New meta-analysis demonstrates heart risks associated with rosiglitazone

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Eleven years after the introduction of the diabetes drug rosiglitazone, data from available clinical trials demonstrate an increased risk for heart attack associated with its use and suggest an unfavorable benefit-to-risk ratio, according to a report posted online today that will appear in the July 26 print issue of *Archives of Internal Medicine,* one of the JAMA/Archives journals. The study was published online in advance of an upcoming Food and Drug Administration meeting that will review the safety of rosiglitazone.

Rosiglitazone was approved in 1999 to treat hyperglycemia (high blood glucose levels) among patients with type 2 diabetes, according to background information in the article. Concerns about the cardiovascular safety of rosiglitazone first arose in 2007, when a meta-analysis demonstrated a significantly increased risk for myocardial infarction (heart attack) and a borderline significant increase for cardiovascular death. The debate over the medication's safety has continued during the past three years, and the U.S. Senate Committee on Finance recently released a report providing additional details about internal analyses conducted by the U.S. Food and Drug Administration and by GlaxoSmithKline (GSK), the drug's manufacturer.

No large, definitive cardiovascular outcomes trials have been conducted with rosiglitazone. However, as a consequence of a 2004 court settlement in New York, GSK was required to post clinical trial results on a public web site. Steven E. Nissen, M.D., and Kathy Wolski, M.P.H., of The Cleveland Clinic Foundation, searched this GSK data and

MEDLINE through February 2010 and identified 56 trials involving 35,531 patients, 19,509 of whom received rosiglitazone and 16,022 who received control medications.

In the combined studies, rosiglitazone therapy was associated with a significantly increased risk of myocardial infarction by an estimated 28 percent to 39 percent, although the risk of cardiovascular death was not increased. "An alternative analysis that included trials with no cardiovascular events found a similar hazard," the authors write. "Subgroups classified by study duration and comparator drug also showed elevated odds ratio estimates."

"These findings are consistent with prior meta-analyses conducted by GSK, the FDA and most independent investigators demonstrating an increased risk of myocardial infarction in patients treated with rosiglitazone," they continue. "The FDA has announced that it will conduct an advisory committee meeting in July 2010 to consider whether to remove rosiglitazone from the market."

The mechanisms by which rosiglitazone may cause cardiovascular harm are not clear, the authors note, but could involve increases in low-density lipoprotein (LDL, or "bad" cholesterol) levels or genetic effects associated with the production of an enzyme linked to plaque rupture.

"The public health implications of these results are considerable. There are more than 23 million persons with diabetes in the United States alone and nearly 300 million worldwide. Cardiovascular disease is the leading cause of death in patients with type 2 diabetes, representing approximately 68 percent of all causes of mortality," the authors conclude. "Although hyperglycemia has been associated with an increased risk of microvascular adverse events, there are now 12 classes of drugs that are approved to lower blood glucose levels, including insulin. Because no unique benefits of rosiglitazone use have been

identified, administration of this agent solely to lower blood glucose levels is difficult to justify."

More information: Arch Intern Med. 2010;170[12]: doi:10.1001/archinternmed.2010.207

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