Intensive Glucose Control May Benefit Subgroups

BY SHERRY BOSCHERT

SAN FRANCISCO — Although three recent major trials found that the potential harms of intensive glycemic control in patients with diabetes generally outweigh potential benefits, substudies of the data may help identify patients who could benefit from intensive therapy.

"Improvement in picking individuals for intensive glycemic control may be the right approach," Dr. Peter D. Reaven said at a meeting sponsored by the American Diabetes Association.

The substudies and other recent analyses suggest that clinicians should avoid aggressive glycemic management (that is, trying to get hemoglobin A_{1c} values down to 6.5% or lower) in patients who are older and who have a longer duration of diabetes, more extensive calcified coronary atherosclerosis, or a higher burden of comorbidities, said Dr. Reaven, professor of clinical medicine at the University of Arizona, Phoenix.

Cardiovascular outcomes did not differ significantly between the intensive-control and usual-control groups in the three major recent studies—the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (N. Engl. J. Med. 2008;358:2545-59), the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial (N. Engl. J. Med. 2008;358:2560-72), and the VADT (Veterans Affairs Diabetes Trial) (N. Engl. J. Med. 2009;360:129-39). The ACCORD trial was stopped early because of increased mortality in the intensive-control group. In the VADT, intensive glycemic control was associated with a tripled risk for hypoglycemia, which was a strong predictor of cardiovascular death.

Substudies have indicated that 'intensive glucose lowering may have a cardiovascular benefit that is most useful in certain subgroups and may be harmful in some individuals.'

However, a subanalysis within the ACCORD trial of prespecified subgroups found less risk of mortality in the intensive-control group if patients entered the study with no history of a cardiovascular event or if they entered the study with an HbA_{1c} level below 8%, he noted.

In the VADT, in which Dr. Reaven participated, a subanalysis found that patients with a shorter duration of diabetes in the intensive-control group appeared to have improved cardiovascular outcomes, compared with the usual-control group. Patients in the intensive group who had diabetes for 15 years or less had a 26% reduction in cardiovascular risk, compared with the usual-care group, but intensive glycemic control appeared to become harmful in patients with longer durations of diabetes.

A separate meta-analysis found a significant 10% reduction in cardiovascular events with intensive glycemic control when data from the ACCORD trial, ADVANCE trial, VADT, and the UKPDS (United Kingdom Prospective Diabetes Study) (Lancet 1998;352:837-53) were combined. Mortality rates did not differ significantly among treatment groups in this meta-analysis (Diabetologia 2009;52:2288-98), which was "somewhat reassuring," though heterogeneity in the individual study results leaves uncertainty about the safety of intensive glycemic control, Dr. Reaven said.

A substudy by Dr. Reaven and associates of 301 patients in the VADT who had baseline CT scans to measure coronary artery calcium in the assessment of coronary atherosclerosis found that intensive glycemic control significantly reduced the risk of cardiovascular events if patients entered the study with lower levels of calcium in their coronary arteries. In the intensive-control group, the risk for cardiovascular events was nearly 10-fold higher in patients with higher coronary artery calcium levels at baseline (Diabetes 2009;58:2642-8).

Nearly 60% of VADT participants had higher levels of coronary artery calcium, he estimated, and the ACCORD and ADVANCE cohorts had a high prevalence of cardiovascular disease, which may help explain why the studies overall did not report cardiovascular benefits from tight glycemic control.

"Perhaps some imaging method may be reasonable to try to assess vascular risk" when considering intensive glycemic therapy, Dr. Reaven said.

The TIBI (Total Illness Burden Index) was assessed in a separate longitudinal observational study of 2,613 patients with diabetes. Cardiovascular risk was significantly reduced with intensive glycemic control in patients who had a lower baseline level of comorbidity, but not in patients who had low TIBI scores and higher HbA_{1c} levels or in patients who had higher TIBI scores (Ann. Int. Med. 2009;151:854-60).

"Intensive glucose lowering may have a cardiovascular benefit that is most useful in certain subgroups and may be harmful in some individuals," he said. ■

Disclosures: *Dr. Reaven has been a board member or adviser for AstraZeneca and Bristol-Myers Squibb, a stockholder in Pfizer and Merck, a speaker for Merck, and a consultant to Takeda. He has received research support from Amylin and Takeda.*

Predialysis Hb Levels Are Low in Diabetic Nephropathy Patients

BY DOUG BRUNK

SAN DIEGO — Patients with diabetic nephropathy have a slightly lower mean level of hemoglobin in the year leading up to the start of renal dialysis, compared with patients who have nondiabetic renal disease, results of a large analysis showed.

The difference persisted after adjustment for several other variables including age, gender, ethnicity, and estimated glomerular filtration rate, Dr. Daniel Ford said in an interview during a poster session at the annual meeting of the American Society of Nephrology.

'It's a small difference, but it's statistically significant.'

DR. FORD

"This reiterates what we know about patients with diabetic nephropathy—that they do have a tendency to have more anemia than patients with nondiabetic renal diseases," said Dr. Ford, of the United Kingdom Renal Registry, Bristol, England. "I suspect it's because patients with diabetic nephropathy have a higher incidence of concurrent diseases, which would make it more likely that they would suffer with more anemia than patients without diabetic renal diseases. However, we did not collect data on concurrent diseases, so we weren't able to adjust for that."

Dr. Ford and his associates evaluated the records of 1,823 patients from the U.K. Renal Registry who underwent renal dialysis between 2001 and 2006. They extracted data at time points 0, 1, 2, 3, 4, 5, 6, and 12 months before dialysis and used a quadratic multilevel model to estimate the average pattern of decline in hemoglobin.

The median age of patients was 66 years. Patients with diabetic nephropathy had slightly lower mean hemoglobin levels prior to undergoing dialysis, compared with those who had nondiabetic renal disease (10.8 vs. 11.0 g/dL, respectively). "It's a small difference, but it's statistically significant," Dr. Ford said. ■

Disclosures: *Dr. Ford had no relevant financial conflicts to disclose.*

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