

The ACCORD trial¹ studied whether very intensive glycemic control can reduce cardiovascular risk more effectively than targeting usual hemoglobin A1c goals in patients with type 2 diabetes. The intensive treatment arm was halted in February 2008 because of increased mortality in the intensive treatment arm of the trial.

ACCORD was a controlled trial of 10,251 diabetic patients with heart disease or ≥ 2 cardiac risk factors (risk of death 5% per year). Study subjects had diabetes for an average of 10 years, an average HbA1c of 8.2%, and a mean age of 62. They were randomized to very intensive treatment (HbA1c goal $< 6\%$) or standard medical treatment (HbA1c 7-7.9%). Intensive treatment included higher doses and/or additional combinations of hypoglycemic agents, more intensive glucose monitoring, and more frequent clinic visits (every 2 months instead of every 4). The median HbA1c levels achieved were 6.4% for the intensive treatment arm, and 7.5% for the standard treatment arm. Surprisingly, the death rate over 4 years of follow-up was 14 per 1,000 person-years in the intensive treatment arm, compared to 11 per 1,000 person-years for the conventional treatment group. Results did not appear to be attributable to any single drug or drug combination. If the results are found to be sound after peer review, it suggests that reducing HbA1c too much ($< 7\%$) might be hazardous for patients with heart disease or multiple risk factors.

In contrast, the recent results of another randomized trial, STENO-2,² indicate that in diabetic patients whose HbA1c levels are less well controlled (around 9%), a multifactorial intervention of tighter control with aggressive management of risk factors (LDL, blood pressure) does substantially reduce mortality. STENO-2 was a controlled trial of 160 patients with type 2 diabetes and persistent microalbuminuria who were randomized to conventional multifactorial treatment or intensified target-driven therapy involving a combination of medications and focused behavior modification designed to achieve HbA1c $\leq 6.5\%$, fasting total cholesterol ≤ 175 mg/dL, triglycerides < 150 mg/dL, systolic blood pressure < 130 mmHg, and diastolic blood pressure < 85 mmHg. All patients received aspirin and an ACE inhibitor or angiotensin receptor blocker. While patients in the intensive therapy group only achieved HbA1c of 7.9% (as compared to 9% in the control group), this treatment strategy was associated with significant reductions in death from cardiovascular events.

How are we to interpret the seemingly conflicting results of these two major clinical trials of glycemic control? Taken together, the results of ACCORD and STENO-2 trials suggest that while very intensive glycemic control (i.e., targeting HbA1c levels well below 7%) may not be indicated, especially for diabetic patients who are at high cardiovascular risk, treatment goals consistent with the recommendations of the American Diabetes Association³ (i.e., target HbA1c of 7%, aggressive risk factor modification, use of aspirin and ACE inhibitor) are clearly beneficial. As always, treatment should be individualized with even higher targets for frail elderly patients.

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¹ <http://www.accordtrial.org/web/public/index.cfm> Funding for ACCORD (Action to Control Cardiovascular Risk in Diabetes) was provided by the National Heart, Lung, and Blood Institute, with the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, and the Centers for Disease Control and Prevention. It took place in over 70 clinics across the U.S. and Canada.

² Gaede P, et al. Effect of multifactorial intervention on mortality in type 2 diabetes. *N Eng J Med* 2008;358(6):580-91.

³ Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006;29(8):1963-72.