Intensive blood sugar treatment in trial of diabetes and cardiovascular disease changed

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The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped one treatment within a large, ongoing North American clinical trial of diabetes and cardiovascular disease 18 months early due to safety concerns after review of available data, although the study will continue.

In this trial of adults with type 2 diabetes at especially high risk for heart attack and stroke, the medical strategy to intensively lower blood glucose (sugar) below current recommendations increased the risk of death compared with a less-intensive standard treatment strategy. Study participants receiving intensive blood glucose lowering treatment will now receive the less-intensive standard treatment.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study enrolled 10,251 participants. Of these, 257 in the intensive treatment group have died, compared with 203 within the standard treatment group. This is a difference of 54 deaths, or 3 per 1,000 participants each year, over an average of almost four years of treatment. The death rates in both groups were lower than seen in similar populations in other studies.

“A thorough review of the data shows that the medical treatment strategy of intensively reducing blood sugar below current clinical guidelines causes harm in these especially high-risk patients with type 2 diabetes,” said Elizabeth G. Nabel, M.D., director, NHLBI. “Though we have stopped this part of the trial, we will continue to care for these

participants, who now will receive the less-intensive standard treatment. In addition, we will continue to monitor the health of all participants, seek the underlying causes for this finding, and carry on with other important research within ACCORD."

In stopping this part of the trial, Nabel accepted the recommendation of the 10-member Data and Safety Monitoring Board (DSMB) – an independent advisory group of experts in diabetes, cardiovascular disease, epidemiology, patient care, biostatistics, medical ethics, and clinical trial design that has been monitoring ACCORD since it began. A specific charge of any DSMB is to monitor participant safety.

ACCORD participants will continue to receive blood sugar treatment from their study clinicians until the planned trial conclusion in June 2009. Those participants in the intensive treatment group will now be treated to the same A1C goals as those already in the standard treatment group.

The intensive treatment group had a target blood sugar goal, measured by hemoglobin A1C, of less than 6 percent. This is similar to blood sugar levels in adults without diabetes. The standard treatment group aimed for a target similar to what is achieved, on average, by those with diabetes in the United States (A1C of 7 to 7.9 percent) and lower than at study entry.

"The ACCORD findings are important, but will not change therapy for most patients with type 2 diabetes. Few patients with high cardiovascular risk like those studied in ACCORD are treated to blood sugar levels as low as those tested in this study, " said Judith Fradkin, M.D., director, Division of Diabetes, Endocrinology, and Metabolic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). "People with diabetes should never adjust their treatment plan or goals without consulting their health care providers."

In ACCORD, intensive treatment group participants achieved, on average, A1C values lower than standard treatment group participants. Half of the participants in the intensive treatment group achieved an A1C of less than 6.4 percent, and half of the participants in the standard treatment group achieved an A1C of less than 7.5 percent. The average blood sugar levels for both groups were lower than when they entered the study.

The ACCORD trial was designed to determine whether intensively lowering blood sugar 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. Prior studies suggested that reducing blood sugar to levels found in non-diabetic adults may reduce the rate of cardiovascular diseases among those with diabetes. However, a randomized clinical trial was needed to determine whether that hypothesis is accurate.

“ACCORD is an important study intended to find new answers to help people with type 2 diabetes reduce their high risk of heart disease,” said Denise G. Simons-Morton, M.D., Ph.D., NHLBI project officer for ACCORD and a member of the ACCORD steering committee. “Hypotheses about treatments to prevent cardiovascular disease in people with type 2 diabetes need to be tested in clinical trials such as ACCORD. The ACCORD results, along with results from other studies, will contribute to determining what the treatment goals should be in patients with various characteristics.”

Conducted at 77 sites nationwide and in Canada, the trial includes adults between the ages of 40 and 82 at enrollment who, in addition to type 2 diabetes, also have two or more other risk factors for heart disease or had been diagnosed with heart disease before entering the study. Thus, participants were included in the ACCORD trial because they were at especially high risk—more risk than is associated with diabetes

alone—for having a heart attack, stroke, or of dying from cardiovascular disease. Participants, who on average had diabetes for 10 years at enrollment, were randomly assigned to either standard (5,123 participants) or intensive (5,128) blood sugar treatment goals. They were also enrolled in one of two other ACCORD randomized clinical trials examining effects of treatments for blood pressure or blood lipids; those study components will continue. Participants had been followed for 2 years to 7 years at the time the intensive blood sugar control treatment was stopped.

These results from ACCORD do not apply to patients with type 1 (juvenile) diabetes, according to Fradkin. It is also unclear whether the results apply to patients with recently diagnosed type 2 diabetes or those whose cardiovascular risk is lower than the participants studied in ACCORD.

Extensive analyses by ACCORD researchers have not determined a specific cause for the increased deaths among the intensive treatment group. Based on analyses conducted to date, there is no evidence that any medication or combination of medications is responsible.

Most participants in the intensive treatment group achieved their lower blood sugar goals with combinations of Food and Drug Administration-approved diabetes medications. For both the intensive and standard treatment groups, study clinicians could use all major classes of diabetes medications available: metformin, thiazolidinediones (TZDs, primarily rosiglitazone), insulins, sulfonylureas, exanatide, and acarbose.

“Because of the recent concerns with rosiglitazone, our extensive analysis included a specific review to determine whether there was any link between this particular medication and the increased deaths. We found no link,” said William T. Friedewald, M.D., ACCORD Steering Committee Chair and Clinical Professor of Medicine and Public Health

at Columbia University.

ACCORD researchers will continue to monitor participants and conduct additional analyses to try and explain the findings. Investigators are preparing a report of the findings for a peer-reviewed publication.

An estimated 21 million Americans have diabetes and 284,000 die from it each year. Sixty-five percent of the deaths are related to cardiovascular causes. Type 2 diabetes increases the risk for heart disease 2 to 4 times.

The National Diabetes Education Program, a program of the NIDDK and the Centers for Disease Control and Prevention (CDC), promotes the diabetes care guidelines of the American Diabetes Association (ADA), which recommend an A1C goal of less than 7 percent for most people with type 2 diabetes. The ADA guidelines are based on established evidence that blood sugar control to this level reduces microvascular complications resulting from diabetes including eye, kidney, and nervous system diseases in people with type 1 or type 2 diabetes, and reduces cardiovascular disease in type 1 diabetes. The guidelines also state that treatment goals should be tailored to the individual. For example, a less stringent A1C goal should be considered for people with severe or frequent low blood sugar or with other medical conditions. These important ACCORD results can now be considered in addition to the guidelines when individualizing treatment.

Source: National Heart, Lung and Blood Institute