Reanalysis of controversial meta-analysis says writing off rosiglitazone may be premature

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Rosiglitazone, a drug marketed by GlaxoSmithKline as Avandia® for the treatment of type 2 diabetes, came under fire after an article published online May 21 by the New England Journal of Medicine linked it to significantly increased risk of heart attack and cardiovascular death.

That article was based on a meta-analysis conducted by Dr. Steven Nissen and Kathy Wolski of 42 clinical trials involving 27,847 patients for whom rosiglitazone was prescribed.

Now, a re-analysis of the data used in the Nissen and Wolski analysis - using different statistical models - suggests that the earlier methodology may have resulted in inflated risk estimates. The new analysis, conducted by researchers at Cedars-Sinai Medical Center, concludes "that only prospective clinical trials designed for the specific purpose of establishing the cardiovascular benefit or risk of rosiglitazone will resolve the controversy about its safety."

In an Annals of Internal Medicine article, cardiologists George Diamond, M.D., and Sanjay Kaul, M.D., describe additional analyses that provide different perspectives on rosiglitazone's safety issues. "Uncertain Effects of Rosiglitazone on the Risk of Myocardial Infarction and Cardiovascular Death" appeared online Aug. 7.

Both physicians testified Monday, July 30, before a Food and Drug Administration advisory committee reviewing the data on rosiglitazone's safety. At the conclusion of hearings, the panel recommended that Avandia carry new risk warnings but stopped short of calling for the drug to be removed from the market.

"The original meta-analysis employed one statistical model, but there are other approaches that deserve consideration as well. Only when different methods give us the same answers should we be confident in the results," say Diamond and Kaul.

In their study, Nissen and Wolski pulled together data from wide-ranging clinical trials that were not necessarily designed to track heart attacks and cardiovascular death. In addition, most of the trials did not report occurrence of any heart attack or cardiovascular death. In this type of "sparse data" situation, the statistical model employed by Nissen and Wolski tends to overestimate risk, and some experts call for applying a "correction factor." When the "corrected" data were recomputed using a different model, risk estimates were found to be lower.

"Although the risks were still elevated, they were no longer statistically significant. There was greater uncertainty about the risk associated with rosiglitazone than was originally reported, with neither increased nor decreased risk established conclusively," the authors say.

Even with the re-analysis, Diamond and Kaul are concerned about the practicality and reliability of combining data from 42 studies that had a variety of trial designs and protocols. Therefore, they believe, the controversy over rosiglitazone's risk will only be resolved when clinical trials focusing on all these issues are completed.

Source: Cedars-Sinai Medical Center