

## THE PERFECT STORM— DRUG SAFETY AND ROSIGLITAZONE

### Abbreviations:

**FDA** = US Food and Drug Administration; **RECORD** = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

On May 21, 2007, the *New England Journal of Medicine* published 2 contributions online on the cardiovascular risks of rosiglitazone (Avandia)—an article by Nissen and Wolski (1) and an accompanying editorial (2). The US Food and Drug Administration (FDA) followed later that day with an FDA alert on rosiglitazone (3). Those 3 communications triggered a flurry of responses, counterresponses, accusations, and cautions that not only further fueled the controversy concerning the potential cardiovascular risks of rosiglitazone but also highlighted some of the most important shortcomings in our nation's method of ensuring drug safety.

At the center of the storm were both the *New England Journal of Medicine* article on rosiglitazone by Nissen and Wolski (1) and the accompanying editorial by Psaty and Furberg (2). The article was a meta-analysis of 42 studies on rosiglitazone. When the authors pooled the data from the studies for analysis, they found that rosiglitazone use was associated with an increased cardiovascular risk. Calculations showed an increased odds ratio of 1.43 for the risk of acute myocardial infarction for patients taking rosiglitazone ( $P = 0.03$ ) and an increased odds ratio of 1.64 for the risk of death from cardiovascular causes ( $P = 0.06$ ).

The editorial by Psaty and Furberg (2) went further, stating that the possibility of cardiovascular benefit from rosiglitazone seemed remote. Their conclusion was that the rationale for prescribing rosiglitazone was unclear.

Nissen and Wolski (1) wrote that their analyses had serious handicaps. They did not have access to original source data and consequently were unable to perform either time-to-end analyses or calculations of dose-response relationships from the data. Even more importantly, and most tellingly, no trials included in the meta-analysis were originally designed to explore cardiovascular outcomes. In fact, the strength of their conclusions was seriously undermined by the potential ambiguities in the data. It was unclear whether there was a uniform description of the adverse events. Moreover, the number of adverse events was small, and the confidence intervals were very wide. Readers cannot even exclude the possibility that misclassification of adverse events may have skewed the reported results.

The term a “perfect storm” was used to describe the recent sequence of events because the firestorm of interest surrounding the article by Nissen and Wolski (1) had multiple unintended and perverse consequences. As an example, the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), which is a major ongoing study specifically designed to examine the risk of cardiovascular outcomes in patients receiving rosiglitazone, may well become a casualty of the heightened media interest. The widespread front-page coverage of the cardiovascular risks of rosiglitazone resulted in the rapid withdrawal of a considerable number of research subjects from the RECORD trial. The number of subjects who have withdrawn from the trial since May 21 may be large enough to prevent the data from being of sufficient statistical power to answer the questions raised by the Nissen and Wolski article (1). Ironically, the intense fears raised by the controversy may prevent us from determining the safety of rosiglitazone in patients with diabetes. Although we know that rosiglitazone has proven glucose-lowering abilities, it also has equally long-established risks for patients with substantially decreased left ventricular function and heart failure. What is not certain is whether it poses a small but significant risk of myocardial infarction for many patients with diabetes, a large risk for only a few patients, or even no increased cardiovascular risk at all. Overall, the available data suggest that rosiglitazone is associated with a small but definitely increased cardiovascular risk.

We are left with unanswered questions, but without any assurance that the answers will be forthcoming. Establishing the cardiovascular risks of rosiglitazone is no longer only an academic pursuit that will be decided dispassionately in a measured and leisurely way. Instead, it has become a very public and widely engaging issue because many patients with diabetes are both upset and fearful. They suspect that, as in the case of troglitazone (Rezulin) in 1997, cerivastatin (Baycol) in 2001, and other medications subsequently removed from the market, the full extent of the risks of rosiglitazone are not being shared with them but rather are being minimized. The widespread apprehension that now exists is influencing decisions in clinical settings throughout the world. There are numerous anecdotal reports of fearful patients discontinuing the use of their medication abruptly, without consultation and without substitution of another method of controlling their glucose levels. These patients may be inadvertently putting themselves at risk for complications. Bad public policy has often led to chaotic decision making, on a bed of uncertainty and confusion. This “perfect storm” has had many unintended and unfortunate consequences.

Clearly, we need a new policy on the continued evaluation of drug safety after a drug achieves FDA approval. Almost everyone is an advocate of drug safety—until the bill comes due. The pharmaceutical companies definitely have a responsibility for postapproval studies. Although it is true that a major current study on the cardiovascular risks of rosiglitazone, the RECORD trial, is funded by GlaxoSmithKline, the developer of rosiglitazone, it clearly came too late because the trial is still in progress almost 8 years after the drug was approved by the FDA. Moreover, if we are serious about drug safety, we must deal with the inherent conflict of interests when we ask the company that is developing the drug to be the only entity to both design and underwrite the definitive studies that potentially could reduce the number of patients for whom the medication will be prescribed.

Where is the federal government, which is so committed to drug safety? Where are the earmarked dollars placed in the National Institutes of Health or the Agency for Healthcare Research and Quality budget to be distributed for the best and most scientifically sound proposals to evaluate the safety of recently approved drugs? And where are trials funded by the well-endowed great universities, medical centers, and foundations? They, too, should have a vested interest in competing to answer the question of whether a drug, approved after well-done randomized controlled trials on homogeneous, relatively healthy patient populations have shown the efficacy of the agent, will be as safe in a wider population, in patients with a more heterogeneous mix of comorbid conditions, varied ethnic and genetic characteristics, and widely different ages.

Our federal legislators and federal administrators appear unwilling to change the status quo, which currently is restricting our postapproval drug safety studies to the ones paid for by someone else—even though more careful and complete ongoing studies would benefit and protect all of us. The rosiglitazone fiasco, still unfolding, is a prime example of our collective failure as a society to put our money where our mouth is. We must develop a policy that, from the moment a new and promising drug is approved, ensures the performance of well-reasoned, robust, ongoing scientific trials. Such investigations must carefully and thoroughly study whether it is safe and

appropriate to use the new drug in the entire population that could potentially be treated, or whether there are differences in some subpopulations in their risk-benefit ratio as compared with the original data. Perhaps at the end of the day, rosiglitazone, for example, may be found to be quite safe in many patients but dangerous in others. As long as we are not serious about paying the bill for drug safety, we will have more “perfect storms,” repeating this current fiasco many times over. Surely our patients deserve better.

## DISCLOSURE

Dr. Hellman is not speaking on behalf of either the National Quality Forum or the American Association of Clinical Endocrinologists. He does not receive any grants or other financial considerations from any manufacturer of glitazones.

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