Intensive Glycemic Control and Cardiovascular Disease Observations From the ACCORD Study

Now What Can a Clinician Possibly Think?

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It goes without saying that the results of randomized clinical trials over the past few years evaluating specific diabetic regimens have been nothing short of surprising. For example, with specific regard to the use of thiazolidinediones, all the data up to the point of conducting randomized, controlled clinical trials for hard cardiovascular outcomes suggest that these agents would more than fulfill their promise to reduce clinical events. Specifically, the effects of these drugs on the surrogate markers, e.g., endothelial function, coagulopathy, and inflammation, all favored a strong clinical result. What was found in clinical studies that assessed hard end points was less than impressive. Interestingly, the expected favorable outcomes with use of thiazolidinediones were not routinely seen, and in some studies and using certain agents, the observation was made that event rates increased. Now, more recently, come the startling findings that intensive glycemic control in a high-risk cohort failed to live up to its promise in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Surprising? Yes! Unexpected? Certainly! Will the findings really impact clinical recommendations and have far reaching implications? We will first need to take a step back and evaluate the study more carefully, and we will only be in a position to suggest changes to current clinical recommendations after the dust settles.

There is no question regarding the benefit of glycemic control in reducing the progression and development of microvascular complications in subjects with type 1 and type 2 diabetes. But, with all data considered, there has been a question of whether glycemic control will have a major impact on cardiovascular disease or all-cause mortality. In this regard, data have clearly demonstrated that hyperglycemia may predict a higher likelihood of fatal and nonfatal cardiovascular events. Studies such as the Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) have also shown that intensive blood glucose–lowering strategies reduce the risk of cardiovascular disease and death but often require a prolonged period of follow-up before benefits become evident (1). In another study of patients with more recent onset of type 2 diabetes than ACCORD, participants showed a trend toward a reduction in myocardial infarction (2). In addition, prospective population studies such as the European Prospective Investigation of Cancer (EPIC)-Norfolk suggest that the glycated hemoglobin concentration seems to explain most of the excess mortality risk of diabetes in men and to be a continuous risk factor through the whole population distribution (3). But the relevant question that remained to be answered in randomized clinical trials was whether intensively lowering blood glucose would reduce the risk of cardiovascular events such as heart attack, stroke, or death from cardiovascular disease, specifically in people with type 2 diabetes who are at particularly high risk for a cardiovascular event. As such, the ACCORD trial, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was conducted to determine whether that hypothesis was accurate.

In the ACCORD study, ~10,000 patients with type 2 diabetes were evaluated, with roughly half randomized to an intensive strategy, i.e., target A1C level of <6.0%, and the other half to a standard therapy, i.e., target A1C of 7.0–7.9%. It is fair to state that the ACCORD trial was really designed to test a strategy rather than a specific antidiabetic regimen and that all commercially available diabetes agents were used to reach glycemic targets. Median A1C level achieved in the intensive treatment group was 6.4 vs. 7.5% in the standard group. There were 257 deaths in the intensive treatment group compared with 203 within the standard treatment group—a difference of 54 deaths, or 3 per 1,000 participants each year. Based on this data, the recommendations of the 10-member Data and Safety Monitoring Board to stop this part of the trial were accepted. It would be logical to assume that the exact reason for the increased death rates with intensive treatment may be secondary to hypoglycemia. But, in preliminary analyses, this did not appear to be the case, and the contribution by any particular drug, specifically use of a glitazone, was not evident. However, it must be remembered that many different drug regimens and combinations were used in ACCORD to achieve tight glycemic control; therefore, attributing increased risk to any specific drug might prove difficult, if not impossible. In fact, at this time, the exact reasons for the increased death rate are not known.

The major clinical question is how these results will indeed affect practice recommendations. First and foremost, the mean level of glycemic control achieved in the ACCORD trial, i.e., A1C of 6.4%, was much lower than that

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ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation.

DOI: 10.2337/db08-0220

achieved in either the DCCT or the UK Prospective Diabetes Study (UKPDS). The ACCORD study was really the first trial to prospectively test the value of glycemic levels below current targets. However, an equally important observation from the ACCORD study is that the population studied may not represent the average patient with type 2 diabetes in clinical practice. In the ACCORD study, participants had type 2 diabetes on average for 10 years at the time of enrollment, had higher A1C levels than most type 2 diabetic patients in the U.S. today (average of 8.2% at baseline), and had known heart disease or at least two risk factors in addition to diabetes, such as high blood pressure, high cholesterol levels, obesity, and smoking. So, does this mean that as clinicians we adjust our strategy in certain phenotypes? Specifically, do we now abandon our attempts to intensively lower glycemia aimed at normalizing blood glucose as it may in fact be detrimental, at least in middle-aged and older adults with vascular disease or multiple risk factors for vascular disease? Clearly this point needs to be discussed, but more data are needed.

The ACCORD study, however, may be the appropriate starting point to suggest that acheving lipid and cholesterol targets in patients with type 2 diabetes in primary care settings would be the initial, most important, and primary strategy rather than focusing on normalizing glycemia. The ACCORD trial will certainly be able to provide some insight on that aspect because, depending on their blood pressure and cholesterol levels, patients in the ACCORD study are assigned to two other treatment regimens. Specifically, the study is testing the combination of a fibrate (to raise HDL cholesterol and lower triglycerides) and a statin (to lower LDL cholesterol) versus a statin alone and the lowering of systolic blood pressure to a target of <120 mmHg versus a target of 140 mmHg. These blood pressure and lipid arms of the study will continue until the study ends as planned in June 2009. But evidence for an aggressive approach to lipid and blood pressure control was supported by the results from the Steno-2 study (4). In Steno-2, investigators used intensified multifactorial intervention with improved glycemia and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents, and evaluated whether this approach would have an effect on the rates of death from any cause and from cardiovascular causes (4). The primary end point at 13.3 years of follow-up was the time to death from any cause. Intensive therapy was associated with a significantly lower risk of death from cardiovascular causes and of cardiovascular events. The Steno-2 study did differ in levels of glycemia achieved when compared with the ACCORD study. A1C was a mean of 8.4% at study entry and 7.0% at end of study intervention for the intensively treated group, whereas it was 8.8% at baseline and 9.0% at study end for conventional treatment. The observational study has continued, and these differences in glycemia between intensive and conventional treatments were much less than at end of intervention. But, over the long-term period of follow-up, intensive intervention with a varied drug regimen and lifestyle modification had sustained beneficial effects with respect to vascular complications and rates of death from any cause and from cardiovascular causes.

In addition to ACCORD, several other studies, such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) will be comparing the effect of tight glycemic control (A1C targets <6.5%) versus usual care on cardiovascular disease outcomes. The results of all these studies will be important to assess before changes can really be recommended for our current glycemic targets. As such, an important additional piece of this puzzle was subsequently supplied by investigators of the ADVANCE trial. ADVANCE is a large-scale, 2×2 factorial, randomized clinical trial designed to investigate the potential benefits of blood pressure lowering and of tighter glucose control using an intensive sulfonylurea-based regimen targeting an A1C of 6.5% versus a standard guidelines-based regimen. The two primary outcomes are a composite macrovascular end point of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death and a composite microvascular end point of new or worsening nephropathy or retinopathy after ~6 years.

In September 2007, the ADVANCE Collaborative Group published results of the blood pressure–lowering arm in *Lancet*, showing that the blood pressure–lowering arm had reduced the death rate among participants. In January 2008, the glucose control arm was completed. On 13 February 2008, a press release was issued on behalf of the ADVANCE principal investigator, Stephen MacMahon of The George Institute for International Health, who stated that "due to the unexpected report from the ACCORD trial, we felt it was in the public interest for us to ask our Data Monitoring and Safety Committee to make a statement as to whether the available data from ADVANCE provide any support for the suggestion that intensive blood glucose lowering may increase mortality." Chairman of the ADVANCE Data Monitoring and Safety Committee, Professor Rory Collins from the University of Oxford, said that "the interim results from ADVANCE provide no confirmation of the adverse mortality trend reported from the ACCORD study." Professor John Chalmers further commented that "doctors and patients should feel reassured that the mortality trend reported by the ACCORD study has not been found in the interim results from ADVANCE. However, we need to await more definitive analyses and reports from both studies before drawing final conclusions." Full results have not yet been published, but one hopes that publication will bring clarity to the situation rather than further confusion.

At this stage, based on what we have learned, one can argue that the wording currently established for the American Diabetes Association guidelines may be appropriate but, based on the ACCORD study, may need some "tweaking." The American Diabetes Association guidelines suggest A1C as the primary target and suggest achieving an A1C level <7%. Current recommendations also suggest that the goals should be "individualized" such that certain populations (children, pregnant women, and elderly patients) require special considerations, and that more stringent glycemic goals (i.e., a normal A1C <6%) may further reduce complications at the cost of increased risk of hypoglycemia. The recommendations also suggest that less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia. With specific regard to the less intensive glycemic goals, perhaps consideration should be given to the high-risk patient with multiple risk factors and heart disease, as evaluated in the ACCORD study.

In summary, the ACCORD study suggests that less-intensive glycemic targets may be indicated in patients with type 2 diabetes considered at high risk for heart disease. Whether these findings do or do not apply to patients with shorter duration of diabetes and/or without

preexisting cardiovascular disease is not known. However, as the patient population studied and the means for achieving the tight glycemic control are not commonly encountered in the majority of primary care practices, the findings may not change the treatment practice of the vast majority of diabetes cases. More information is clearly needed and will be provided in the next few years with the completion of other like studies. What should not be lost in the findings from the ACCORD study, as it may be the most important recommendation, is the need for aggressive lipid and blood pressure management in subjects with type 2 diabetes. As for aggressively treating those risk factors and aiming at lowered targets, there is no argument.

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