University, to develop methods for post-market surveillance of medical devices; chairs a cardiac scientific advisory board for UnitedHealth; is a participant/participant representative of the IBM Watson Health Life Sciences Board; and is the founder of Hugo, a personal health information platform.

Funding

Dr. Lipska receives support from the National Institute on Aging and the American Federation of Aging Research through the Paul Beeson Career Development Award (K23AG048359) and the Yale Claude D. Pepper Older Americans Independence Center (P30AG021342).

Role of the Funder

The funders did not have a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Rodriguez-Gutierrez R, Montori VM. Glycemic Control for Patients With Type 2 Diabetes Mellitus: Our Evolving Faith in the Face of Evidence. *Circ Cardiovasc Qual Outcomes*. 2016; 5:504–512. (1941-7705 (Electronic)).
2. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013; 369(14):1317–1326. [PubMed: 23992601]
3. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015; 373(3):232–242. [PubMed: 26052984]
4. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016
5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015; 373(22):2117–2128. [PubMed: 26378978]
6. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016

7. Abaira C, Duckworth W. The need for glycemic trials in type 2 diabetes. *Clin Diabetes*. 2003; 21:107–111.
8. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012; 367(4):319–328. [PubMed: 22686416]
9. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Dec. 2008 last accessed on November 8, 2016, available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf>