Data Add to Doubts About Tight Glucose Control

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Intensively lowering blood glucose levels did not significantly reduce cardiovascular risk in older patients with poorly controlled diabetes whose blood pressures and cholesterol levels were well controlled, a major long-term study found.

The 1,791-patient Veterans Affairs Diabetes Trial identified two predictors of cardiovascular risk—hypoglycemic episodes and the duration of diabetes—and included a secondary analysis of the safety of using rosiglitazone. The study found no increased risk for MI in patients on rosiglitazone. (See box.)

The VA Diabetes Trial is the third major randomized, controlled study to report no overall cardiovascular benefit from intensive glycemic control, following on the heels of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, in which intensive glycemic control increased the risk of death, and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study.

"Our patients had the worst glycemic control of the three trials," with baseline hemoglobin A_{1c} levels averaging 9.5%, Dr. Carlos Abraira said at a press conference at the annual scientific sessions of the American Diabetes Association.

The HbA_{1c} levels fell to a median of 6.9% within 6 months with intensive therapy. The study was designed to maintain a 1.5% difference in HbA_{1c} levels between the intensive and usual-care group, which reached an HbA_{1c} level of 8.4%, to highlight any effects of intensive therapy.

Patients in the study averaged 60 years of age at enrollment, and 97% were male. About 40% had a history of prior cardiovascular events. At baseline, 80% had hypertension, 50% had lipid abnormalities, and most were obese. The trial strictly controlled blood pressure and cholesterol levels, achieving targets after 2 years of therapy that were maintained during the average 6-year follow-up, reported Dr. Abraira of the Miami Veterans Affairs Medical Center. Dr. Abraira is cochair of the VA Diabetes Trial and professor of medicine at the University of Miami.

Far fewer cardiovascular events occurred than were expected, totalling 231 events in the intensive group and 263 with usual care, probably because of the excellent control of blood pressure and lipids, improved diet and exercise, and treatment with aspirin, said Dr. William C. Duckworth, cochair of the trial and director of diabetes research at the Veterans Affairs Medical Center in Phoenix. Increases in levels of "good" HDL cholesterol in the study greatly decreased the chance of a cardiovascular event.

The study found cardiovascular benefits in patients who started intensive glycemic therapy early after diagnosis of diabetes, less likelihood of benefits for patients with longer-duration diabetes, and a suggestion of potential harm from intensive glycemic control in those with long-standing diabetes before starting the regimen, he said.

"Start intensively treating early after diagnosis, no matter how old they are," Dr. Duckworth suggested.

An episode of severe hypoglycemia was associated with roughly a doubling in risk for a cardiovascular event within 3 months and a tripled risk for death from cardiovascular causes. The study may be the first to document the association between hypoglycemia and cardiovascular risk, which most physicians have assumed to be true, Dr. Duckworth added.

The trial will continue as an observational study for another 9 years.

Dr. Duckworth said the results so far illustrate the inadvisability of setting one glycemic target for all patients with diabetes.

Dr. Duckworth consults for, or has received research funds from, companies that make medications for diabetes, hypertension, or hypercholesterolemia including Sanofi Aventis, Novo Nordisk, Kos Pharmaceuticals, and Amylin Pharmaceuticals. Dr. Abraira has received research support from GlaxoSmithKline, which makes rosiglitazone, and from other companies that make medications for diabetes, hypertension, or hyperlipidemia. ■

No Increase in MI Seen in VA Trial of Rosiglitazone

Three secondary safety analyses of data from the VA Diabetes Trial found neutral effects or protection against cardiovascular events with use of the thiazolidinedione, rosiglitazone, contrary to previous findings.

"We feel that rosiglitazone is not causing any harm to the patients," said statistician Thomas E. Moritz of the Hynes (Ill.) Veterans Affairs Hospital.

A meta-analysis of 42 randomized, controlled studies previously reported a significant 43% increase in the odds of developing an MI and a trend toward higher risk of death from cardiovascular causes in patients with type 2 diabetes treated with rosiglitazone, he noted (N. Engl. J. Med. 2007;356:2457-71). In response, the VA medical system removed the drug from its formulary and the Food and Drug Administration issued a black box warning about potential cardiovascular risks with rosiglitazone.

The meta-analysis findings prompted the VA Diabetes Trial investigators to take a hard look at their data on rosiglitazone. A retrospective case-control analysis matched patients who had cardiovascular events with similar patients who did not have events. "In every analysis we did, the frequency or dosage of rosiglitazone was increased in the group that did *not* suffer the event."

A time-dependent covariate survival analysis looked at changes in rosiglitazone doses over time, and the time to MI, cardiovascular death, a combination of the two outcomes, or heart failure. "If anything, rosiglitazone showed a protective effect rather than a harmful effect" for each outcome, he added.

An intention-to-treat analysis found neither cardiovascular benefit nor harm from taking rosiglitazone. Mr. Moritz has no association with GlaxoSmithKline.

Hemoglobin A_{1c} to Be Expressed as 'Estimated Average Glucose'

BY MIRIAM E. TUCKER
Senior Writer

SAN FRANCISCO — Hemoglobin A_{1c} levels can now be accurately expressed as estimated average glucose for most patients with type 1 and type 2 diabetes.

In a study presented at the annual scientific sessions of the American Diabetes Association, data from both continuous glucose monitoring and fingerstick monitoring over 3 months individuals with and without diabetes were compared with hemoglobin A_{1c} values to derive a formula that relates average glucose levels to HbA_{1c}.

The finding means that laboratories will now report both numbers (as well as the actual value in mmol/mol), and physicians can begin discussing glucose control with their patients in the same units that patients are familiar with from their home blood-glucose monitoring. "Right now, patients hear that their glucose control is some percentage, and are asked to adjust their therapy to achieve results in another unit. We thought it made sense to have both the day-to-day monitoring and the [HbA_{1c}] in the same units," said lead author Dr. David M. Nathan.

The shift to what is now being called the "estimated average glucose," or "eAG," began in 2002, when the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) published a new reference method that measures the concentration of only one molecular species of glycated hemoglobins (the A_{1c}), as opposed to the mixture that had previously been measured. Recognizing that the IFCC's adoption of the new reference method would cause confusion in the clinical setting, an international working group decided in 2004 to launch the study for which final results are now being reported. The study will also appear in the August issue of Diabetes Care (2008;31:1-6).

The participants, who were recruited from 11 centers in the United States, Europe, Africa, and Asia, generated about 2,400 glucose measurements each by wearing the continuous glucose meter for at least 2 days at baseline and then every 4 weeks during the next 12 weeks, and another 300 values by performing eight fingerstick glucose measurements per day for at least 3 days per week. Hemoglobin A_{1c} values were measured at baseline and monthly for 3 months, Dr. Edward S. Horton, professor of medicine at Harvard Medical School, Boston, explained during the briefing.

Of the 507 analyzed study participants, 268 had type 1 diabetes, 159 had type 2, and 80 were not diabetic. Of the initial 661 patients recruited into the study, 18% had baseline hemoglobin A_{1c} values greater than 8.5%; 44% had values of 6.6%-8.5%; and 38% had values of 4.0%-6.5%. These levels generally remained stable throughout the study, with 96% of the subjects maintaining values within 1 percentage point of their baseline value.

At the end of 3 months, the relationship between the HbA_{1c} level and the calculated average glucose (AG) during the preceding 3 months could be expressed in the following formula: AG (in mg/dL) = 28.7 X HbA_{1c} – 46.7. That translates to an eAG of 97 mg/dL for an HbA_{1c} of 5%; 126 mg/dL for 6%; 154 mg/dL for 7%; 183 mg/dL for 8%; 212 mg/dL for 9%; 240 mg/dL for 10%; 269 mg/dL for 11%; and 298 mg/dL for 12%, Dr. Horton said.

In the fall of 2007, a joint consensus statement from the American Diabetes Association (ADA), the European Association for the Study of Diabetes, the IFCC, and the International Diabetes Federation had called for labs to begin reporting HbA_{1c} in the familiar percentage, in the new eAG, and in the actual values in mmol/mol, pending the results of this study (Diabetes Care 2007;30:2399-400).

Study coauthor, Dr. Robert Heine, now with Eli Lilly & Co., noted that although lab reports will now contain three different numbers expressing the same value instead of two, the "whole idea behind the study is to simplify education in clinical practice. ... we really hope that just one number will be applied in clinical practice, and that's the eAG. … The advantage of having this eAG is that we can now educate our patients in a way that they can understand the relationship between long-term glycemic control and what they're doing at home, making it much easier for them to appreciate what blood glucose control means."

The timetable for the new reporting standard is not clear. Manufacturers will need to upgrade laboratory machines with new software, which may not necessarily happen all at once. New point-of-care machines will come with the new standard, but the machines that some physicians already have in their offices will be "more of a challenge" to upgrade, said Dr. Nathan, professor of medicine at Harvard Medical School. In the meantime, the ADA has an online calculator (www.diabetes.org/ag) that can be used to make the conversion, an ADA official commented. ■