

# The Rosiglitazone Story — Lessons from an FDA Advisory Committee Meeting

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On July 30, 2007, the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) convened to discuss the myocardial ischemic risk associated with rosiglitazone treatment in patients with type 2 diabetes mellitus. The joint committee, which I chaired, consisted of 24 experts in cardiovascular disease, epidemiology, biostatistics, and endocrinology. After lengthy discussions, we concluded that the use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischemic events than placebo, metformin, or sulfonylureas.

That conclusion was based primarily on three independently conducted meta-analyses demonstrating an increase in the relative risk of myocardial infarction, angina, or sudden death among patients taking rosiglitazone (see Table 1).<sup>1</sup> Presentations by FDA staff members suggested that a subgroup of patients with type 2 diabetes who are at higher risk for these events includes those

with long-term nitrate use and those receiving concomitant insulin therapy. Still, there were several caveats inherent in the meta-analyses, including the facts that most of the clinical trials lasted only 6 months (although the two largest trials, which contributed most of the end points, were longer), that there were relatively few myocardial events overall, and that differences existed in adjudication of ischemic events. Ultimately, the committee voted to recommend not that rosiglitazone be removed from the market but rather that label warnings and extensive educational efforts be instituted immediately. The committee also requested further studies, but disconcertingly, none of the several proposed analyses of the ongoing clinical trials is likely to define an absolute risk for myocardial ischemic events in patients with diabetes who are taking this drug.

The basic plot of the rosiglitazone story quickly became obvious to the advisory committee: a new “wonder drug,” approved prematurely and for the wrong reasons by a weakened and underfunded

government agency subjected to pressure from industry, had caused undue harm to patients. Notwithstanding this characterization, as well as the emotional nature of the hearing and the media distractions, the committee meeting attempted to demonstrate the dispassionate application of scientific evidence to public health decision making. In fact, several basic tenets emerged at this meeting that might ideally be used as guiding principles for improving the process of approving new drugs: first, the pathogenesis of disorders that require intervention must be fully understood; second, treatment options for these diseases should be clarified through an evidence-based system; and third, a uniform approach should be used to determine the societal benefits and risks associated with a given intervention.

It has been 80 years since insulin was discovered and 50 years since sulfonylureas were introduced. Since those developments occurred, tremendous strides have been made in understanding the origins and sequelae of diabetes mellitus. For example, because it accelerates atherosclerosis, type 2 diabetes quadruples the risk of macrovascular disease. And ischemic heart disease continues to be a major cause of death among patients with diabetes. Yet the results of our current therapies fall short of our high expectations for chronic disease management.

For example, we know that in type 1 diabetes, metabolic control

**Table 1. Results of FDA Meta-Analysis of 42 Randomized Trials Comparing Rosiglitazone with Other Drugs or Placebo.**

Adverse Event	Rosiglitazone Group (N=8604)	Control Group (N=5633)	Odds Ratio (95% CI)	P Value
	<i>% of patients</i>			
Any ischemia	2.0	1.5	1.4 (1.1–1.8)	0.02
Serious ischemia	1.0	0.8	1.4 (1.0–2.1)	0.06
Myocardial infarction, cardiovascular death, or stroke	0.73	0.67	1.2 (0.7–1.8)	0.40

can reduce the risk of microvascular complications. On the other hand, the two largest randomized, placebo-controlled trials in patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study and the University Group Diabetes Program, failed to find a significant reduction in cardiovascular events even with excellent glucose control.<sup>2</sup> Moreover, we are facing a troubling paradox: preliminary data that were presented at the meeting and published by Gerrits et al.<sup>3</sup> suggest that among the thiazolidinediones — a class of drugs that has been shown to improve metabolic control — rosiglitazone may increase cardiovascular risk whereas pioglitazone may reduce it. Until we have a better grasp of the pathogenesis of atherosclerosis in type 2 diabetes, it will be difficult to design therapies to prevent this complication or even to determine how the currently available agents that act at multiple sites may affect clinical outcomes in very different ways.

Not surprisingly, glycemic control has been the centerpiece of therapeutic interventions in type 2 diabetes for many years. Within the past decade, several new drugs that result in “glycemic durability” — a reduction in the glycated hemoglobin level — have been approved by the FDA. However, change in the glycated hemoglobin level is a relatively poor surrogate for cardiovascular outcomes in type 2 diabetes, accounting for only 5 to 15% of the variation in ischemic risk.<sup>2</sup> This finding represents a major dilemma for practitioners, regulatory agencies, and patients who seek the newest and best treatments for this disease.

The controversy surrounding

biochemical surrogates versus clinical outcomes was also highlighted at the FDA meeting when the advisory committee reviewed one of the largest randomized trials of rosiglitazone, A Diabetes Outcome Prevention Trial, or ADOPT. In that study, the percentage decrease in glycated hemoglobin was greater with rosiglitazone than with metformin or sulfonylureas, yet the risks of congestive heart failure and cardiovascular ischemia were higher.<sup>4</sup> These data suggest that we urgently need to change the regulatory pathway for drugs for the treatment of type 2 diabetes to make clinical outcomes, not surrogates, the primary end points. This is not a radical proposal: 20 years ago, the FDA shifted its primary efficacy end point for osteoporosis drugs from bone mineral density (a reasonable surrogate for the risk of fracture) to fractures themselves. Without a regulatory sea change with regard to diabetes drugs, we are certain to be in the same position 5 years from now that we are in now: we will again find ourselves in possession of a new wonder drug that is designed to treat a devastating chronic disease but that may do more harm than good.

Drugs are approved or removed from the market on the basis of evidence from randomized, controlled trials. In the FDA hearing on rosiglitazone, several meta-analyses (see Table 1) revealed a significant increase in the risk of myocardial ischemic events among patients taking rosiglitazone. However, an interim analysis of the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, which was

designed specifically to assess cardiovascular risk among patients receiving rosiglitazone, failed to demonstrate a similar risk.<sup>5</sup> In addition, two large observational studies, one conducted by Tricare for the Department of Defense and one conducted by WellPoint (the largest health insurer in the United States), noted no appreciable signal of increased cardiovascular risk with either of the available thiazolidinediones (see Table 2). The contrasts among the levels of evidence and the results regarding the safety of rosiglitazone raised new questions about relative and absolute risks but also highlighted the weaknesses of observational studies examining events that are common and whose rates are likely to be increased only slightly by a given drug, even in a large cohort (such as that used by WellPoint, which comprised 160,000 patient records).

This issue led to an interesting sidelight at the meeting. Recently, there have been calls for the FDA to fund and oversee phase 4 post-marketing studies as a means of determining the safety of newly approved drugs. The two observational studies on thiazolidinediones whose results were presented at our meeting had been performed independently of the manufacturers and the FDA. The indeterminacy of their results, due to the inevitable effects of the many confounding variables inherent in such studies, illustrates why this approach alone will neither solve the overriding problems of drug safety nor ultimately help a chronically underfunded federal agency. There is no doubt that it will be costly to undertake true safety and efficacy studies of new

**Table 2. Risk of Cardiac Events with Rosiglitazone and Pioglitazone as Compared with Other Oral Antidiabetic Agents, According to the WellPoint Observational Study.\***

Drug	Total No. of Patients	Acute Myocardial Infarction			Acute Myocardial Infarction or Unstable Angina				
		No. of Events	Incidence per 100,000 Patient-Yr	Hazard Ratio (95% CI)	P Value	No. of Events	Incidence per 100,000 Patient-Yr	Hazard Ratio (95% CI)	P Value
Rosiglitazone	22,050	212	0.73	1.029 (0.886–1.194)	0.710	415	1.43	1.086 (0.979–1.205)	0.117
Pioglitazone	23,768	232	0.74	1.044 (0.905–1.205)	0.553	414	1.33	0.987 (0.890–1.095)	0.808
Other oral antidiabetic agents	120,771	866	0.72	1.000		1613	1.34	1.000	

\* Data are from the FDA advisory committee testimony of Samuel Nussbaum, M.D., executive vice president and chief medical officer, WellPoint.

drugs using clinical outcomes as primary measures, but in the long run, these efforts will save time, energy, and money.

The rosiglitazone story thus carries lessons for scientists, practitioners, and regulators alike. One can only hope that the energy generated by the advisory committee meeting will be channeled into improving the open hearing process to better serve all interested parties.

Dr. Rosen chaired the FDA advisory committee meeting on rosiglitazone on July 30, 2007; the views expressed in this article are those of the author and do not necessarily

reflect those of the advisory committee or the FDA.

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## FOCUS ON RESEARCH

# Bridge to Life — Cardiac Mechanical Support

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Even with well-managed care, many patients with severe heart failure reach a stage at which medical therapy is insufficient to sustain an acceptable level of cardiac function. It is estimated that 0.2% of persons over 45 years of age in the United States, or nearly 200,000 people, may fit this description.<sup>1</sup> Since

only approximately 2000 donor hearts are available in the United States each year for transplantation, the need for another approach to cardiac replacement is well established.

Investigators and the medical-device industry have been pursuing the development of mechanical cardiac support for more

than four decades. The earliest forms of such support to see clinical use were cardiopulmonary bypass, introduced in 1953 and used for cardiopulmonary support during cardiac surgery, and intraaortic balloon counterpulsation, introduced in 1962 and used for temporary partial hemodynamic support and to improve