

Cardiovascular Risk Increases with Ultra-Tight Glycemic Control in Diabetic Patients

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*The Action to Control Cardiovascular Risk in Diabetes Study Group, (ACCORD)¹ and The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, (ADVANCE),² were recently published in the *New England Journal of Medicine* (2008;358(24):2545-72.). These two important and controversial studies present clinicians and clinical educators with a clinical conundrum and a bit of clinical wisdom. These studies challenged the widely-held opinion that tighter glycemic control is the goal of treating people with diabetes and achieving tight control will prevent long term cardiovascular complications of diabetes.^{3,4} This hypothesis, which has guided clinician education, training and practice for many years, is now questioned. These findings and implications are as detailed and complex as they are important and warrant thorough review.*

Both studies were well designed and well executed randomized multicenter trials enrolling over 21,000 type 2 diabetics over several years. Both were designed to evaluate the presumed salutary impact of intensive glycemic control in type 2 diabetics.^{1,2} The hypothesis driving the study design is the generally accepted tenant that tighter glycemic control is better. These studies did not examine levels of diabetes control related to a specific treatment regimen. Lifestyle and dietary management or management of common concomitant conditions (such as dyslipidemia and hypertension) were not protocol targets for likewise aggressive control. Intensive glycemic control was defined as a glycated Hg < 6.0% in ACCORD¹ and <6.5% in ADVANCE². These control target numbers fall below commonly recommended targets (glycated Hg between 7.0-7.9).

In terms of achieving the stated research/clinical objective, obtaining glycated hemoglobin levels in

the 6.0-6.5% range, both studies hit their numbers and achieved the stated treatment strategic goals of "intensive glycemic control. So, from that standpoint these were successful strategies and showed that aggressive treatment using standard medications you can reduce glycemic levels. In ACCORD, (median time of treatment 3.5 years), stable median glycated hemoglobin levels of 6.4% and 7.5% were obtained¹ and in ADVANCE, (median time of treatment 5 years), levels of 6.5% and 7.31% were obtained² in the intensive-therapy groups and the standard-therapy groups, respectively

Beyond these numbers, the data pointed to a much more important finding for patients. Bringing subjects tight glycemic control led to significantly higher levels of cardiovascular mortality.⁵ Briefly, in the ACCORD trial, the target of ultra tight control was achieved but the intensive-therapy group had a significantly increased cardiovascular mortality (2.6% vs. 1.8%; hazard ratio, 1.35; 95% CI, 1.04 to 1.76; P=0.02) compared to the control group.¹ These results were considered so problematic that according to the published report, "...the (safety review committee at one of its periodic mandatory review meetings) concluded that the harm associated with the increased rate of death from any cause in the intensive-therapy group, as compared with that in the standard-therapy group, outweighed any potential benefits and recommended that the intensive regimen be discontinued for safety reasons." Soon after this recommendation the ACCORD intensive glycemic control leg of the trial was stopped seventeen months early and patients were switched to standard glycemic control regimens.¹

Similarly, in ADVANCE, achieving the targeted glycemic levels resulted in a modest 10% reduction in the combined scoring of major micro- and macrovascular events during treatment (the reported reduction in new or worsening kidney disease was 4.1 percent in the tight control group as compared to 5.2 percent in

those with standard levels of control).² Yet, and most importantly to overall clinical care, the overall effect on complications of macrovascular events in the ADVANCE trial was, according to most editorial reviews,⁴⁻⁶ clearly negative.

If this were not problematic enough, a review of the data showed that in both studies intense control was very difficult for patients to obtain. Many subjects, particularly in the ACCORD trial, had to take complicated regimens of oral agents and insulin that required multiple titration steps to reach the numeric goals. In both studies the incidence of hypoglycemia and other side-effects in the intensive care groups was higher and deemed problematic. In the ACCORD trial the intensive-therapy group also had significantly higher rates of hypoglycemia, weight gain, and fluid retention compared to those in the standard therapy group. The annualized rate of hypoglycemia requiring medical assistance was 3.1% in the intensive-therapy group and 1.0% in the standard-therapy group, and the mean weight gain at 3 years was 3.5 kg and 0.4 kg in the two groups, respectively.¹

In the ADVANCE trial, severe hypoglycemia was more frequent in the intensive-control group (2.7%) than in the standard-control group (1.5%). Minor hypoglycemia was also more frequent. Approximately 47% of patients in the intensive-control group and 62% of those in the standard-control group remained free of any hypoglycemic event during the follow-up period. For reasons unspecified, these studies did not establish protocol parameters for lifestyle and dietary modification, long held to be a mainstay of clinical care for diabetics. Nor did the protocols include specific target-goal strategies or treatment parameters for control or that even promoted moderately aggressive hypertension or dyslipidemia management, two conditions frequently found in diabetics that should and can be managed effectively even with conservative therapy.²

Critical review, post-hoc and sub-analyses of ACCORD and ADVANCE and new studies to learn more about diabetes management will follow. While it is still early in the extended analysis period, most reviewers believe that the study results should not alter glycemic control as a mainstay of diabetes care. There is, however, a

“sweet-spot” for glycemic control that seems to hover around current standards for glycemic control. These studies reaffirm the importance of active management of lifestyle factors, diet and concomitant conditions such as hypertension, dyslipidemia and coagulation abnormalities that are associated with both type 1 and type 2 diabetes.^{5,6}

While ACCORD and ADVANCE were specific to type 2 diabetes they are relevant to the care of all patients. Clinicians must monitor the whole patient, not just a strategy, a set of numbers, or one physiologic parameter. Lifestyle management matters. Complicated regimens often set patients up for non-adherence, iatrogenically-induced side effects and treatment failures as well as likely increasing cost for monitoring tests. Lastly, research studies in subject populations must be carefully and systematically translated into clinical care guidelines and then into clinical care wisdom.

Maybe after all is said and done, the most important lasting lesson these two studies contribute is to reaffirm the need to treat the people who come to us for care, not their numbers.

References

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