

ease. When glycosylated hemoglobin values under 7% are the goal, clinicians will need to balance the incremental benefit of a reduction in microvascular events with the increased rates of adverse events; these patients may benefit from consultation with a specialist.

Neither the ADVANCE trial nor the ACCORD trial undermines the importance of meeting the current guidelines for care, and they should not be interpreted as diminishing the importance of glycemic control. The lower-than-anticipated rate of cardiovascular events seen in the intensive-treatment group and the standard-treatment group in these studies is an affirmation of the success of modern therapeutics, even when incompletely implemented. The results also underscore the difficulty of showing additional improvements in outcome, since care is progressively optimized. Clinicians caring for patients with diabetes should continue to focus on smoking cessation, dietary and exercise counseling, blood-pressure control, and providing aspirin and a statin to a greater extent than achieved even in the ADVANCE and ACCORD studies. For now, rather than changing our current glycemic target, we may best serve our patients with type 2 diabetes by implementing programs to help more of them reach the currently recommended goals.¹³

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Glycemic Targets and Cardiovascular Disease

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Cardiovascular disease in patients with diabetes is clearly associated with the degree of hyperglycemia, as measured clinically with the use of glycosylated hemoglobin.¹⁻³ However, there remains an unanswered question in diabetes management: Does the targeting of near normal levels of glycosylated hemoglobin reduce the rate of cardiovascular events? Randomized clinical trials that address this question are ongoing.

In this issue of the *Journal*, results are presented from two recently completed multicenter clinical trials, the ACCORD (Action to Control Cardio-

vascular Risk in Diabetes) trial (ClinicalTrials.gov number, NCT00000620)⁴ and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial (ClinicalTrials.gov number, NCT00145925).⁵ However, the two trials provide somewhat different results regarding glycemic control and cardiovascular events for patients with type 2 diabetes.

The ACCORD trial and the ADVANCE trial share a number of common features, and both were well designed and randomized. Both were

designed to evaluate the effects of intensive treatment for glycemic control on vascular outcomes in patients with type 2 diabetes who were considered to be at high risk. Both evaluated an intensive blood-glucose-control strategy, rather than a specific therapeutic regimen, to achieve glycemic targets at levels well below those that are currently recommended.^{6,7}

In the ADVANCE trial, intensive treatment was reported to produce a relative reduction of 10% in the primary composite outcome of major macrovascular and microvascular events, primarily as a consequence of a reduction in nephropathy (a microvascular complication). However, with respect to the fundamental question of the effect of glycemic control on macrovascular complications, there should be no misunderstanding that the ADVANCE trial had clearly negative results. Specifically, when major macrovascular events were considered separately, there was no observed significant reduction. This result does not diminish the importance of the trial, since negative findings are still vitally important in the assessment of the association between glycemic targets and cardiovascular disease. However, by virtue of the significant reduction in nephropathy, the ADVANCE trial extended our understanding of intensive glycemic control on microvascular events in patients with type 2 diabetes.

In contrast, in the ACCORD trial, the intensive-therapy group had an increased rate of death from any cause; differences in mortality appeared within 1 to 2 years and persisted during the follow-up period. Because of the increased mortality, the intensive glycemia treatment was discontinued 17 months before the scheduled end of the study, and the patients were switched to the standard glycemia regimen. A closer look reveals that for the composite primary outcome (i.e., major fatal or nonfatal cardiovascular events), there were no statistical differences between the two groups. Paradoxically, the data reveal that there were fewer occurrences of the composite primary outcome in the intensive-therapy group and that the rates began to separate after 3 years, favoring the intensive-therapy group, although the difference was not significant. However, there were inconsistencies in the direction of the components of the composite outcome. For example, the rates of death from any cause and from cardiovascular causes were significantly higher in the intensive-therapy group than in the standard-therapy group, but the rate of nonfatal myocardial infar-

tion was significantly lower in the intensive-therapy group. The rates of nonfatal stroke and either fatal or nonfatal congestive heart failure did not differ significantly between the two groups.

How can we explain the reported differences in clinical outcomes in these two trials? First, although the absolute levels of glycemia in the intensive-therapy groups in both studies were similar, the rate of reduction in glycated hemoglobin differed markedly. In the ACCORD trial, patients in the intensive-therapy group had a very rapid rate of decline in the median glycated hemoglobin level (an absolute decrease of 1.4% within 4 months). In the ADVANCE trial, the absolute decrease in the glycated hemoglobin level was 0.5% at 6 months and 0.6% at 12 months. Did the rate of decline in glycated hemoglobin contribute to the differences in reported cardiovascular outcomes between the two studies? Neither study was designed to address that question, which is left open to consider in future trials.

Second, although both trials used a very aggressive pharmacologic intervention, the strategies were different. In the ACCORD trial, the rate of use of the thiazolidinediones and insulin was much higher than that in the ADVANCE trial. In the ADVANCE trial, the intensive strategy was based on use of a specific sulfonylurea, glimepiride (modified release), in more than 90% of the patients. However, differences in drug use in the ACCORD trial did not provide an explanation for the differences in mortality.

Finally, weight gain differed during the course of each study. In the intensive-therapy group in the ACCORD trial, the mean weight gain from baseline was 3.5 kg, and a weight gain of more than 10 kg was reported in more than 27% of the patients. Surprisingly, in the intensive-therapy group in the ADVANCE trial, patients had a minimal weight gain of 0.7 kg, as compared with the standard-therapy group. The weight gain may not be a trivial point, since achieving glycemic control with such an aggressive drug strategy is clearly not equivalent to achieving such control through lifestyle changes (i.e., nutritional therapy and increased physical activity).

What are the implications of these studies for therapeutic guidelines for patients with type 2 diabetes? Both trials showed that targeting glycated hemoglobin levels that are below currently accepted standards in high-risk patients with type 2 diabetes did not have a beneficial

effect on cardiovascular disease. The current recommendations suggest the adoption of “individualized” goals for certain populations, noting that less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia.⁶ On the basis of the data presented, special consideration may now need to be given to high-risk patients with multiple risk factors and heart disease. A target glycosylated hemoglobin level of approximately 7% may be appropriate in this high-risk population, especially when the use of aggressive pharmacologic therapy is under consideration. As clearly stated by the investigators in the ACCORD trial, the potential existed for undetected adverse effects owing to an increased number of changes in drug regimens and an increased use of multiple drug classes and at increased doses.

Are the results of these studies broadly applicable to the treatment of the majority of patients with type 2 diabetes? Unfortunately, these studies did not address strategies for lowering of glycosylated hemoglobin levels in low-risk patients who did not have cardiovascular disease or additional cardiovascular risk factors. In the ACCORD trial, patients in the intensive-therapy group who did not have a history of a cardiovascular event or whose baseline glycosylated hemoglobin level was below 8% had significantly fewer fatal and nonfatal cardiovascular events than did patients at higher risk. These findings suggest that intensive therapy was beneficial at least in this subgroup. Whether achieving glycemic targets below 7% will be beneficial to the vast majority of patients with type 2 diabetes and a low risk of cardiovascular disease remains another unanswered question.

Thus, both studies are important contributions to the field but do not provide a definitive answer to the problem of glycemic control and cardiovascular disease. Other ongoing clinical trials will provide additional clarification.⁸⁻¹¹ It will be important to have all trials completed so that the entire body of work can be reviewed. At

that time, we will have substantially more medical and scientific data on which to base such treatment decisions.

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Neuroblastoma — Linking a Common Allele to a Rare Disease

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Neuroblastoma has a notorious reputation among solid tumors of childhood because of its frequently massive and widespread tumor burden. Yet stage for stage, this embryonal neoplasm of the

sympathetic nervous system has become the most curable of the common pediatric solid tumors.¹ More than 90% of patients with localized neuroblastomas, including those with spread to the re-