

Diabetes and Cardiovascular Disease: Does Lowering Hemoglobin A_{1c} Help or Harm?

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ABSTRACT: Conflicting data about the safety and effectiveness of intensive glycemic control have caused confusion over the best approach to cardiovascular risk reduction in patients with diabetes. A recent meta-analysis has helped reconcile these seemingly contradictory data. The optimal mechanism, speed, and extent of glycosylated hemoglobin reduction are different for differing populations. For patients with recently diagnosed diabetes, aggressive treatment will lower cardiovascular risk. In patients who have diabetes of more than 15 years' duration and are older and have other comorbidities, less aggressive treatment is indicated. For all patients, treatment of the dyslipidemia and hypertension that are associated with diabetes further reduces cardiovascular risk.

Key words: diabetes mellitus,
hemoglobin A_{1c},
cardiovascular disease

Case 1: Mr A. is a 55-year-old man who comes to your office for a routine physical examination. He is a traveling salesman and has recently gained weight. He does not exercise much and is a frequent visitor to fast-food establishments. His father had "a touch of diabetes" and died of a myocardial infarction (MI) at age 59. The patient says he feels fine and is able to work 60 hours a week without any difficulty. His body mass index (BMI) is 32, and blood pressure is 148/88 mm Hg (measured 3 times);

there are no other significant physical findings. Laboratory studies reveal the following values: fasting blood glucose (FBG), 136 mg/dL; hemoglobin A_{1c} (HbA_{1c}), 6.8%; low-density lipoprotein (LDL) cholesterol, 155 mg/dL; high-density lipoprotein (HDL) cholesterol, 32 mg/dL; and triglycerides, 233 mg/dL.

Case 2: Mrs B. is a 77-year-old woman with a 25-year history of type 2 diabetes mellitus. She is new to your practice. She recently moved to town to live with her daughter after her husband died 8 months earlier. You provide care to the daughter and her family. The patient has osteoarthritis and retinopathy and had an MI 7 years earlier. Her daughter thinks her mother is having some memory problems. Medications include metformin, 1000 mg bid; glipizide, extended release, 10 mg/d; atorvastatin, 10 mg/d; lisinopril, 10 mg/d; aspirin, 81 mg/d; and acetaminophen as needed. BMI is 26, and blood pressure is 127/64 mm Hg; diminished pedal pulses and sensory loss above the ankles bilaterally are noted. Laboratory studies reveal the following values: FBG, 176 mg/dL; HbA_{1c}, 7.8%; LDL-cholesterol, 145 mg/dL; HDL-cholesterol, 45 mg/dL; and triglycerides, 283 mg/dL. Serum creatinine level is 1.1 mg/dL. Glomerular filtration rate is higher than 60 mL/min/1.73 m², and the urine microalbumin/creatinine ratio is 120 µg/mg.

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How would you answer the following questions about these cases?

1. What HbA_{1c} goal would you try to help each of these patients achieve?
2. What is the value of reaching goal for HbA_{1c}?
3. What treatment options would you use to lower HbA_{1c} levels in these patients?
4. Would you consider other treatment options to lower cardiovascular risk in these patients?

In the United States, diabetes is the sixth leading cause of death; the most common cause of blindness, end-stage renal disease, and non-traumatic limb amputations; and a major contributor to cardiovascular disease (CVD).¹⁴ Cardiovascular events are responsible for 70% of the mortality and morbidity in persons with diabetes, and these patients have a 2- to 4-fold higher risk of CVD.^{5,6} Prevention of these complications is the major goal of diabetes care.

The risk of complications can be reduced by controlling the hyperglycemia, hyperlipidemia, and hypertension associated with diabetes. Two landmark studies, the Diabetes Control and Complications Trial (DCCT)⁷ and the United Kingdom Prospective Diabetes Study (UKPDS),⁸ provide excellent evidence that lowering HbA_{1c} levels to 7% or less reduces the incidence of retinopathy, neuropathy, and nephropathy (microvascular complications). For every 1% drop in HbA_{1c}, a 33% to 37% reduction in each of these microvascular complications occurs. In the initial UKPDS, a reduction in the incidence of CVD (macrovascular complications) was

observed, but it was not statistically significant.

HbA_{1c} REDUCTION AND CVD RISK: WHAT THE DATA SHOW

Benefits of intensive therapy. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, the original patients in the DCCT were followed for an average of 17 years. The patients in the intensive therapy group were no longer treated intensively, but they demonstrated a 42% reduction in risk of any cardiovascular event. The authors concluded that the initial 6.5 years of intensive treatment created a “metabolic memory” that provided some protection against CVD.⁹

The patients in the UKPDS were followed up for an additional 5 years after the initial data analysis, and no attempt was made to continue the initial intensive therapy. Within 1 year, HbA_{1c} levels were similar in the intensive and conventional treatment groups.

In the sulfonylurea-insulin arm of the UKPDS, reductions in risk of any diabetes-related end point (9%) and microvascular disease (24%) persisted after 10 years; risk reductions for MI (15%) and death from any cause (13%) emerged over time. In the metformin group, risk reductions persisted for any diabetes-related end point (21%), MI (33%), and death from any cause (27%). All of these end points reached statistical significance. The protective effect of early intensive therapy was called the “legacy effect” by the study authors.¹⁰ This study demonstrated the extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes, some of whom were followed up for up to 30 years.

Apparent drawbacks of intensive therapy. In 2008, when the results of the 10-year follow-up of pa-

tients in the UKPDS were released, 2 studies that contradicted the protective effect of lowering HbA_{1c}, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study¹¹ and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,¹² were published. The results of the ACCORD study seemed to indicate that reducing HbA_{1c} to lower or near-normal levels increased mortality. The study was stopped prematurely because of this finding. The ADVANCE investigators concluded that lower to near-normal blood glucose levels did not reduce cardiovascular events.

In January 2009 the Veterans Affairs Diabetes Trial (VADT) was published.¹³ This study concluded that intensive therapy in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications.

Weighting the evidence. Before making a clinical decision on the basis of these trials, consider that the patients in the UKPDS trials had *newly diagnosed* diabetes; moreover, they were younger and only 7.5% had a history of CVD. In the ACCORD and ADVANCE trials, 33% of participants had a history of CVD; they were 8 to 10 years older than the patients in UKPDS, and they had been treated for diabetes for 8 to 10 years. These were very different populations, and decisions need to be made with these facts in mind.

Results of a meta-analysis. In May 2009 a meta-analysis was published that reviewed 5 prospective, randomized, controlled trials (33,040 patients) to assess the effect of an intensive glucose-lowering regimen on death and cardiovascular outcomes compared with a standard regimen.¹⁴ The meta-analysis included the UKPDS, ACCORD, ADVANCE, and VADT. The authors concluded, “In-

tensive compared with standard glycemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed, and extent of A_{1c} reduction might be different in differing populations.”¹⁴

At the American Diabetes Association (ADA) meeting in June 2009, the lead authors of the ACCORD and VADT studies concluded that intensive glycemic control does not account for the increase in cardiovascular deaths.¹⁵ Rapid changes in glycemia, older age, and comorbidities—not low blood glucose levels—increased cardiovascular mortality in intensively treated patients. In the ACCORD trial, a decline in HbA_{1c} was associated with a lower risk of death. “Patients with the [consistently] lowest A_{1c} levels had the lowest risk. The excess mortality risk was in those patients who failed to achieve and sustain A_{1c} levels between 6% and 7%.”¹⁵

The VADT patient population was different from the ACCORD study population. They were older, were mostly male, and had poor glucose control despite optimal medical therapy. Risk reduction varied depending on the duration of diabetes. Patients with diabetes of 4 to 15 years’ duration had a 40% reduction in cardiovascular events. Patients with a longer history of diabetes and multiple comorbidities had a higher risk of death. Those with diabetes of more than 21 years’ duration had 2 times the risk of a cardiovascular event if they were in the intensively treated group.¹³

ANSWERS TO QUESTIONS ABOUT CASES 1 AND 2

1. What HbA_{1c} goal would you try to help each of these patients achieve?

If you are treating a patient with newly or recently diagnosed diabetes, such as the man in Case 1, the goal is clear. Take advantage of the legacy

effect and metabolic memory, and treat to a target HbA_{1c} as close to 6% as possible without placing the patient at risk. Reaching the goal should be accomplished at a reasonable pace.

The HbA_{1c} goal is higher in older patients with multiple comorbidities and diabetes of long duration, such as the woman in Case 2. Values of 7.5% and 8% may be more appropriate for them. Cardiovascular risk reduction can also be accomplished by treating the dyslipidemia and hypertension that are associated with diabetes.

Finally, some patients—especially those who have had diabetes for more than 10 years—may not be able to sense hypoglycemia. Thus, regardless of the HbA_{1c} goal, emphasize to the patient the importance of glucose monitoring when any unusual symptom develops. Teach the patient early in the disease process that what they feel may or may not be hypoglycemia and that blood glucose levels are the gold standard for detection.

2. What is the value of reaching goal for HbA_{1c} ?

We now have good evidence that lowering HbA_{1c} levels will decrease the risk of CVD, retinopathy, neuropathy, and nephropathy. An additional benefit of maintaining near-normal HbA_{1c} and glucose levels in patients with recently diagnosed type 2 diabetes may be preservation of the beta cell.

A sequence of metabolic events that eventually leads to type 2 diabetes may be present for 10 years before the appearance of an elevation in fasting blood glucose.¹⁶ Increasing resistance to the effects of insulin in muscle, the liver, and adipose tissue starts the process. The pancreas responds by secreting more insulin. Eventually, the beta cell is unable to secrete sufficient insulin to overcome the hyperglycemia of insulin resistance.

At the time of diagnosis, beta cell function may be decreased by 50% and there is a loss of beta cell mass as a result of cell apoptosis (cell death).¹⁷ The apoptosis is secondary to glucotoxicity, lipotoxicity, and inflammatory cytokines. Glucotoxicity is defined as beta cell damage produced by elevated levels of glucose for a prolonged period. Lipotoxicity results from elevations of circulating free fatty acids that are toxic to the beta cell. Insulin resistance at the level of the adipose tissue leads to excessive free fatty acid levels.¹⁷ Uncontrolled diabetes is also associated with an increased secretion of inflammatory cytokines from adipose tissue that may be toxic to the beta cell.¹⁷

Several drugs that are used to treat diabetes aid in preserving beta cell function. Studies with the thiazolidinediones (TZDs)^{18,19} and glucagon-like peptide 1 (GLP-1) agonists²⁰ indicate that they contribute to prolonged beta cell survival, unlike metformin, sulfonylureas, and insulin. As noted in the UKPDS, patients who used metformin and sulfonylureas lowered their HbA_{1c} levels to less than 7% (some to 6%) in the first year or so; but if no other agent was added, by year 8 levels were well above 8%. The TZD studies demonstrated the durability of the HbA_{1c} -lowering effect for up to 5 years.^{18,19}

3. What treatment options would you use to lower HbA_{1c} levels in these patients?

Two good guidelines for treating hyperglycemia and lowering HbA_{1c} are available:

- The ADA/European Association for the Study of Diabetes (EASD) consensus algorithm.²¹
- The Diabetes Road Map from the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE).²²

The ADA/EASD consensus algorithm provides a 3-step process to

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THE TAKE-HOME MESSAGE FOR PRIMARY CARE PRACTICE

It has been well known for some time that diabetes is associated with increased cardiovascular risk. On the basis of epidemiological studies,^{5,6} most clinicians felt that reducing HbA_{1c} would also lower cardiovascular risk. This was confirmed by the results of the DCCT/EDIC⁹ study and the UKPDS 10-year study.¹⁰ The patients in the DCCT/EDIC study all had type 1 diabetes, and those in the UKPDS 10-year study all had newly diagnosed type 2 diabetes. In both of these studies, the intervention group received intensive treatment only in the first 5 to 6 years of the study. This led to the theory that early intensive treatment creates protection against future complications. This protective effect was named “metabolic memory” in the DCCT/EDIC study and “legacy effect” in the UKPDS.

In contrast, results of 3 other studies, the ACCORD,¹¹ ADVANCE,¹² and VADT,¹³ suggested no benefit and potential harm from lowering HbA_{1c}. This created significant confusion for many clinicians. In May 2009 a meta-analysis that included all these studies found that intensive glycemic control reduced cardiovascular events without an increase in cardiovascular mortality. The authors of the meta-analysis cautioned that the optimal mechanism, speed, and extent of HbA_{1c} reduction are different in differing populations.¹⁴ The study groups for ACCORD and VADT reevaluated their data and discovered that patients in whom HbA_{1c} lowering had negative effects were older and had a longer duration of diabetes and comorbidities.¹⁵

The bottom line. The issues now seem to be clearer. For patients with recently diagnosed diabetes, aggressive treatment will lower cardiovascular risk. In patients who have had diabetes for more than 15 years and who are older and have other comorbidities, less aggressive treatment is indicated.

follow. It suggests starting with lifestyle modification and metformin and recommends making changes to the regimen if the HbA_{1c} level is 7% or higher. It lists some treatments as well validated and others as less well validated.²¹

The Diabetes Road Map²² from the ACE and the AACE is evidence-based and provides one road map if the patient is naive to therapy and another if the patient is currently being treated. The ACE/AACE goal for HbA_{1c} is 6.5% or lower. A helpful feature of this road map is the guidance it provides by level of HbA_{1c}. If the presenting HbA_{1c} is 6% to 7%, the recommendations are different from those for an HbA_{1c} of 7% to 8%.

Treatment plan for Case 1. This patient has newly diagnosed diabetes, so I would be aggressive in lowering his HbA_{1c} level to as close to normal as possible. Lifestyle changes and metformin are good initial choices for him and conform to both the ADA/EASD and ACE/AACE guidelines. But it is important to monitor him closely. As noted in the UKPDS, his decrease in HbA_{1c} may not last more than 2 to 3 years. If the HbA_{1c} rises, glucotoxicity and lipotoxicity may produce additional beta cell damage. A second drug should be added at this point. A sulfonylurea is the least expensive choice, and it will do an excellent job for another 2 to 3 years. The nega-

tive aspects of using a sulfonylurea include weight gain, hypoglycemia and, like metformin, no beta cell preservation. Another option included in both guidelines is to add basal insulin at this point.

As previously mentioned, TZDs and GLP-1 agonists will preserve beta cell function. But they are more expensive than sulfonylureas, and the TZDs are associated with weight gain. Once the HbA_{1c} begins to rise, these medications can be considered along with dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin.

Treatment plan for Case 2. This patient is older; has had a longer history of diabetes; has several comorbidities (retinopathy, nephropathy, neuropathy, and a previous MI); and may have dementia. Given the lessons learned from the ACCORD, ADVANCE, and VADT studies, I would proceed very deliberately with this patient and first get to know her. Because she has been living alone and recently lost her husband, she may be depressed. My initial treatment would focus on ensuring she is taking her medications and reinforcing lifestyle changes. I would also want to determine whether the memory problems are related to hypoglycemia. She has chronic renal disease and that will influence future medication decisions.

4. Would you consider other treatment options to lower cardiovascular risk in these patients?

The patient in Case 1 is at high risk for a cardiovascular event. In addition to his hyperglycemia, he has dyslipidemia (low HDL-cholesterol, high triglyceride, and high LDL-cholesterol levels) and hypertension. His triglycerides will decrease and HDL-cholesterol will increase with lifestyle changes and a reduction in his HbA_{1c} level. His LDL-cholesterol level may actually increase because it was calculated and a high level of triglyc-

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erides will create a lower calculated LDL.

I would prescribe a statin, an angiotensin-converting enzyme (ACE) inhibitor, and aspirin to reduce his cardiovascular risk. He may need additional drugs to achieve a goal of less than 100 mg/dL for his LDL-cholesterol, higher than 40 mg/dL for HDL-cholesterol, less than 150 mg/dL for triglycerides, and less than 130/80 mm Hg for blood pressure.

The patient in Case 2 is already taking a statin, an ACE inhibitor, and aspirin. She has had one significant cardiovascular event and has chronic renal disease. Her ideal goals are an LDL-cholesterol level of less than 70 mg/dL, an HDL-cholesterol level of more than 50 mg/dL, a triglyceride level of less than 150 mg/dL, and blood pressure of less than 130/80 mm Hg. After I get to know her better and see what effects lifestyle changes produce, I would consider increasing the dosage of the statin she is now taking. ■

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