Resistance to Intensive Tx Key

ACCORD *from page 1*

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.

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 associated 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}, compared with 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. … Using an intensive strategy, some people with type 2 can safely achieve A_{1c} levels below 7%, whereas others who do not readily reduce their A_{1c} levels may be at increased risk if they persist with this strategy," she concluded.

Dr. Saul Genuth, professor of medicine at Case Western Reserve University, summarized findings from two studies published last year suggesting that symptomatic, severe hypoglycemia was indeed 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 who had 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, Dr. Genuth said.

During the trial, 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. It really does help," Dr. Genuth said.

Baseline characteristics associated with an increased risk for severe hypoglycemia included African American race, male gender, increased age, peripheral neuropathy, longer diabetes duration, and higher serum creatinine. Body mass index was a negative predictor: 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 treatment group, but quadrupled it in the standard group (BMJ 2010;340:b5444 [doi:10.1136/bmj.b5444]).

In both treatment groups, mortality progressively increased with the number of severe hypoglycemic events experienced at any time during the trial. 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, nearly the same as the overall 22% increase for the intensive treatment group in the trial, suggesting that severe hypoglycemia was not the reason for the increased deaths in the intensive group, he said.

Importantly, the incidence of severe hypoglycemia was increased the higher the average HbA_{1c} achieved and maintained during the trial.

This is the opposite of what was seen with type 1 patients in the Diabetes Control and Complications Trial, wherein hypoglycemia was increased as HbA_{1c} was lowered. And, contrary to what had been postulated, 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 were also assessed to determine the incidence of severe hypoglycemia as an acute cause of death. In all, hypoglycemia was judged to have played a definite role in just 1 patient (in the intensive arm) of 451 deaths associated with hypoglycemia and possibly or probably involved in another 41. This did not differ between groups, Dr. Genuth said (BMJ 2010;340:b4909 [doi:10.1136/bmj.b4909]).

The findings imply 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.

But, Dr. Ismail-Beigi said that in light of ACCORD he now tries even harder to normalize glucose levels in newly diagnosed, young to middle-aged patients. "In those patients, I tend to be more aggressive. I try to get them to normal if I can do it safely. New-onset diabetes is far easier to control, with fewer medications," he said, adding that this was his personal opinion, not the opinion of the ACCORD panel.

More ACCORD data are due to come out during 2010, including results on microvascular outcomes. These data are necessary to develop a risk-benefit analysis for glucose management, Dr. Ismail-Beigi said in an interview. "Basically, we're trying to balance microvascular versus macrovascular, so we need to know the microvascular part of the equation."

The ACCORD study was funded by the National Institutes of Health and the Centers for Disease Control and Prevention, with supplies and medications contributed by 13 drug/supply companies. Dr. Ismail-Beigi is a consultant to Eli Lilly. Dr. Seaquist and Dr. Genuth stated that they had no relevant disclosures. ■

Diabetic Patients Can Benefit From Carpal Tunnel Surgery

BY NEIL OSTERWEIL

Diabetic neuropathy should not be a barrier to carpal tunnel release surgery, because diabetic patients with carpal tunnel syndrome experience the same degree of neurophysiologic recovery after the procedure as do nondiabetic patients, according to Swedish investigators.

In a prospective case-control study, there were virtually no significant differences in neurophysiologic recovery after carpal tunnel syndrome (CTS) release between diabetic patients and controls, or among diabetic patients with or without peripheral neuropathy.

At 1-year follow-up, there were no significant differences between diabetic and nondiabetic patients in most categories of neurophysiologic recovery.

"We therefore recommend that diabetic patients with CTS are offered the same opportunities for surgical carpal tunnel release as nondiabetic patients," wrote Dr. Niels O.B. Thomsen of Malmö (Sweden) University Hospital and his colleagues.

The authors looked at pre- and postoperative data on 35 consecutive diabetic patients and 31 age- and sex-matched nondiabetic controls treated for CTS during 2004-2007. All cases and controls also had nerve conduction studies 1 year after surgery.

Diabetic patients were diagnosed with peripheral neuropathy if they had abnormal preoperative neurophysiologic values in sural nerve sensory conduction velocity (SCV), sensory nerve action potential (SNAP), and peroneal nerve motor conduction velocity studies.

At 1-year follow-up, there were significant differences in neurophysiologic recovery between diabetic patients and controls in only two categories: The SNAP values from digit III improved significantly more in nondiabetic patients, at a mean change from baseline of 2.1 mcV vs. 4.8 mcV, respectively. In contrast, diabetic patients had significantly greater antidromic elbow-wrist improvement, at a mean of 17.6 m/sec vs. 6.9 m/sec for nondiabetic patients.

There were no significant between-group differences in distal motor latency, motor conduction velocity, compound muscle action potential, wrist-palm SCV, or palm–digit III SCV (Clin. Neurophysiol. 2010 April 21 [doi:10.1016/j.clinph.2010.03.014]).

The investigators also looked at whether preoperative nerve conduction values could predict whether patients would improve following surgery, and found that in general, patients with the greatest presurgical disability had the highest postsurgical improvement. Still, few patients had nerve conduction values within the normal range at 1 year.

"The clinical implication … is that even though diabetic patients with CTS have significantly impaired nerve conduction parameters compared to nondiabetic patients with CTS, they obtain the same degree of neurophysiologic recovery after surgical carpal tunnel release. This result even applies to diabetic patients with evidence of peripheral neuropathy," the researchers wrote.

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