

Rosiglitazone: seeking a balanced perspective



"Health alert over diabetes drug linked to heart risks", ran the headline in one UK newspaper. Shares in Glaxo-SmithKline (GSK) proceeded to plummet. Financial analysts predicted troubled times for the company. And on May 21, 2007, the US Food and Drug Administration (FDA) published a "safety alert", concluding that "serious concern" existed over GSK's rosiglitazone, a drug approved for the treatment of type 2 diabetes.

The occasion for this sudden anxiety was a systematic review of 42 trials published in the *New England Journal of Medicine* by Steven Nissen and Kathy Wolski from the Cleveland Clinic. They reported an odds ratio of 1.43 (95% CI 1.03–1.98) for myocardial infarction (MI) in those taking rosiglitazone compared with controls. The odds ratio for cardiovascular death was 1.64 (95% CI 0.98–2.74). GSK had already submitted its own pooled analysis to the FDA, which suggested that short-term use of rosiglitazone might increase the risk of heart attack by some 30–40%.

The tone of the *NEJM* paper was one of urgency. In an accompanying editorial, Bruce Psaty and Curt Furberg went further and questioned the whole rationale for prescribing rosiglitazone. GSK has responded by saying that it "strongly disagrees" with the conclusions of the *NEJM* paper. Who is right?

The two most reliable studies to inform decision-making are ADOPT (published in the *NEJM*) and DREAM (published in *The Lancet*). DREAM included 5269 adults. The MI and MI/stroke/cardiovascular composite event rates in the rosiglitazone group were 0.6% (control, 0.3%) and 1.2% (control, 0.9%), respectively. Neither result was statistically significant. ADOPT included 4360 patients. The only significantly relevant finding was an excess of congestive heart failure episodes for rosiglitazone-treated patients compared with glyburide (22 vs nine events).

Taken together, these results, although based on very small numbers of events, certainly raise a signal of concern and indicate the need for more reliable information about rosiglitazone's safety. But the FDA, physicians, and patients can reasonably await the results of RECORD, a phase III trial designed specifically to study cardiovascular outcomes. Until the results of RECORD are in, it would be premature to overinterpret a meta-analysis that the authors and *NEJM* editorialists all acknowledge contains important weaknesses.

To avoid unnecessary panic among patients, a calmer and more considered approach to the safety of rosiglitazone is needed. Alarmist headlines and confident declarations help nobody. ■ *The Lancet*

The printed journal includes an image merely for illustration

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For the ADOPT study see
N Engl J Med 2006; **355**: 2427–43.
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For the DREAM study see
Articles Lancet 2006; **368**:
1096–105.