Intensive glucose control reduced the progression of diabetic retinopathy (DR) compared with standard glucose control, and combination lipid therapy with a fibrate and a statin reduced disease progression compared with statin therapy alone in high-risk adults with type 2 diabetes. However, intensive blood pressure control provided no additional benefit to patients compared with standard blood pressure control, based on results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study.\(^1\)\(^2\)

**ACCORD**

“The ACCORD Eye Study clearly indicates that intensive glycemic control and fibrate treatment added to statin therapy separately reduce the progression of diabetic retinopathy,” Emily Chew, MD, chair of the eye study and chief of the Clinical Trials Branch of the Division of Epidemiology and Clinical Applications at the National Eye Institute (NEI), said in a news release. “The main ACCORD findings showed that fibrate treatment added to statin therapy is safe for patients like those involved in the study. However, intensive blood sugar control to near normal glucose levels increased the risk of death and severe low blood sugar, so patients and their doctors must take these potential risks into account when implementing a diabetes treatment plan.”

**BACKGROUND**

The ACCORD study was a landmark clinical trial that included 10,251 adults with type 2 diabetes who were at especially high risk for myocardial infarction, stroke, or cardiovascular death. The study evaluated three intensive strategies compared with standard treatments for lowering cardiovascular risks associated with diabetes.

Intensive treatments included control of blood glucose to near normal levels, control of blood pressure to normal levels, and combination treatment of multiple blood lipids with fenofibrate and simvastatin compared with standard treatment with simvastatin alone. Fenofibrate treatment lowers triglycerides and raises high-density lipoprotein (HDL) cholesterol levels, while simvastatin lowers low-density lipoprotein (LDL) cholesterol levels. All participants were enrolled in the glucose trial and in either the blood pressure or lipid trial.

**ACCORD EYE**

The ACCORD Eye Study involved a subset of 2,856 participants. Researchers analyzed the effects of the treatment strategies on blood vessels in the eye by identifying diabetic retinopathy progression over 4 years. In the study, disease progression was identified through retinal photographs that indicated blood vessel changes or by the need for laser or eye surgery to treat abnormal blood vessels.

Compared with standard blood glucose control, intensive control decreased the progression of DR by about one-third, from 10.4% to 7.3%, over 4 years. Participants in the intensive control group had a median blood sugar level of 6.4%. The standard blood sugar control group maintained a median level of 7.5%.

No previous clinical trial has shown that the combination of fenofibrate and simvastatin reduces the progression of diabetic eye disease.
“Previous clinical trials have shown the beneficial effects of intensive blood sugar control on slowing the progression of [DR] in people with type 1 diabetes or newly diagnosed type 2 diabetes,” said NEI director Paul A. Sieving, MD, PhD. “The ACCORD Eye Study expands these findings to a larger population of adults who had type 2 diabetes for an average of 10 years, and demonstrates that the eye benefits from the reduction of glucose below previously established levels.”

Walter T. Ambrosius, PhD, is a professor of biostatistical sciences in the Division of Public Health Sciences at Wake Forest University Baptist Medical Centre, Winston-Salem, North Carolina, and principal investigator of the ACCORD Eye Study’s coordinating center. “This is the largest study to date examining the effects of blood sugar, combination lipid therapy, and blood pressure control on the prevention of DR progression using retinal photographs,” Dr. Ambrosius said in a news release. “Many people with diabetes have microvascular problems, which can result in problems with the kidneys and amputation of toes and feet, and the only place that you can directly observe the microvasculature is in the back of the eyes. What we have seen in the eyes is potentially an indicator of what is happening in other parts of the body.”

In addition, compared with simvastatin treatment alone, combination lipid therapy with fenofibrate plus simvastatin also reduced disease progression by about one-third, from 10.2% to 6.5%, over 4 years. No previous clinical trial has shown that the combination of fenofibrate and simvastatin reduces diabetic eye disease progression.

NO EFFECT IN BLOOD PRESSURE GROUP

There were no differences in the progression of DR among participants treated to an intensive systolic blood pressure target of less than 120 mm Hg compared with those treated to a standard target of less than 140 mm Hg.

MAIN STUDY AND HISTORY

In the main study, none of the three treatment strategies resulted in a significant decrease in the combined rates of myocardial infarction, stroke, or cardiovascular death compared with standard treatments. However, during 3.5 years of follow-up, participants in the intensive glucose control group had a 22% higher risk of death (5% vs 4%) and a three times higher risk of seriously low blood sugar (10.5% vs 3.5%) compared with participants in the standard blood sugar control group.

ACCORD began in 2001, and participants were treated and monitored for an average of 5 years. Results of the blood sugar clinical trial were reported in 2008, when the intensive blood sugar therapy was stopped 18 months early due to an increased risk of death in that treatment group compared with the standard blood sugar control group. Findings from the blood pressure and lipid clinical trials appeared in the New England Journal of Medicine.

“A key question in the main ACCORD study was whether intensive glucose control, previously demonstrated to reduce risk of microvascular disease—including eye problems—in diabetes, would reduce large vessel disease that causes problems like [myocardial infarctions],” said Susan B. Shurin, MD, acting director of the National Heart, Lung, and Blood Institute, the primary sponsor of the ACCORD study. “Investigators are continuing to evaluate the risks and benefits of the treatment strategies in these high-risk patients with type 2 diabetes. Clinicians should individualize treatment for each patient to prevent complications, also incorporating information about conditions such as cardiovascular or visual problems. Lifestyle interventions, including physical activity, weight loss and healthy diets, can improve diabetes control and reduce onset of diabetes.”

EDITORIAL COMMENTS

An editorial by Barbara E.K. Klein, MD, MPH, from the Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, Madison accompanies the ACCORD report in the New England Journal of Medicine.2

“An exciting finding is the 40% reduction in the odds of having progression of DR that is conveyed by fenofibrate (taken along with simvastatin) in the ACCORD Eye study over a 4-year period,” Dr. Klein wrote. “The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study previously reported a protective effect of fenofibrate on laser treatment for proliferative DR, but there was no evidence of a concomitant decrease in serum triglyceride levels,” Dr. Klein continued. “In the ACCORD Eye trial, the effect of fenofibrate was independent of glycemia. Whether an enhanced effect of fenofibrate in the ACCORD Eye study is the result of an interaction with simvastatin will be an interesting topic for further research.”

Overall, the ACCORD Eye trial has added substantially to our knowledge and confidence about the importance of glycemic control in the progression of DR, Dr. Klein said: “The findings also strongly suggest the need for further evaluation of the potential importance of fenofibrate in our armamentarium of treatments for this condition.”