Near-normal blood sugar target did not delay risk of organ damage in people with diabetes

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In people with longstanding type 2 diabetes who are at high risk for heart attack and stroke, lowering blood sugar to near-normal levels did not delay the combined risk of diabetic damage to kidneys, eyes, or nerves, but did delay several other signs of diabetic damage, a study has found. The intensive glucose treatment was compared with standard glucose control.

These findings are from the NIH-funded Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Although intensive treatment produced some beneficial changes, this approach was reported in 2008 to increase death rates.

The new ACCORD findings appear June 29, 2010 in The Lancet's special online diabetes issue, coinciding with a presentation of the study results at the American Diabetes Association's 70th annual scientific sessions in Orlando.

Over time, diabetes damages the small blood vessels of the eyes, nerves, kidneys and other organs, leading to pain and disability. Heart disease due to damaged large blood vessels is a major cause of death in persons with type 2 diabetes. The longer a person has diabetes, the greater the chances of serious complications, including vision loss and blindness, foot ulcers and amputations, kidney disease and kidney failure, and heart disease and stroke.

"In these ACCORD participants with established type 2 diabetes and

additional risk factors for cardiovascular disease, intensive lowering of blood glucose reduced some markers of eye, nerve and kidney disease compared with standard glucose control, but the groups did not differ in the rate of progression to kidney failure, nerve disease, and major vision loss," said lead author Faramarz Ismail-Beigi, M.D., Ph.D., of Case Western Reserve University, Cleveland.

The ACCORD clinical study compared the effect of intensive control of blood sugar, blood pressure, and blood lipids to standard, less-intensive treatments on the risk of major cardiovascular events in more than 10,000 adults with established type 2 diabetes. The study's intensive glycemia arm was halted in February 2008 due to excess deaths in that group. At that time, participants in the intensively treated group were moved to standard glucose control.

At enrollment, ACCORD participants averaged 62 years of age and were obese. In addition to having type 2 diabetes for an average of 10 years, about one-third had pre-existing heart disease, and the remainder had at least two additional cardiovascular disease risk factors. They also had high blood sugar, as measured by the hemoglobin A1C test, which shows average blood sugar in the preceding two to three months. Half of participants had an A1C over 8.1 percent— above the currently recommended target for good control. A1C values in people without diabetes are less than 6 percent.

Previously reported results showed that over about three-and-a-half years of follow up, participants in the intensive blood sugar group had a 22 percent higher risk of death (5 percent versus 4 percent) and a three times higher risk of seriously low blood sugar (10.5 percent versus 3.5 percent) compared with participants in the standard blood sugar control group.

A secondary goal of the ACCORD blood sugar trial was to determine

the effects of near-normal glucose control compared with standard control on microvascular, or small blood vessel, damage to organs and tissues. Earlier, well conducted clinical trials in patients with newly diagnosed type 1 and type 2 diabetes had proven lowering blood sugar levels reduced eye, nerve and kidney disease. ACCORD builds on this earlier data by studying benefits of further reduction of glucose to targets near normal, and by studying participants with long-standing rather than newly diagnosed diabetes.

In ACCORD, the A1C target for the intensively treated group was less than 6 percent, a level seen in adults without diabetes and significantly lower than the levels tested in earlier trials. The goal for standard control was an A1C of 7 to 7.9 percent, an average range achieved by individuals treated for type 2 diabetes in the United States. Both groups were treated with Food and Drug Administration-approved diabetes medications, as prescribed by their study clinician.

Eye, nerve, and kidney complications in the two groups were compared after 3.7 years, when intensive control was halted, and again at the study's end after 5 years. When intensive glucose treatment was halted in the group receiving such treatment, half those participants had an A1C of 6.4 percent or lower, which rose to 7.2 percent at study end. In the standard treatment group, that A1C measure was 7.5 percent, rising to 7.6 percent by the end of the study.

The treatment groups did not differ in the rate of progression to kidney failure, major vision loss, or advanced peripheral neuropathy, a common nerve problem in diabetes that usually begins as tingling or numbness in the feet. However, people in intensive control had less deterioration in a vision test, and 20 percent fewer cataract surgeries compared with those in standard control. They also had a 30 percent lower rate of protein leakage in the urine, a sign of kidney disease and increased risk of heart disease. Testing for vibratory sensation, an indicator of nerve health,

showed no difference between the groups, but the intensively controlled group scored better on other nerve tests.

ACCORD is continuing follow-up to assess whether the early changes seen in this study will result in differences in blindness, nephropathy and neuropathy. "The study had a relatively short time period - 3.7 years - to see significant differences in serious complications. Diabetes is a chronic disease, and prevention of complications should be measured over many years," said Ismail-Beigi.

The effects of intensive blood sugar control on vision are consistent with findings from the ACCORD Eye Study, which explored the effects of intensive treatments on progression of diabetic retinopathy in a subset of about 3,000 ACCORD participants. The most common cause of vision loss in working-age Americans, diabetic retinopathy is a disease in which blood vessels in the eye's light-sensitive retinal tissue are damaged by diabetes. Intensive blood sugar control was found to be beneficial in retarding the progression of diabetic retinopathy.

"ACCORD provides important data on the risks and benefits of intensive glucose control in people with established type 2 diabetes," said Susan B. Shurin, M.D., acting director of the NIH's National Heart, Lung, and Blood Institute (NHLBI). "Although increasing treatment to try to achieve near-normal blood sugar provides some benefit, clinicians and patients should note that this treatment strategy also potentially increases the risk of adverse effects in patients with additional risk factors for heart disease, such as those studied in ACCORD."

"Earlier landmark trials have proven that intensive glucose control early in the course of diabetes provides long-term benefits in reducing microvascular complications. ACCORD fills an important gap by studying adults with diabetes later in the disease and examining even more stringent glucose control than that previously proven beneficial,"

said Judith Fradkin, M.D., director of the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). "This new information will help tailor therapy for individuals with long established diabetes who are at high risk of cardiovascular events or already have cardiovascular disease."

About 24 million people in the United States have diabetes. It is the main cause of kidney failure, limb amputations, and new onset blindness in adults and a major cause of heart disease and stroke. Type 2 diabetes, which accounts for up to 95 percent of all diabetes cases, becomes more common with increasing age. It is strongly associated with obesity, physical inactivity, family history of diabetes, history of gestational diabetes (diabetes that occurs during pregnancy), and impaired glucose metabolism, and it is more common in minority groups. The prevalence of diagnosed diabetes has more than doubled in the last 30 years, due in large part to the upsurge in obesity and aging of the population.

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