Canadians Document Excess Mortality with Rosiglitazone (Avandia)

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TORONTO, Dec. 11 -- More than three years of thiazolidinedione monotherapy for diabetes was associated with a 40% increase in relative risk of myocardial infarction and a 29% increase in relative risk of death, researchers here found.

The thiazolidinedione treatment's adverse effects were "primarily with rosiglitazone (Avandia)," Lorraine I. Lipscombe, M.D., M.Sc., of the University of Toronto, and colleagues, concluded in the Dec. 12 issue of the Journal of the American Medical Association. There was also a 60% rise in the relative risk of congestive heart failure associated with rosiglitazone.

Compared with other oral hypoglycemic therapy, treatment with rosiglitazone was associated with a rate ratio of 1.76 for MI (95% CI: 1.27 to 2.44, P0.001) and 1.98 (95% CI: 1.44 to 2.72, P0.001) for congestive heart failure.

Dr. Lipscombe and colleagues concluded that the excess cardiovascular events appeared to be limited to rosiglitazone, But they also said they found no evidence that pioglitazone (Actos) reduced the risk of MI and cardiovascular death, a protective effect reported by other researchers.

"In contrast to clinical trial data, which suggested that both pioglitazone and rosiglitazone are associated with an increased risk of congestive heart failure, we observed this association only with rosiglitazone," they wrote.

Last month the FDA ordered that an MI warning be added to the black box on the rosiglitazone label, and it asked for extensive long-term trials to determine the drug's cardiovascular safety. Both rosiglitazone and pioglitazone carry black box warnings for congestive heart failure. (See: FDA Adds MI Warning to Rosiglitazone (Avandia) Black Box)

The nested case-control study of almost 160,000 diabetes patients age 66 or older who were taking at least one hypoglycemic agent was the latest analysis to report a 40% or greater increase in MI among patients taking rosiglitazone, a finding first reported by Steven Nissen, M.D. of the Cleveland Clinic, in a meta-analysis published online by the New England Journal of Medicine more than six months ago.

Dr. Lipscombe and colleagues compared risks of MI, congestive heart failure, and death between patients treated with thiazolidinediones -- rosiglitazone and pioglitazone -- and other oral hypoglycemic agent combinations, after matching and adjusting for prognostic factors.

During a median follow-up of almost four years, 12,491 patients were hospitalized at least once for heart failure, 12,578 for MI, and there were 30,265 deaths.

Over four years, the estimated numbers needed to harm with thiazolidinediones therapy were 34 patients for congestive heart failure, 26 for MI, and 22 for death, Dr. Lipscombe wrote.

The study, the authors wrote, was "to our knowledge the first study to evaluate thiazolidinedione-related outcomes among an entire population of older patients with diabetes." And the study was, they added, the first to "document an increase in mortality among thiazolidinedione users.

"Although we could not determine the cause of death in our study, the fact that cardiovascular events were also increased with thiazolidinediones suggests a possible cardiovascular etiology in this older, high-risk population," they wrote.