Mortality Found No Higher With Rosiglitazone

BY MIRIAM E. TUCKER

NEW ORLEANS — Findings from the RECORD study confirm the growing consensus that rosiglitazone should not be used in patients with a history of heart failure, with previous problems that might have led to myocardial damage, or in women who are at increased risk for fractures.

However, "Although our evidence is insufficient to rule out a small increased risk of myocardial infarction caused by rosiglitazone when compared with other glucose-lowering agents, it appears that for people with type 2 diabetes, rosiglitazone can be used without concern that there is increased overall cardiovascular morbidity and mortality, or for that matter, all-cause mortality," study chair Philip D. Home said at the annual scientific sessions of the American Diabetes Association.

"We recommend monitoring for fluid retention," added Dr. Home, professor of diabetes medicine at Newcastle University, England.

In the prospective, multicenter, open-label Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial, funded by GlaxoSmithKline, addition of rosiglitazone (Avandia) to either sulfonylurea or metformin therapy in people with type 2 diabetes increased their risk for heart failure but did not increase the risk of overall cardiovascular morbidity or mortality in a mean follow-up of 5.5 years (Lancet 2009 June 5 [doi:10.1016/S0140-6736(09)60953-3]).

The study was originally designed to evaluate noninferiority of rosiglitazone on cardiovascular outcomes and glucose control, compared with sulfonylurea, over a 6-year period. It included a total of 4,447 patients with type 2 diabetes whose glucose levels were inadequately controlled with either sulfonylurea or metformin alone.

Patients in the trial—seen in 364 centers in 25 countries in Europe and Australasia—were aged 40-75 years, had a body mass index greater than 25 kg/m^2, and had hemoglobin A_{1c} levels between 7.0% and 9.0% (mean 7.9%) despite maximal doses of either sulfonylurea or metformin monotherapy. Patients who were taking sulfonylurea initially were randomized to add-on treatment of either rosiglitazone or metformin (as "active comparator") while those already on metformin were randomized to the addition of either rosiglitazone or sulfonylurea.

Hazard ratios for rosiglitazone patients were 2.10 for heart failure and 1.57 for bone fractures.

DR. HOME

Rosiglitazone was added at a starting doses of 4 mg/day and titrated up as needed to achieve a target HbA_{1c} of 7.0% or less. Any patient who had an HbA_{1c} of 8.5% or more with the two agents was "rescued" with either a third oral agent (if taking rosiglitazone) or transferred to insulin if on metformin/sulfonylurea. A total of 2,220 were randomized to receive rosiglitazone, and 2,227 to the active control group (sulfonylurea plus metformin).

The overall rate of the primary end point, cardiovascular hospitalization or cardiovascular death, was 28 per 1,000 person-years, occurring in 321 rosiglitazone patients and 323 active control patients. The hazard ratio of 0.99 met the prespecified noninferiority criteria. Excluding cardiovascular events not of atherosclerotic origin gave similar results (HR 0.97).

The predefined composite secondary end point of cardiovascular death, myocardial infarction, and stroke gave a hazard ratio of 0.93 for rosiglitazone vs. active comparator, suggesting a slight but not statistically significant benefit for rosiglitazone. Cardiovascular death and all-cause death were also slightly in favor of rosiglitazone but not statistically significant (HR 0.84 and 0.86, respectively). The hazard ratio for MI was 1.14—there were eight excess cases with rosiglitazone—but this was also statistically nonsignificant.

Heart failure was highly significantly increased with rosiglitazone, with a hazard ratio of 2.10. Increased heart failure with rosiglitazone has been reported previously in other studies, and in an earlier interim analysis of RECORD (N. Engl. J. Med. 2007;357:28-38).

The overall incidence of participant-reported bone fractures was higher in the rosiglitazone group than in the active control group, with a risk ratio of 1.57, higher for women than men (1.82 vs. 1.23). Fractures of the upper limb and distal lower limb were increased, but hip and femur fractures were not.

In the final results, the statistical power for RECORD was less than initially planned because the overall primary event rate in the 4,447 patients followed for a mean of 5.5 years was substantially lower than anticipated. Reasons for this aren't entirely clear, but an editorial that accompanied the interim analysis of the study suggested that incomplete analysis due to a high loss to follow-up (10%) and the differences in medical care in the various countries where the trial was conducted were possible factors.

Dr. Home disclosed that he is on an advisory panel and speakers bureau for, and receives research support from, GlaxoSmithKline. He also has financial relationships with a variety of other companies that make diabetes-related products. ■

Medical Therapy, Revascularization Equal in Type 2 Diabetics

BY DOUG BRUNK

NEW ORLEANS — There were no differences in total mortality among patients with type 2 diabetes and stable coronary heart disease who underwent early coronary revascularization compared with those who underwent intensive medical therapy alone, results from a large 5-year trial showed.

However, those who underwent coronary artery bypass grafting (CABG) had significantly lower rates of major cardiovascular events compared with medical therapy alone, an association that was not seen among those who underwent percutaneous coronary intervention (PCI).

In addition, the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D), which also studied two glucose-lowering strategies, found no difference in outcome whether the patients received insulin-providing or insulin-sensitizing therapy.

The trial results were presented by Dr. Trevor J. Orchard at the annual scientific sessions of the American Diabetes Association.

"I don't think our results will change [clinical] practice, except to reassure clinicians and patients alike that treatment with insulin sensitizers is a perfectly safe and reasonable approach," Dr. Orchard, professor of epidemiology at the University of Pittsburgh Graduate School of Public Health, said during a press briefing about the study.

BARI 2D is the first randomized study conducted in patients with mild symptoms and stable ischemic heart disease to show a benefit of CABG in reducing major cardiovascular events, "which were primarily nonfatal myocardial infarction," said cardiologist Robert L. Frye, chair of the trial and professor of cardiovascular medicine at the Mayo Clinic in Rochester, Minn.

During January 2001–March 2005, researchers in six countries enrolled 2,368 patients with type 2 diabetes and stable coronary artery disease who were candidates for elective PCI or CABG. Each patient was selected to either a CABG stratum group or to a PCI stratum group (N. Engl. J. Med. 2009;360:2503-15).

Of the 763 patients in the CABG stratum group, 385 were randomly assigned to medical therapy (194 to insulin provision and 191 to insulin sensitization) and 378 were randomly assigned to revascularization with CABG, with 190 and 188 assigned to receive insulin provision and sensitization, respectively.

Of the 1,605 patients in the PCI stratum group, 807 were randomly assigned to medical therapy (399 to insulin provision and 408 to insulin sensitization) and 798 were randomly assigned to revascularization with PCI, with 402 and 396 assigned to receive insulin provision and sensitization, respectively.

Mortality was similar, but CABG had lower rates of major cardiovascular events than medical therapy.

DR. ORCHARD

The study's primary end points were the rate of death and the rate of major cardiovascular events, defined as a composite of death, myocardial infarction, or stroke.

At the time of study entry, the mean age of patients was 64 years, 70% were male, and 66% were white. Mean HbA_{1c} level was 7.7% and mean duration of diabetes was 10 years.

Dr. Orchard reported that at 5 years, there were no statistically significant differences in the rates of survival between the revascularization group and the medical therapy group (88.3% vs. 87.8%, respectively) nor between the insulin-sensitization group and the insulin-provision group (88.2% vs. 87.9%).

There also were no differences in the rates of freedom from major cardiovascular events between the revascularization group and the medical therapy group (77.2% vs. 75.9%, respectively) nor between the insulin-sensitization and insulin-provision groups (77.7% vs. 75.4%).

When the researchers analyzed data from the PCI stratum alone, they observed no statistically significant differences in the primary end points between the revascularization group and the medical therapy group.

However, when they analyzed data from the CABG stratum alone, the rate of major cardiovascular events was significantly lower in the revascularization group compared with the medical therapy group (22.4% vs. 30.5%, respectively). This benefit appeared to be greatest in those who underwent CABG and received insulin-sensitizing drugs.

The BARI 2D was supported by grants from the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases. Support was also provided by GlaxoSmithKline, Lantheus Medical Imaging, Astellas Pharma, Merck, Abbott Laboratories, Pfizer, MediSense, Bayer, Becton Dickinson, J.R. Carlson Labs, Centocor, Eli Lilly & Co., LipoScience, Novartis, and Novo Nordisk. Dr. Orchard has served on advisory boards and received consulting fees from several companies that make diabetes-related pharmaceuticals and products, and has an equity interest in Bristol-Myers-Squibb. Dr. Frye is on the advisory boards of Sanofi-Aventis and Schering-Plough. ■