Subanalysis Sheds Light on ACCORD Mystery

BY MIRIAM E. TUCKER

BOSTON — It's still not clear why mortality was higher with the intensive glycemic control strategy of the ACCORD trial, but new analyses of the data highlight the fact that higher glucose levels, not lower, remain the most likely culprit.

At a special evening session held during the annual meeting of the American Association of Clinical Endocrinologists, researchers from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial summarized results of recent subanalyses of the trial data and suggested ways in which the new findings, while still lacking an ultimate conclusion, might nonetheless help inform clinical decisions—at least among patients who resemble the study population.

In ACCORD, all-cause mortality was greater among patients randomized to intensive glycemic control, with the aim of getting patients to a hemoglobin A_{1c} below 6%. When the glycemic arm of the study was stopped early, at 3.4 years rather than the planned 5.6 years of follow-up, the hazard ratio was 1.22, compared with standard treatment (N. Engl. J. Med. 2008;358:2545-59).

Panel moderator Dr. Faramarz Ismail-Beigi said that the overall conclusion from the glycemia arm of the ACCORD trial pertains only to that patient group: In older patients with a longer duration of diabetes and established cardiovascular risk factors, attempting to achieve normoglycemia does not reduce all-cause or cardiovascular mortality and may increase the risk.

However, he said, it's important to remember that the 10,194 patients enrolled in ACCORD did not represent the entire type 2 diabetes population. The ACCORD patients had an average age of 62 years, a 10-year duration of diabetes, and a median HbA_{1c} of 8.1%. A third had experienced prior cardiovascular events.

"This cohort represents a little bit less than half of all U.S. patients with type 2 diabetes. So it represents a large group of people, but not everybody. We're not talking about people who are newly diagnosed with diabetes, middle-aged, or younger," said Dr. Ismail-Beigi, professor of medicine at Case Western Reserve University, Cleveland.

Several possible mechanisms to explain the results were put forward at the time the glycemia arm of ACCORD was stopped in 2008, including hypoglycemia, weight gain, individual drugs, drug combinations, or the rapid reduction of glucose levels early in the trial. But now, new data refute some of these hypotheses.

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Dr. Elizabeth R. Seaquist, professor of medicine and director of the Center for Diabetes Research at the University of Minnesota, Minneapolis, presented just-published data showing that the excess risk of all-cause mortality associated with intensive treatment in ACCORD was associated with persistently high HbA_{1c} rather than low HbA_{1c}, regardless of treatment group assignment.

Average HbA_{1c} was the strongest predictor of death for both groups: A 1-percentage-point increase was linked with a 22% increase in mortality, after adjustment for a variety of potentially confounding baseline factors. When each group was examined separately, the relationship between HbA_{1c} and death was much stronger among those in the intensive treatment group, with a statistically significant 66% increase in all-cause mortality for every 1-percentage-point higher HbA_{1c} vs. a nonsignificant 14% increase for the standard treatment group.

The greatest excess risk of death associated with the intensive treatment group occurred among the patients whose average HbA_{1c} remained above 7% despite their treatment assignment. In the intensive treatment group, there was a steady increase in mortality as the HbA_{1c} rose from 6% to 9%, whereas no such relationship was seen in the standard treatment group. The excess mortality in the intensive group was seen only at an HbA_{1c} above 7%, not below, Dr. Seaquist reported.

The relationship between mortality and the last HbA_{1c} recorded before death and the decrease in HbA_{1c} over the first year did not differ between the two groups, suggesting that the rate of change in HbA_{1c} from baseline was not associated with increased risk of death. "These analyses do not support the view that rapid reduction of glucose levels or lower average A_{1c} independent of other factors led to the excess risk of death," she said.

Dr. Saul Genuth, professor of medicine at Case Western Reserve University, summarized findings from two studies published last year suggesting that severe hypoglycemia was a risk factor for increased mortality in ACCORD, but that the relationship between hypoglycemia and mortality did not explain the difference in outcomes between the intensive and standard treatment groups.

Patients with poorer glycemic control had a greater risk for hypoglycemia in both groups, and among those who experienced severe hypoglycemia, the risk of death was actually lower in the intensive treatment arm, he said.

The frequency of severe hypoglycemia events requiring medical assistance was 4.3 per 100 person-years for the intensive arm, compared with 1.4 for standard treatment. There was a slow decline in severe hypoglycemic events over the 3.4 years of the trial in the intensive group, whereas the rate remained steady in the standard treatment group. "This should encourage all of us to keep educating our patients about preventing hypoglycemia," Dr. Genuth said.

Baseline characteristics linked with increased risk for severe hypoglycemia included African American race, male gender, increased age, and longer diabetes duration. Higher BMI actually protected against severe hypoglycemia, presumably owing to greater insulin resistance. Insulin treatment at baseline nearly doubled the risk of severe hypoglycemia in the intensive group, but quadrupled it in the standard group (BMJ 2010;340:b5444).

Among just the patients with no severe hypoglycemic events, the mortality risk was increased by 25% in the intensive treatment group compared with standard treatment, similar to the 22% increase for the entire intensive treatment group, suggesting that severe hypoglycemia was not the reason for the increased deaths in the intensive group, he said.

Importantly, the higher the average HbA_{1c} achieved and maintained during the trial, the more the incidence of severe hypoglycemia increased. The risk of hypoglycemia was greatest among those whose HbA_{1c} barely declined in the first 4 months of treatment, and was least among those whose HbA_{1c} fell rapidly.

Finger-stick data implied that the occurrence of severe hypoglycemia identifies patients with type 2 diabetes at increased risk for death, particularly in those whose HbA_{1c} does not respond to intensification of treatment, Dr. Genuth concluded (BMJ 2010;340:b4909).

More ACCORD data are due to be published during 2010, including results on microvascular outcomes. ■

Disclosures: *ACCORD was funded by the National Institutes of Health and the Centers for Disease Control and Prevention, with supplies and medications contributed by 13 companies. Dr. Ismail-Beigi is a consultant to Eli Lilly. Dr. Seaquist and Dr. Genuth reported no relevant disclosures.*

Coronary Disease Seen in 2/3 of Young Adults With Diabetes

BY MITCHEL L. ZOLER

ATLANTA — Two-thirds of young adults with diabetes who were aged 40 years or younger had significant coronary artery atherosclerosis, on the basis of coronary CT examinations of 130 such patients at one U.S. medical center.

Results from the study also showed that when compared with more than 3,500 similarly aged young adults without diabetes, patients with diabetes had an adjusted, fourfold increased prevalence of coronary atherosclerosis, Dr. Nikhil Daga and his associates from Harbor-UCLA Medical Center reported in a poster at the annual meeting of the American College of Cardiology.

These findings run counter to current recommendations of the American Diabetes Association, which recommend routinely starting statin treatment of patients with diabetes only in those older than 40 years (Diabetes Care 2010;33:S11-61).

"ADA guidelines should consider statin use in patients aged 40 or younger who exhibit subclinical atherosclerosis to reduce future cardiovascular disease events in this vulnerable population," noted Dr. Daga, a physician at Harbor-UCLA Medical Center in Torrance, Calif., and his associates. The findings also highlighted the useful role that coronary CT can play in identifying subclinical atherosclerosis in these patients, they added.

VITALS

Major Finding: Two-thirds of 130 patients aged 40 years or younger who had diabetes also had significant coronary atherosclerosis, compared with a 27% prevalence among 3,581 people of the same age without diabetes.

Data Source: Coronary CT examinations of 3,711 young adults at Harbor-UCLA Medical Center.

Disclosures: Dr. Daga said that he had no disclosures. Among his associates on the study, the only disclosure was from Dr. Matthew Budoff, who is on the speakers bureau for General Electric, a company that markets CT equipment.

The researchers performed coronary CT examinations on 3,711 people aged up to age 40 years, including 130 patients with diabetes and 3,581 people without diabetes. The average age of the entire group was 36 years, and 54% were men. The study presumed that the presence of any coronary calcium indicated significant atherosclerosis.

The CT examinations revealed a low coronary calcium score of 1-99 in 52% of the patients with diabetes and in 24% of those without diabetes. An intermediate score of 100-399 occurred in 12% of those with diabetes and in 2% of people without diabetes. A high score of 400 or greater occurred in 4% of those with diabetes and in 0.5% of those without diabetes. Overall, 68% of the patients with diabetes had some degree of coronary artery calcification, compared with a 27% prevalence in people without diabetes.

In an analysis that adjusted for age, sex, dyslipidemia, hypertension, and smoking, patients with diabetes had a statistically significant, fourfold increased risk for having coronary artery calcium, compared with similarly aged young adults without diabetes. ■