VIEWPOINT

Is Hemoglobin A_{1c} the Right Outcome for Studies of Diabetes?

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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, duration 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 US Food and Drug Administration (FDA) began to approve drugs for the treatment of diabetes based on hemoglobin A_{1c} (HbA_{1c}) levels as the outcome. The prevailing concept was that risk reduction could be achieved by a clinical focus on reaching target values of HbA_{1c}, agnostic to the strategies used. This concept, analogous to early notions about lipid lowering, persisted despite the failure of trials evaluating tight glycemic targets, as assessed by HbA_{1c} levels, 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 glucocentric approach. In these trials, drugs that lowered HbA_{1c} to similar levels had different effects on patient outcomes.[2-6] For example, empagliflozin and liraglutide compared with placebo decreased cardiovascular events and mortality.[4,5] Levels of HbA_{1c} were similar between the groups because investigators were encouraged to adjust background therapies to achieve glycemic control according to local guidelines. The results of these studies 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 historical reliance on surrogate markers and toward studies that assess outcomes such as heart disease and mortality to identify drugs that achieve the goals of diabetes care.

Evolving Approaches

For many decades, glycemic control was a well-established primary objective in diabetes care, supported by the results from the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS).[7] Both of these key trials showed that more intensive glycemic control (HbA_{1c} levels of approximately 7% of total hemoglobin) 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). However, these studies were conducted prior to the widespread use of cardioprotective therapies, such as statins and renin-angiotensin system inhibitors, and at a time when HbA_{1c} levels were generally higher than today. Subsequently, 3 major clinical trials demonstrated that lowering HbA_{1c} levels to less than 7% of total hemoglobin 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 (ie, rosiglitazone) was paradoxically associated with increased cardiovascular risk. As a result, in 2008, the FDA began to require postapproval trials that could reasonably exclude cardiovascular risk associated with new glucose-lowering agents.[8]

The FDA guidance led to multiple large clinical trials designed to evaluate the effect of new diabetes 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. To do so, these trials compared a new agent vs 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 (a sodium-glucose cotransporter 2 inhibitor) and treatment with liraglutide (a glucagon-like peptide 1 [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 dipeptidyl peptidase 4 inhibitors showed noninferiority in the rate of cardiovascular events with the use of these agents compared with placebo.[2,3] One trial found a significantly increased risk of hospitalization for heart failure 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 observed were likely unrelated to differences in the glucose-lowering efficacy of the evaluated drugs.

These trials reinforce the evolving approach in diabetes care: the need to assess outcomes other than HbA_{1c} levels 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 in patients.

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 that 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 also 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 HbA_{1c}.[9] 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.

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 with established cardiovascular disease and at high risk for recurrent events may benefit from treatment with drugs that lower this risk, such as empagliflozin and liraglutide. 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 HbA_{1c} level is important. The optimal glycemic control target will depend on patients' risk for complications, their preferences, and the strategy used to lower glucose levels.

Implications for Design of Trials

The FDA does not require postmarketing studies to ensure that drugs used for the treatment of type 2 diabetes do not increase (and instead hopefully reduce) microvascular events. In fact, the FDA advises that drugs that lower HbA_{1c} 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."[8]

Recent evidence suggests that this assumption may also not be valid, particularly in contemporary practice. 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 end points, but increased the risk of retinopathy. In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial (clinicaltrials.gov identifier 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 impact on outcomes of all treatment options.

ARTICLE INFORMATION

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