Intensive BP, combined lipid therapies do not help adults with diabetes

14 March 2010

Lowering blood pressure to normal levels - below currently recommended levels - did not significantly reduce the combined risk of fatal or nonfatal cardiovascular disease events in adults with type 2 diabetes who were at especially high risk for cardiovascular disease events, according to new results from the landmark Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial. Similarly, treating multiple blood lipids with combination drug therapy of a fibrate and a statin did not reduce the combined risk of cardiovascular disease events more than treatment with statin alone. The study of more than 10,000 participants is sponsored by the National Institutes of Health.

ACCORD is one of the largest studies ever conducted in adults with type 2 diabetes who were at especially high risk of cardiovascular events, such as heart attacks, stroke, or death from cardiovascular disease. The multicenter clinical trial tested three potential strategies to lower the risk of major cardiovascular events: intensive control of blood sugar, intensive control of blood pressure, and treatment of multiple blood lipids. The lipids targeted for intensive treatment were high density lipoprotein (HDL) cholesterol and triglycerides, in addition to standard therapy of lowering low density lipoprotein (LDL) cholesterol.

The results of the ACCORD blood pressure and lipid clinical trials appear online in the *New England Journal of Medicine* (NEJM) today and will be in the April 29, 2010, NEJM print edition. The results are also being presented today at the American College of Cardiology's 59th annual scientific session in Atlanta. Results of the ACCORD blood sugar clinical trial were reported in 2008.

"ACCORD provides important evidence to help guide treatment recommendations for adults with type 2 diabetes who have had a heart attack or stroke or who are otherwise at especially high risk for cardiovascular disease," said Susan B. Shurin, M.D., acting director of the NIH's National Heart, Lung, and Blood Institute (NHLBI), the primary sponsor of ACCORD. "This information provides guidance to avoid unnecessarily increasing treatment that provides limited benefit and potentially increases the risk of adverse effects."

ACCORD researchers from 77 medical centers in the United States and Canada studied 10,251 participants between the ages of 40 and 79 who had type 2 diabetes for an average of 10 years. When they joined the study, all participants were at especially high risk of cardiovascular events because they had pre-existing cardiovascular disease, evidence of subclinical cardiovascular disease, or at least two cardiovascular disease risk factors in addition to diabetes.

All participants were enrolled in the ACCORD blood sugar treatment clinical trial and maintained good control of blood sugar levels during the study. In addition, participants were enrolled in either the blood pressure trial or the lipid trial and were treated and followed for an average of about five years.

The ACCORD blood pressure trial is the largest clinical trial to test the effect on cardiovascular disease of systolic blood pressure (the top number in a blood pressure reading) below 120 mmHg, which is considered normal. Current blood pressure guidelines recommend that adults with type 2 diabetes maintain systolic blood pressure at less than 130 mm Hg. Previous clinical trials have only proven benefits to less than 140 mm Hg; however, observational studies have linked systolic blood pressure levels of 120 mmHg or below to lower cardiovascular disease rates in adults with type 2 diabetes. A clinical trial was needed to determine the effects of treatment to reach this normal systolic blood pressure level in these patients.

Researchers randomly assigned 4,733 participants

with elevated blood pressure to a target systolic blood pressure of either less than 120 mmHg (the intensive group) or to less than 140 mmHg (the standard group). A variety of FDA-approved blood pressure medications was used to reach blood pressure goals. After an average follow-up of about five years, researchers found no significant differences between the intensive group and the standard group in rates of a combined endpoint including nonfatal heart attack, nonfatal stroke, or cardiovascular death. There were 208 cardiovascular events in the intensive group and 237 events in the standard group.

Lowering blood pressure to below the standard level significantly cut the risk of stroke by about 40 percent. The intensive blood pressure group had 36 strokes, compared to 62 strokes in the standard group. The researchers caution, however, that participants in the intensive blood pressure group were more likely to have complications such as abnormally low blood pressure or high levels of blood potassium. They noted 77 events in the intensive groups compared to 30 in the standard group. In addition, some laboratory measures of kidney function were worse in the intensive therapy group, but there was no difference in the rates of kidney failure.

"Our results provide no conclusive evidence that targeting a normal systolic blood pressure compared with targeting a systolic blood pressure of less than 140 mmHg lowers the overall risk of major cardiovascular events in high risk adults with type 2 diabetes," said William C. Cushman, M.D., chief of the Preventive Medicine Section, Veterans Affairs Medical Center, Memphis, Tenn., and lead author. "However, the study suggests that lower blood pressure levels in patients like those in ACCORD may reduce the risk of stroke. This finding is consistent with other blood pressure trials."

"Our results also showed a higher risk of serious adverse events with more intensive blood pressure control," Cushman added. "Diabetic patients should discuss their systolic blood pressure goal with their health care provider and, as with any treatment, weigh the risks and benefits of various treatments to lower blood pressure."

The ACCORD lipid trial studied whether adding a fibrate to a statin to improve multiple blood lipids is more effective at lowering the risk of cardiovascular events than treatment with a statin alone. Both statins and fibrates are commonly used medications to treat abnormal levels of blood lipids. Statins lower LDL, or bad cholesterol, and are proven to lower cardiovascular disease risk in people with diabetes. Fibrates primarily lower fats in the blood known as triglycerides and raise HDL or good cholesterol. Fibrates are sometimes used in combination with statins. High triglycerides and low HDL levels are common in diabetes patients.

ACCORD is the first large clinical trial to compare the cardiovascular effects of a statin (simvastatin) and placebo, or inactive pill, to combination therapy of a statin (simvastatin) and a fibrate (fenofibrate) in high-risk adults with type 2 diabetes. The ACCORD lipid trial involved 5,518 participants. Researchers found that, overall, the combination therapy was safe, but it did not lower the risk of heart attack, stroke, or death from cardiovascular disease more than statins alone.

The researchers noted that participants who started the study with the lowest levels of HDL cholesterol plus the highest levels of triglycerides had lower rates of cardiovascular events if they received the combination therapy compared to similar participants who received only statin therapy. Although a similar effect has been seen in other studies, more research is needed on the effects on this subgroup, which comprised 17 percent of the ACCORD participants. The researchers also found that men may have benefitted from the combination lipid therapy whereas women on combination therapy appeared to have more cardiovascular problems than those on statins alone.

"Overall, the results of the ACCORD lipid trial do not support the use of combination therapy with a fibrate and a statin to reduce cardiovascular disease in most high-risk adults with type 2 diabetes," said lead author Henry N. Ginsberg, M.D., director of the Irving Institute for Clinical and Translational Research at Columbia University College of Physicians and Surgeons, New York City. "Although our analysis suggests that certain patients may benefit from combination therapy, this

study provides important information that should spare many people with diabetes unneeded therapy with fibrates."

"The lack of benefit from fibrates should not obscure the proven value of statins in preventing cardiovascular disease, which is well established from earlier studies," Ginsberg added. "Patients should discuss with their health care provider the implications of this research for their lipid therapy management."

An estimated 24 million Americans have diabetes, which is the seventh leading cause of death in the United States. Adults with type 2 diabetes are two to four times more likely than adults without diabetes to die from heart disease, and 65 percent of deaths in people with diabetes are from cardiovascular causes.

"These new ACCORD results indicate that we do not generally need to treat even more intensively than standard practice," said Denise G. Simons-Morton, M.D., Ph.D., co-author and former NHLBI project officer for ACCORD. Simons-Morton now directs the NHLBI's Division for the Application of Research Discoveries. "The treatment strategies used in the ACCORD standard control groups have previously been shown to be effective. So the findings in no way detract from the important point that controlling blood pressure and LDL cholesterol levels reduce cardiovascular risk - not only in patients with diabetes, but in all patients with elevated levels."

The researchers caution that the results from the ACCORD clinical trial might not apply to patients who are at lower risk of cardiovascular disease than the ACCORD participants or to patients with more recently diagnosed type 2 diabetes.

More information: Questions and Answers About the ACCORD Clinical Trial, www.nhlbi.nih.gov/health/prof/ … other/accord/q_a.htm

Provided by National Institutes of Health