

## EDITORIALS



## Intensive Glycemic Control in the ACCORD and ADVANCE Trials

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Diabetes is associated with a reduced lifespan, largely as a consequence of cardiovascular disease.<sup>1-3</sup> Although diabetes significantly increases the risk of cardiovascular events,<sup>1</sup> the relative increase in events for each percent increase in glycated hemoglobin is modest.<sup>4</sup> Microvascular complications of diabetes remain the leading causes of blindness and renal failure in the developed world and are much more closely associated with hyperglycemia than with macrovascular complications.<sup>4</sup>

Though there is a link between hyperglycemia and cardiovascular risk, there is less evidence that glucose lowering is associated with reduction in risk. Patients with type 2 diabetes whose glycated hemoglobin levels were reduced from 8 to 7% in the United Kingdom Prospective Diabetes Study (UKPDS) did not exhibit a reduction in cardiovascular events, although a subgroup of patients treated with metformin had a lower risk of cardiovascular events.<sup>5</sup> Among patients with type 1 diabetes studied in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), glucose lowering was associated with a long-term benefit with regard to cardiovascular complications that became apparent only years after recruitment.<sup>6</sup>

Two studies in this issue of the *Journal* — the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial<sup>7</sup> (ClinicalTrials.gov number, NCT00000620) and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial<sup>8</sup> — sought to determine the effect of the lowering of glucose to near-normal levels on cardiovascular risk. Although the ACCORD and ADVANCE trials both compared intensive and standard glucose-lowering targets in type 2 diabetes, the trials differed substantially (Table 1).

Most patients in both studies received drugs from a variety of classes, with or without insulin. However, in the ACCORD study, there were no restrictions on glucose-lowering treatments to reach glycemic targets, whereas in the ADVANCE study, all patients in the intensive-control group were required to receive the sulfonylurea gliclazide (modified release) at initiation. Thiazolidinedione treatment was infrequent during the ADVANCE trial (<20% of participants), whereas rosiglitazone was used in 90% of the intensive-therapy group and in 58% of the standard-therapy group during the ACCORD trial. Both trials used a factorial design to test additional and different treatment interventions in their study participants: in the ACCORD study, participants were randomly assigned to undergo intensive therapy or standard therapy for the lowering of blood pressure or to receive fenofibrate or placebo; in the ADVANCE study, patients were randomly assigned to receive a combination of perindopril and indapamide or to receive placebo.<sup>9</sup> Neither study appears to have emphasized lifestyle or dietary modification.

The strengths of both studies include the large number of participants with complete follow-up for a median of approximately 3.5 to 5.0 years. The baseline characteristics of the participants in both studies were typical for adults with type 2 diabetes: mean age, 62 to 66 years; duration of diabetes, 8 to 10 years; and median glycated hemoglobin level, 7.2 to 8.1%. Approximately one third of patients in each study had a history of macrovascular disease, so both trials assessed the effect of intensive glycemic control in patients with and in those without preexisting macrovascular disease.

The primary outcome in the ADVANCE trial was a composite end point of macrovascular and microvascular events. Mixing end points that prob-

**Table 1. Differences between the ACCORD and ADVANCE Studies.**

Characteristic	ACCORD	ADVANCE
<b>Baseline data</b>		
No. of participants	10,251	11,140
Mean age (yr)	62	66
Duration of diabetes (yr)*	10	8
Median glycated hemoglobin at baseline (%)	8.1	7.2
History of macrovascular disease (%)	35	32
<b>Intervention</b>		
Target glycated hemoglobin value (%)	<6.0	≤6.5
Median duration (yr)	3.4	5.0
Medical treatment at study completion (intensive vs. standard) (%)		
Insulin	77 vs. 55	41 vs. 24
Metformin	95 vs. 87	74 vs. 67
Secretagogue (sulfonylurea or glinide)	87 vs. 74	94 vs. 62
Thiazolidinedione	92 vs. 58	17 vs. 11
Incretin	18 vs. 5	Not reported
Statin	88 vs. 88	46 vs. 48
Any antihypertensive drug	91 vs. 92	89 vs. 88
Angiotensin-converting-enzyme inhibitor	70 vs. 72	Not reported
Aspirin	76 vs. 76	57 vs. 55
<b>Outcome (intensive vs. standard)</b>		
Median glycated hemoglobin at study end (%)	6.4 vs. 7.5†	6.4 vs. 7.0†
<b>Death</b>		
From any cause (%)	5.0 vs. 4.0†	8.9 vs. 9.6
From cardiovascular causes (%)	2.6 vs. 1.8†	4.5 vs. 5.2
Nonfatal myocardial infarction (%)	3.6 vs. 4.6†	2.7 vs. 2.8
Nonfatal stroke (%)	1.3 vs. 1.2	3.8 vs. 3.8
Major hypoglycemia requiring assistance (ACCORD), or severe hypoglycemia (ADVANCE) (%/yr)	3.1 vs. 1.0†	0.7 vs. 0.4
Weight gain (kg)	3.5 vs. 0.4	0.0 vs. -1.0†
Current smoking (%)	10 vs. 10	8 vs. 8

\* Duration of diabetes is the median for the ACCORD trial and the mean for the ADVANCE trial.

† The comparison of the intervention with the standard therapy was significant.

ably have differing pathophysiological bases is problematic. The role of glucose lowering in the prevention of cardiovascular events is the principal unanswered question; it is already well known that intensive glycemic control reduces microvascular complications.

In the ADVANCE study, nonglycemic cardiovascular risk factors were not optimally controlled. Only about half the participants were receiving aspirin and only about half were receiving statins at the end of follow-up in both the intensive-control group and the standard-control group. In the ACCORD trial, the fractions were substantially higher: approximately 75% and 88%, respectively. Although on average, patients in the intensive-control group in the ADVANCE trial met the treatment goal of a mean glycated hemoglo-

bin value of 6.5%, few patients in the ACCORD trial met the treatment goal of a level below 6%. The early termination of the ACCORD trial, resulting in a shorter follow-up period, is a limitation.

The most compelling message from both studies is that near-normal glycemic control for a median of 3.5 to 5 years does not reduce cardiovascular events within that time frame. However, the ADVANCE trial reconfirmed the predicted reductions in new-onset microalbuminuria and nephropathy.<sup>4</sup> A troubling finding from the ACCORD trial is that near-normal glucose control (achieved with the use of combination therapy incorporating heavy use of thiazolidinediones, sulfonylureas, metformin, and insulin) is associated with significantly increased risks of death from any cause and death from cardiovascular

causes, the very outcomes the trial was designed to prevent.

The cause of these unexpected, excess deaths in the ACCORD trial is of great interest. Nineteen of the 41 excess deaths from cardiovascular causes in the study were attributed to “unexpected or presumed cardiovascular disease,” which may plausibly be related to or may have been precipitated by hypoglycemia and misclassified as having a cardiovascular cause. Combination therapies, such as a sulfonylurea with insulin, are known to be associated with an increased risk for hypoglycemia and appear to have been used routinely in this study. If hypoglycemia was indeed a contributing cause of death in the ACCORD trial, future studies of cardiovascular risk reduction should focus on targeting near-normal glycemic levels with the use of strategies and therapies associated with a lower risk of hypoglycemia.

Several other comparisons of the ACCORD and ADVANCE trials are noteworthy. Thiazolidinediones were widely prescribed during the ACCORD trial (92% in the intensive-therapy group vs. 58% in the standard-therapy group, with rosiglitazone used almost exclusively) but were administered more sparingly in the ADVANCE trial (17% in the intensive-control group vs. 11% in the standard-control group). Though a meta-analysis concluded that rosiglitazone use is associated with a significant increase in the risk of myocardial infarction and a nearly significant increase in the risk of death from cardiovascular causes,<sup>10</sup> the ACCORD trial investigators concluded that patients in the standard-control group and those in the intensive-control group had similar risks and rates of death, whether or not they were prescribed rosiglitazone. Insulin treatment is associated with weight gain, particularly if patients are also receiving either thiazolidinediones or sulfonylureas. The frequent use of thiazolidinediones and insulin in the ACCORD trial probably explains the 3.5-kg mean weight gain noted in the intensive-therapy group; in contrast, the change in body weight was negligible in the ADVANCE trial (Table 1). A subgroup of participants in the ACCORD trial gained substantial weight (28% gained more than 10 kg); it is unclear whether these patients had higher rates of cardiovascular events or death than patients with less weight gain. Such large changes in weight could reflect an increase in body fat, which could result in increased risk or, alternatively, thiazolidinedione-induced sodium retention and heart failure.

Secondary analyses will be able to investigate whether particular combinations of medicines, glucose patterns, or coexisting risk factors can predict an increased mortality in patients with diabetes. If predictive characteristics can be identified, there would still be hope that longer-term cardiovascular risk reductions could be studied in subgroups of patients most likely to benefit. For example, in the ACCORD trial, there were significant reductions in fatal and nonfatal cardiovascular events in patients who did not have known cardiovascular disease before randomization.<sup>8</sup> Determining the causes of these excess deaths in the ACCORD trial will inform the design of future studies to examine the association between intensive glycemic control and cardiovascular risk.

The results of the ACCORD and ADVANCE studies have implications for our understanding of the pathogenesis and reversibility of atherosclerosis in patients with type 2 diabetes. The contribution of glucose lowering to the reduction of macrovascular events in UKPDS and the ADVANCE and ACCORD trials appears to be minimal, at least in the first few years of treatment. Although improved glucose control can clearly protect against the development of microvascular complications, the absence of a reduction in macrovascular events implicates an additive effect of nonglycemic risk factors that often accompany diabetes, such as hypertension, hyperlipidemia, and hypercoagulability.

The results of the ACCORD and ADVANCE studies should be interpreted in the context of comprehensive care of patients with diabetes. There is clear evidence that aspirin, a statin, and the targeted lowering of blood pressure are each associated with substantial reductions in cardiovascular risk in patients with diabetes; there may be even greater benefit when these reductions are achieved together.<sup>11,12</sup> The associated therapies are evidence based, widely endorsed, and worthwhile but can be difficult, time-consuming, and resource intensive to implement, even when care is provided in a dedicated diabetes center. Before new targets are defined, it is worth reflecting that the currently established targets for hyperglycemia, hypertension, and hyperlipidemia are achieved in few patients (<10%).<sup>13,14</sup>

The most appropriate target for glycated hemoglobin should remain 7%, though lower individualized targets may be appropriate when the focus is primary prevention of macrovascular dis-

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.<sup>13</sup>

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1. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes,

other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.

2. Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications* 2001;15:44-54.

3. Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM. Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population based study. *BMJ* 2001;322:1389-93.

4. 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;321:405-12.

5. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65. [Erratum, *Lancet* 1998;352:1558.]

6. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-53.

7. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.

8. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.

9. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-40.

10. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71.

11. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580-91.

12. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93.

13. American Diabetes Association. Standards of medical care in diabetes — 2008. *Diabetes Care* 2008;31:Suppl 1:S12-S54.

14. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335-42.

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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.<sup>1-3</sup> 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)<sup>4</sup> and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial (ClinicalTrials.gov number, NCT00145925).<sup>5</sup> 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