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.

"There is some hope, which is that 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 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.

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 prior cardiovascular event or if they entered the study with a hemoglobin A_{1c} (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 showed a 26% reduction in cardiovascular risk, compared with the usual-care group, but intensive glycemic control appeared to become harmful in patients who had 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 (an Agatston score of 100 or greater), compared with patients who had lower scores (Diabetes 2009;58:2642-8). ■

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