Implications of Intensive Glycemic Control on Cardiovascular Disease: Early Reports From the ACCORD and ADVANCE Trials

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[Rev Cardiovasc Med. *2008;9(1):1-4*]

People with type 2 diabetes mellitus have greater risk of cardiovascular disease (CVD) than people without diabetes. Moreover, diabetes confers a 2- to 4-times increased risk of death from CVD.[1,2] Controlling glucose by lowering hemoglobin A_{1c} (HbA_{1c}) levels has been shown to reduce microvascular complications, such as diabetic nephropathy, neuropathy, and retinopathy. However, the benefit of intensive glycemic control in macrovascular complications has remained in question.

The goal of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was to provide definitive data on the effects of intensive glycemic control on CVD event rates in people with diabetes. However, the ACCORD researchers prematurely halted the intensive glucose arm of the trial because preliminary data showed that patients in this arm had higher overall mortality than patients

in the standard therapy arm. Preliminary results of the Action in Diabetes and Vascular Disease (ADVANCE) trial seem to contradict the ACCORD report; in ADVANCE, patients in the intensive glucose control arm did not have an increased mortality rate. Therefore, clinicians are now faced with the question of what level of glycemic control should be targeted to ensure CVD event reduction.

Hyperglycemia in diabetes has long been associated with microvascular and macrovascular complications. In the UK Prospective Diabetes Study (UKPDS), patients treated with an intensive therapeutic regimen experienced a significant long-term decrease in the adjusted incidence of microvascular complications of type 2 diabetes as compared with patients who received standard treatment. Each 1% reduction in HbA_{1c} was associated with a 37% decrease in the risk of microvascular complications.[3] Patients in the intensive-therapy group also experienced a reduction in the adjusted incidence of myocardial infarction, although their reduction of CVD-related mortality was only borderline significant. However, studies in patients with type 1 diabetes have shown a significant reduction in macrovascular disease over extended follow-up. The Epidemiology of Diabetes Interventions and Complications (EDIC) study—the long-term follow-up study of the landmark Diabetes Control and Complications Trial (DCCT)—found a 57% risk reduction of nonfatal myocardial infarction, stroke, and CVD death in patients with type 1 diabetes who received intensive glycemic control.[4] In a recent meta-analysis of randomized trials examining the impact of glycemic control on macrovascular disease in patients with type 1 or type 2 diabetes mellitus, researchers concluded that improvements in glycemic control modestly reduced the risk of macrovascular events in both types of patients.[5] Long-term follow-up in the Steno-2 trial showed that patients in the intensive glycemic control arm had a 13% absolute risk reduction of death from cardiovascular causes. A goal in the Steno-2 trial was to reduce HbA_{1c} levels to less than 6.5%. By the end of the study, however, average HbA_{1c} was 7.9% in the intensive therapy group and 9% in the control group.[6] Therefore, a major aim of the ACCORD trial was to determine if lowering HbA_{1c} to less than 6.0% in patients with type 2 diabetes would result in an additional significant reduction of cardiovascular events.

ACCORD

The ACCORD trial is a randomized, multicenter, 2 × 2 factorial study from the National Heart, Lung, and Blood Institute (NHLBI) designed to analyze how CVD events are affected by intensive glycemic control in patients with type 2 diabetes who have either known heart disease or at least 2 CVD risk factors in addition to diabetes. Patients were randomized to receive intensive glycemic control with a target HbA_{1c} level below 6.0% or to receive standard glycemic control with a target HbA_{1c} level of 7.0% to 7.9%. Within these 2 glycemic control arms, patients were then further randomized to test the benefits of raising high-density lipoprotein and lowering triglycerides, and of lowering systolic blood pressure to a target below 120 mm Hg. Preliminary reports from the NHLBI indicate that patients enrolled in the study were on average 62 years old, had an average duration of diabetes of 10 years, and had a baseline HbA_{1c} level of 8.2%.

The median HbA_{1c} level achieved was 6.4% in the intensive glycemic control arm versus 7.5% in the standard arm. Both groups experienced a lower CVD event rate than had been predicted based on earlier data on these rates drawn from observational and randomized clinical trials. However, the intensive glycemic control arm of the study was stopped because of an excess of 3 deaths per 1000 participants per year over an average of 4 years of treatment. The data showed 14 deaths per 1000 participants per year in the intensive glycemic control group versus 11 deaths per 1000 participants per year in the standard glycemic control group. Elizabeth G. Nabel, MD, director of the NHLBI, reported that there was a trend toward reduction of nonfatal CVD events in the intensive therapy arm, and that the death rate in both arms was lower than that in people with type 2 diabetes with similar CVD risk factors, in whom the risk of death is approximately 50 deaths per 1000 per year. The intensive glycemic control arm was stopped because the benefits were outweighed by the increased mortality. The lipid and blood-pressure arms of the study in the standard glucose control group will continue until the study ends as planned, in June 2009.[7]

ADVANCE

The ADVANCE trial is a randomized, controlled, multicenter, 2 × 2 factorial trial designed to examine the hypothesis that lowering blood pressure with a combination of angiotensin-converting enzyme inhibitors and diuretics (in both hypertensive and nonhypertensive patients) and intensive glycemic control with a sulphonylurea-based regimen in high-risk patients with type 2 diabetes reduces the incidence of macrovascular and microvascular disease. Following 6 weeks of treatment with an open-label perindopril-indapamide

combination, participants were randomized to a specific regimen of a perindopril-indapamide combination (initially 2.0/0.625 mg/d, increased to 4.0/1.25 mg/d after 3 months) or placebo, and then randomized to receive intensive gliclazide MR-based glycemic control, with a goal HbA_{1c} level of less than 6.5%, or local standard therapy. Participants in the ADVANCE trial are on average 66 years old, have an average duration of diabetes of 8 years, and had a mean HbA_{1c} level of 7.5% at baseline.[8] Primary outcomes of the study include the composite of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death, and the composite of new or worsening nephropathy or diabetic eye disease, with average duration of treatment and follow-up of 4.3 years.

Preliminary results indicate no difference in overall mortality between the 2 glycemic treatment arms, with final data pending because the study is just coming to an end. When the intensive glycemic control arm of the ACCORD trial was stopped, the investigators in the ADVANCE trial published a statement reporting on their preliminary data. The average HbA_{1c} level was 6.4% among patients in the intensive glycemic control group versus 7% among patients in the standard glycemic control group. There was no increase in mortality in patients who received the intensive treatment as compared with those who received the less intensive treatment.

Commentary

The preliminary data from the ACCORD and ADVANCE trials appear to be discordant with regard to the risk of mortality from intensive glycemic control. Participants in the intensive glycemic control arms of both trials achieved the same mean HbA_{1c} level of 6.4%. However, the 2 trials had different approaches to glycemic control: the ACCORD trial utilized a strategic approach with multiple different drug therapies, whereas the ADVANCE trial used a specific drug therapy. Other differences between the 2 trials were related to patient characteristics, with patients in the ACCORD trial having higher baseline HbA_{1c} levels and longer duration of diabetes compared with patients in the ADVANCE trial.

It is possible that if the intensive glycemic control arm of the ACCORD trial had been continued, then the higher mortality rate might have disappeared or even been reversed during follow-up. In addition, the higher mortality rate could have been related to adverse effects of a particular drug combination (although it was stated that no particular drug was responsible or linked to the higher mortality rate in the intensively treated group) or the intensity of the intervention. However, the discordance in mortality rates between these 2 trials cannot be attributed solely to the difference in drug therapies or the difference in patient characteristics, and without more data it is difficult to speculate on other potential reasons for the findings. As noted by the ADVANCE Management Committee Chair, John P. Chalmers, MD, PhD, more definitive analyses and reports from both studies are needed before we can draw any final conclusions.

Until final data and reports can be analyzed from the ACCORD and ADVANCE trials, what level of HbA_{1c} should clinicians target in this subset of patients? And beyond the specific level of HbA_{1c} to target, what conclusions can be drawn regarding glycemic control and CVD? Given the absence of definitive data, clinicians should continue to aim for an HbA_{1c} level of less than 7% in all people with type 2 diabetes, as per the American Diabetes Association guidelines. Investigators from the ACCORD trial suggest that an HbA_{1c} level "around 7%" may be more appropriate in patients with a similar profile to those in the ACCORD trial: patients with type 2 diabetes who are an average of 62 years or older, with duration of diabetes of 10 years or more, and with high CVD risk. The Steno-2 trial achieved significant reduction in CVD events with a reduction of HbA_{1c} from 9% to 7.9%, but, of note, more than 70% of the CVD risk reduction was accounted for by lipid reduction.[9] The conclusion may be drawn that people with type 2 diabetes benefit most from a combination of lipid reduction, blood pressure control, and glycemic control, rather than by achieving levels of HbA_{1c} less than 6.5% alone. Future analysis of the ACCORD and ADVANCE trials should examine the contributions of multifactorial intervention in order to shed light on the best approach to achieving CVD disease reduction in type 2 diabetes. ■

Given the absence of definitive data, clinicians should continue to aim for an HbA_{1c} level of less than 7% in all people with type 2 diabetes, as per the American Diabetes Association guidelines.

References

1. Barr EL, Zimmet PZ, Welborn TA, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation*. 2007;116:151-157.
2. Morrish NJ, Wang SL, Stevens LK, et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*. 2001;44(suppl 2):S14-S21.

3. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
4. Nathan D, Cleary P, Backlund JY, et al, for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.
5. Stettler C, Allemann S, Jüni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J*. 2006;152:27-38.
6. Goede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008; 358:580-591.
7. National Heart, Lung, and Blood Institute. ACCORD telebriefing prepared remarks. Available at: http://www.nhlbi.nih.gov/health/prof/heart/other/accord/index.htm. Accessed February 6, 2008.
8. ADVANCE Collaborative Group. ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline. *Diabet Med*. 2005; 22:882-888.
9. Gaede P, Pedersen O. Intensive integrated therapy of type 2 diabetes: implications for long-term prognosis. *Diabetes*. 2004;53(suppl 3):S39-S47.