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EDITORIAL

Avandia and Risk for Acute Cardiovascular Events: Science or Sabotage?

In a recent paper published in the *New England Journal of Medicine*, Nissen and Wolski suggest that the use of rosiglitazone maleate (Avandia; GlaxoSmith Kline, Philadelphia, PA) to control hyperglycemia in patients with diabetes mellitus increases risk for acute myocardial infarction and death.[1] This study was featured as "breaking news" on websites and as front page articles in many of the most influential newspapers and periodicals in the world. The findings were sensational and were followed by the usual news bites about how the Food and Drug Administration leaves dangerous drugs on the market. Senator Charles E. Grassley (D - IA) and U.S. Representative Henry A. Waxman (D - CA) immediately called for Congressional hearings and the hunt was on. Once again, our broken system just had to be righted and fixed. By golly, Americans and people throughout the world were being put in harm's way and the truth, irrespective of stock valuations and drug czar power play, would be brought to shining light!

In a manner similar to the publication in *JAMA* of an analysis of the cardiovascular safety of muraglitizar, the analysis of rosiglitazone was published as an "emergency paper" because of the purported effect size and the potential consequences of this impacting millions of lives around the world.[2] The results alarmed patients and physicians alike. Specialty organizations such as the American Diabetes Association, the American College of Cardiology, and the American Heart Association urged calm and advised patients to discuss the situation with their doctors. Sage but ultimately safe and limited (to the point of uselessness) advice. Many doctors were uncertain as to how to respond given that the vast majority did not have a chance to either read or interpret the paper before the phone calls set in. Many simply discontinued the drug out of fear of being sued or because patients insisted on being taken off. Within a couple of days, plaintiff lawyers were advertising widely and encouraging patients to contact them if they thought they had been injured by Avandia. The press was interpreting the data. Thanks a lot,

NEJM. Only this time, after a few days, there was some push back. The sensational news began to be balanced by significant skepticism, a questioning of the methods behind the analysis, as well as some of the intangibles that may have colored the tent housing the three ring circus.

Patients had some interesting things to say. One asked if I could give him all of the Avandia samples I had because nothing else was able to control his glycemia as well. Another wanted to know if all of the specialty organizations were as clueless as the ones quoted above. Correctly, they surmised that the advice given was shallow and did not provide viable direction to patients or physicians. Still another astute observer asked why this was not presented to the FDA first, rather than Rep. Waxman. If drug safety was the true goal, why turn the issue into a political lynching?

It is known that new legislation is winding its way through Congressional Committees. Perhaps somewhere, somehow, an example, a scapegoat, just had to be found to prove that the FDA was not doing its job. Patients are indeed smarter than we often give them credit for. The FDA was wide awake as well and stood its ground: it did not recommend that patients go off of the drug or that they be switched to other antiglycemic medications. In an online editorial, *The Lancet* also noted: "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."

Why am I skeptical? The analysis in question was a "meta-analysis" of 42 studies, most of which were not powered to evaluate the effect sought, namely adverse impact on risk for cardiovascular events. Many of the studies had 1 vs 0, 2 vs 1, or 0 vs 1 events and confidence intervals were often wide. Comparators could be placebo or active drug, no distinction was drawn. Studies that did not have cardiovascular events were excluded. This exclusion in and of itself could have substantially thrown the principal finding one way or the other. We have no idea how well groups of patients were matched for risk factor background and intensity of therapies that affect cardiovascular risk (ie, statins, aspirin, angiotensin converting enzyme inhibitors, etc). Most of the studies were of short duration (6 months), not an adequate period of time to evaluate risk for myocardial infarction and death. Hazard ratios could not be calculated because the authors did not carry out a time-to-event analysis. Summary data rather than source data was used. The accompanying editorials were supportive of the core conclusion despite these significant methodological flaws.

Then came the rebuttals. Prospective clinical trial data always carry more weight than a meta-analysis. In the A Diabetes Outcome Progression (ADOPT) trial, there was no statistically significant difference in risk for a cardiovascular event between rosiglitazone and either metformin or glyburide. An analysis of data from the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial showed no significant elevation in risk for rosiglitazone compared to placebo. In a large managed care database containing 33,363 patients (The Balance Cohort Study), no signal for increased risk has emerged. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial is a prospective trial evaluating the effect of rosiglitazone on risk for cardiovascular events in patients with diabetes mellitus. In response to the Nissen and Wolski analysis, an interim analysis was performed showing that there is no statistically significant difference between

groups. However, in the accompanying editorials written by the same authors who lent commentary on the Nissen meta-analysis, the authors argue in every way possible that despite this lack of significance, the results echo that of the meta-analysis. Suddenly we have a new standard: a simple trend in the absence of statistical significance now clearly and definitely shows *significance*. Just exactly how significant is that which is non-significant? A question truly worthy of Hegel and Heidegger. How interesting. Academia will never, ever be the same again. An interim analysis of the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial funded by the National Institutes of Health also uncovered no signal for harm by rosiglitazone that would compel the investigators to discontinue the study. In the end, nothing seemed to be enough for the NEJM.[3,4]

Despite a call by Psaty and Furberg for the FDA to take regulatory action against Avandia,[5] Andrew von Eschenbach, MD, Commissioner of the FDA, informed members of Congress that the evidence for increased risk for cardiovascular events "remains inconclusive" and that the "FDA is not justified in taking additional regulatory action or recommending that patients stop using it." I agree. As a physician in practice, I have found both thiazolidinediones (rosiglitazone and pioglitazone) to be valuable and efficacious medications for treating diabetes mellitus. Until either one is definitively proven to be harmful, I will continue to use them.

Medications need to be depoliticized. Some of our most revered medical journals have assumed a distinctly hostile attitude toward pharmaceutical companies. However, many of these same journals commit more pages to pharmaceutical advertising than they do to science. It is no secret that they compete for large trials. I suspect one of the reasons for this is so they can attract large sums of money to generate reprints of the article for worldwide distribution to physicians. Did the politicians find the drug target they were hoping for in Avandia? I doubt it. So which drug is next? If aspirin or warfarin were brought before regulatory authorities in the year 2007, would they be approved? They are associated with adverse events, but also unquestionably save lives. How about acetaminophen? Use your imagination. There must be some semblance of sanity in finding an appropriate balance between therapeutic benefit and risk for adverse events. In either case, the data must be convincing. Is lowering blood sugar good? We have known that the answer is yes from the time of Banting and Best. I ask myself everyday: without drugs, how much good can I do my patients? In a Norman Rockwell world, probably some. However, people want and deserve more than this.

So, science or sabotage? Like many other physicians, I suspect a little of both.

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