No Effect on All-Cause Mortality

Glycemic Control *from page 1*

United Kingdom Prospective Diabetes Studies (UKPDS); the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE); the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE); the Veterans Affairs Diabetes Trial (VADT); and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

These studies all were randomized trials of intensive glycemic control vs. either standard care or less intense intensive control; showed significantly different hemoglobin A_{1c} levels between groups during follow-up; and used cardiovascular events as a primary end point. They included 33,040 subjects with longstanding diabetes.

The meta-analysis shows a beneficial effect of intensive treatment on nonfatal MI and CHD, with no effect on mortality.

DR. RAY

The meta-analysis showed that intensive glycemic control, as evidenced by a 0.9% reduction in HbA_{1c}, significantly decreased nonfatal MI by 17% and CHD events by 15%. It also decreased stroke by a nonsignificant 7%.

Intensive glycemic control did not affect heart failure rates or all-cause mortality, however.

"The absence of convincing data and concerns about possible harm [have] led consensus groups to provide a conservative endorsement for the cardiovascular benefits of intensive glycemic control.

"Our quantitative analysis of randomized controlled trials provides reliable large-scale evidence of a consistent beneficial effect of intensive treatment on nonfatal MI and CHD, without increased risk in all-cause mortality," Dr. Ray wrote (Lancet 2009;373:1765-72).

Dr. David Kendall, medical director at the International Diabetes Center in Minneapolis concurred, noting that another meta-analysis of the same data, published online last month, came to similar conclusions (Nutr. Metab. Cardiovasc. Dis. 2009 May 8 [doi:10.1016/j.numecd.2009.03.021]).

These findings should help clarify a series of apparently contradictory or inconclusive reports for clinicians. This analysis is particularly important given that the ACCORD trial showed a 22% increase in mortality in patients on intensive glucose control and was halted early. "This meta-analysis allows us to look at the entire data set, which indicates that with a preponderance of evidence, there is evidence of a benefit of intensive glucose control—without undue mortality risk," Dr. Kendall said in an interview.

He stressed that the findings on this apparently small effect of glucose on macrovascular complications "should not steer us away from the importance of glucose control and its proven benefit for prevention of eye disease, kidney disease, and other serious microvascular complications." Dr. Kendall was an investigator in ACCORD and has received research support from and is a consultant for several manufacturers of diabetes drugs.

Intensive glycemic control was associated with adverse effects, including greater weight gain (a mean of 2.5 kg) and nearly double the number of patients with severe hypoglycemic episodes as found with less intensive control (2.3% vs. 1.2%).

Dr. Ray reports receiving honoraria from Novartis. ■

Depression, Death Tied in Diabetes

LONG BEACH, CALIF. — People with diabetes have far higher scores on a depression scale than do those without diabetes, according to a large epidemiologic study.

Furthermore, depression also is associated with increased 10-year mortality in people with diabetes, but not in those without the condition, according to Xuanping Zhang, Ph.D., of the Centers for Disease Control and Prevention, Atlanta, and his colleagues. Dr. Zhang reported the findings at a conference on diabetes sponsored by the CDC.

The study used data collected between 1982 and 1992 by the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Survey (NHEFS). The investigators compared 558 people with diabetes to 7,063 people without the disease, and included all individuals for whom they had complete survival data and scores on the Centers for Epidemiologic Studies Depression (CES-D) scale. Scores of 16 and above indicate clinical depression, scores of 16-21 indicate moderate depression, and scores of 22 or greater indicate severe depression.

Among people with diabetes, the mean CES-D score was 26.3, compared with 15.8 among those without diabetes, a statistically significant difference.

In a multivariate analysis that adjusted for age, sex, race, marital status, education, working status, smoking status, physical activity, alcohol consumption, BMI, self-rated health, and the presence of other serious diseases, people with diabetes who also had a CES-D score of 16 or above were 54% more likely to die over 10 years than were those with lower depression scores, a statistically significant increase in risk.

Among people who did not have diabetes, high depression scores conferred a 3% increase in mortality risk, and that increase was not statistically significant.

Dr. Zhang reported that he had no conflicts of interest to disclose.

—Robert Finn

Colesevelam Kept Glucose Down in Extension Study

BY MIRIAM E. TUCKER

HOUSTON — Colesevelam maintained its glucose-lowering effect up to 78 weeks in an open-label extension study involving 146 patients with type 2 diabetes who were also taking metformin.

Colesevelam (Welchol) is a bile acid sequestrant approved for both glycemic control in adults with type 2 diabetes and lowering low-density-lipoprotein cholesterol levels in adults with primary hypercholesterolemia, Dr. Harold E. Bays and his colleagues said in a poster presentation at the annual meeting of the American Association of Clinical Endocrinologists.

Subjects with type 2 diabetes who completed one of three previous 26-week randomized, double-blind, placebo-controlled trials evaluating colesevelam in combination with metformin, insulin, or sulfonylurea were invited to join the 52-week open-label extension study.

All received 3.8 g/day of colesevelam (as six 625-mg tablets), taken either once a day with dinner (six tablets) or twice a day (three tablets with lunch and three with dinner). Patients were given the choice of schedule. All had been previously taking metformin, and continued to take it through the extension study. Doses could be adjusted, however, and other glucose-lowering agents could also be added with the aim of achieving a hemoglobin A_{1c} of less than 7%, said Dr. Bays of the Louisville (Ky.) Metabolic and Atherosclerosis Research Center and his associates.

A total of 222 patients completed the initial randomized, controlled study, and 146 enrolled in the open-label extension. Of those, 81 had received colesevelam in the randomized study and 65 were on placebo (both in combination with metformin). Of those, 56 and 41, respectively, completed the open-label extension.

At the end of the initial 26 weeks, HbA_{1c} levels had dropped from a mean of 8.2% to 7.6% in the colesevelam group, while remaining nearly unchanged in the placebo group (8.1% to 8.2%). These HbA_{1c} levels were maintained over the 52-week extension in the group that had been taking colesevelam the entire 78 weeks, with a final HbA_{1c} of 7.7%.

Those who had been on placebo during the randomized study and were now taking colesevelam achieved a mean HbA_{1c} value of 7.4% by the end of the 52-week extension.

Nine patients discontinued the entire study because of adverse events, including three serious events. Nonserious events deemed possibly or probably related to colesevelam included wheezing, dyspnea, and cough in one patient, abnormal liver function test in one, and dyspepsia in two.

Of 15 serious events reported, 13 were deemed not related to the study drug and two were considered unlikely to be related. Overall compliance in all phases of the study was 88.5%, the investigators reported.

The study was funded by Daiichi Sankyo Inc., which markets colesevelam. ■

Quick-Release Bromocriptine Approved for Type 2 Diabetes

BY ELIZABETH MECHCATIE

Cycloset, a quick-release oral formulation of bromocriptine mesylate, was recently approved by the Food and Drug Administration as a treatment for type 2 diabetes, either as monotherapy or as adjunctive therapy to currently marketed type 2 diabetes drugs, according to the drug's manufacturers.

Cycloset is the first diabetes drug to gain approval since the agency published new guidance for the cardiovascular safety of diabetes drugs last December. Drug makers VeroScience and S2 Therapeutics Inc., announced the approval on May 6. Cycloset is taken by mouth once daily in the morning, and results in a "brief pulse of dopamine agonist activity shortly after its administration," which improves postprandial glucose without increasing plasma insulin concentrations, according to a statement issued by VeroScience.

Bromocriptine is a sympatholytic dopamine D2 receptor agonist that can "exert inhibitor effects on serotonin in the central nervous system," according to a ClinicalTrials.gov summary of a phase III study of Cycloset. In its description, the site says, "It has been proposed that bromocriptine can reverse many of the metabolic alterations and obesity associated with insulin resistance by resetting central (hypothalamic) circadian organization of monoamine neuronal activities."

Cycloset is approved for monotherapy or as adjunctive therapy to currently marketed type 2 diabetes drugs. Postmarketing studies required by the FDA will assess bioavailability and feasibility in pediatric patients between ages 10 and 16, as well as a randomized, double-blind controlled safety and efficacy study in such patients. The FDA waived requirements for pediatric study in patients under age 10 due to the low number of potential participants. ■