# Analysis Ties Rosiglitazone to Increased MI Risk

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Rosiglitazone may be associated with an increased risk of myocardial infarction, according to the results of a meta-analysis of 42 published and unpublished randomized trials.

Patients who received rosiglitazone (Avandia) were 43% more likely to have an MI than were patients who received an active comparator drug or a placebo during 24-52 weeks of treatment. This result was significant but had a wide confidence interval that placed the increase in risk between 3% and 98%. Rosiglitazone also was associated with a nonsignificant 64% increase in the odds of death from cardiovascular causes, reported Dr. Steven E. Nissen and Kathy Wolski of the Cleveland Clinic (N. Engl. J. Med. 2007 [Epub doi: 10.1056/NEJMoa072761]).

"Because exposure of such patients to rosiglitazone is widespread, the public health impact of an increase in cardiovascular risk could be substantial if our data are borne out by further analysis and the results of larger controlled trials," they wrote.

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**DR. NISSEN**

In response to the current study, the manufacturer of rosiglitazone, GlaxoSmithKline, issued a statement saying that the company "strongly disagrees with the conclusions … which are based on incomplete evidence and a methodology that the author admits has significant limitations."

The meta-analysis involved 5 studies that originally were submitted to the Food and Drug Administration for an advisory board hearing on the drug's approval, 35 clinical trials initially identified in GlaxoSmithKline's clinical-trial registry (9 published and 26 unpublished), and 2 large, recently published clinical trials (DREAM—Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication and ADOPT—A Diabetes Outcome Progression Trial). These trials included 15,560 patients who were randomized to receive regimens that included rosiglitazone and 12,283 assigned to control groups that received an active comparator or placebo.

The small number of MIs (86 with rosiglitazone and 72 with control) and deaths from cardiovascular causes (39 with rosiglitazone and 22 with control) make the results susceptible to small changes in the classification of events. The lack of a standard method for identifying or validating outcomes in the trials might have caused these events to be missed or misclassified, Dr. Bruce M. Psaty of the University of Washington, Seattle, and Dr. Curt D. Furberg of Wake Forest University, Winston-Salem, N.C., wrote in an accompanying editorial (N. Engl. J. Med. 2007 [Epub doi:10.1056/NEJMoa072761]).

The investigators had access to only trial-level data and not to patient-level data, and thus could not determine the outcome of the composite of death or myocardial infarction. Time-to-event data for cardiovascular events were not available for these trials, so hazard ratios could not be calculated.

GlaxoSmithKline is conducting the randomized, open-label Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial. In a teleconference on May 21, Dr. Robert J. Meyer of the FDA's Center for Drug Evaluation and Research said an interim analysis of the safety data from RECORD was "reassuring." In its statement, GlaxoSmithKline said it "has not found any safety risk that would interrupt" of the trial.

An unpublished reanalysis of the DREAM trial also provides "contradictory evidence about the risk in patients treated with Avandia," compared with the current meta-analysis, Dr. Meyer said.

The FDA does not know if the potential increased risk of MI or heart-related death extends to other thiazolidinedione drugs, such as pioglitazone (Actos), he said.

Dr. Meyer said the FDA received a meta-analysis from GlaxoSmithKline in August 2006 that included 42 randomized, controlled trials (many of which are likely the same as those in the current study). The FDA is reanalyzing this study because of some issues with the way in which the company conducted its analysis. That meta-analysis also indicated an increased

risk of MI and heart-related adverse events.

Dr. Nissen, chairman of cardiovascular medicine at the Cleveland Clinic, said, "I would not consider an analysis by the company to be useful here. We really have to focus on analyses done by independent people, and that includes perhaps the FDA and certainly outside physician-scientists,"

The rosiglitazone label was recently changed to include a warning about a potential increase in heart attacks and heart-related chest pain in some individuals. This warning was based on the result of a controlled clinical trial in patients with existing heart failure, according to the FDA.

In their editorial, Dr. Psaty and Dr. Furberg said that, "in view of the potential cardiovascular risks and in the absence of evidence of other health advantages, except for laboratory measures of glycemic control, the rationale for prescribing rosiglitazone at this time is unclear. Unless new data provide a different picture of the risk-benefit profile, regulatory action by the FDA is now warranted."

According to Dr. Nissen, "the FDA needs to begin to think more clearly about these kinds of risky situations and act earlier."

Dr. Meyer said that the FDA would not exclude any regulatory action at this point, and an advisory board committee meeting could take place in the next few months.

The investigators said their results led them to question "the appropriateness of the current regulatory pathways for the development of drugs to treat diabetes," a sentiment that was echoed in the editorial.

"Rosiglitazone was approved on the basis of short-term studies of the surrogate end point of glycemic control," Dr. Psaty and Dr. Furberg wrote.

But the underlying assumption that high levels of glycated hemoglobin increase risk and that a reduction in this measure will improve health outcomes "ignores the many actions of the genes activated by PPAR-γ agonists, only some of which are currently known. Many physicians did not require proof of health benefits as a criterion for selecting rosiglitazone as a therapy for type 2 diabetes," they added.

Rosiglitazone potentially could contribute to the risk of MI by increasing LDL cholesterol levels or modestly reducing hemoglobin levels, which could provoke ischemic events in those with heart failure, the investigators said.

Dr. Richard Hellman, president of the American Association of Clinical Endocrinologists, noted that glitazones probably affect more than 100 human genes. "When an agent is so active at the gene level, postmarketing studies need to address the issue of special populations," said Dr. Hellman, clinical professor of medicine, University of Missouri, Kansas City. The findings "provide more ammunition for increased caution" in prescribing rosiglitazone. ■