Intensive Glucose Lowering: Questions Remain

BY KATE JOHNSON

MONTREAL — Better identification of risk, but lack of explanation for it, continues to frustrate investigators as they search for reasons for the excess mortality associated with intensive glycemic control in the ACCORD trial.

However, complex interactions between baseline characteristics, postrandomization characteristics, and treatment strategy are still being explored.

In the latest set of analyses, "neither rapid reduction of blood glucose nor the achievement of near normal hemoglobin A_{1c} levels led to an excess risk of all-cause or CV death with the intensive strategy," said Dr. Matthew Riddle, who presented an update on the Action to Control Cardiovascular Risk in Diabetes trial at the World Diabetes Congress.

"We haven't been able to find either baseline characteristics or obvious events during the course of treatment that strongly predicted which group was at risk for cardiovascular death," he said in an interview.

ACCORD compared intensive versus standard glycemic control in 10,251 adults from 77 sites. The hypothesis was that lowering HbA_{1c} levels below 6% would reduce cardiovascular events compared with levels of 7.0%-7.9%. However, the intensive arm of the trial was stopped early when it showed a 22% increase in all-cause mortality compared with standard treatment. There were 257 deaths in the intensive treatment arm, compared with 203 in the standard treatment arm.

Several previous analyses of the data have revealed baseline characteristics such as high HbA_{1c} (8.5% or more), self-reported neuropathy, and aspirin use as predictors for increased mortality risk with intensive treatment, said Dr. Riddle, professor of medicine at Oregon Health and Science University in Portland.

It could be hypothesized that a high HbA_{1c} is a surrogate for relative severity of metabolic control, neuropathy is a surrogate for established and significant microvascular disease, and aspirin use may be a surrogate for cardiovascular disease, he suggested.

However, this still does not explain the excess risk seen with intensive versus standard treatment. "We still do not know the mechanisms involved in this unfavorable finding," he said.

An epidemiologic analysis of the whole study population showed every 1% increase in average HbA_{1c} above normal was associated with a 20% increased risk of all-cause mortality, CV mortality, MI, and stroke. Further investigation into the interaction between this finding and treatment strategy suggests patients who were unable to lower HbA_{1c} levels with intensive treatment were at greatest risk for all-cause and cardiovascular mortality. "This supports a lot of people's intuitive idea that the further along in the course of diabetes patients are, the higher their risks from any kind of intensive intervention, and thus the more cautious the approach should be," he said in an interview.

"When should we stop being aggressive?" Dr. Rury Holman of the Diabetes Trials Unit at the University of Oxford (England) asked during the question period. "What is it that tells us that we're not winning, and if we continue to be aggressive the patient will fall into this high-risk category?"

"I can't speak for ACCORD as a whole," answered Dr. Riddle, "but my own opinion is that I think we know within the first 6 months of attempting an intervention whether that person is going to succeed. If they are struggling with it for any reason, whether it's a physiologic reason, a medication-adherence reason, or any recurrent illness reason, I believe that would be a reason to back off."

The investigators are still working on several other hypotheses for the excess risk seen with intensive treatment, including hypoglycemia, "although we've been unable to find a direct relationship," he said. In addition, "weight gain remains on the table as a serious possibility, and certainly, possible unfavorable effects of high doses of the medications."

Dr. Riddle has received lecture fees or research grants from Sanofi-Aventis, Amylin, Eli Lilly & Co., and GlaxoSmithKline; and has done advisory board work with Amylin, Eli Lilly, Sanofi-Aventis, and Valeritas Inc. ■