



The Cardiovascular Safety of Diabetes Drugs — Insights from the Rosiglitazone Experience

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The management of type 2 diabetes has been challenged by uncertainty about possible cardiovascular effects related to treatment intensity and choice of drug. Although the Food and Drug

Administration (FDA) considers a decrease in glycated hemoglobin an approvable end point, very intensive glycemic control is associated with increased cardiovascular and all-cause mortality.¹ The safety of specific drugs for type 2 diabetes — particularly the thiazolidinediones — has also been questioned. After rosiglitazone had been approved in the United States in 1999 and in Europe in 2000, a highly publicized meta-analysis in 2007 reported a 43% increase in myocardial infarction ($P=0.03$) and a 64% increase in death from cardiovascular causes ($P=0.06$).² This report and subsequent FDA advisory committee

reviews led to a boxed warning of myocardial ischemia in 2007 and highly restricted access to rosiglitazone in 2010. In 2010, the FDA placed a full clinical hold on the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial (ClinicalTrials.gov number, NCT00879970), a large cardiovascular-outcome trial designed to evaluate the benefit of rosiglitazone and pioglitazone as compared with placebo (superiority hypothesis) and the safety of rosiglitazone as compared with pioglitazone (noninferiority hypothesis). In part owing to the rosiglitazone experience, the FDA issued an updated Guidance for Industry in 2008 requiring that

preapproval and postapproval studies for all new antidiabetic drugs rule out excess cardiovascular risk, defined as an upper bound of the two-sided 95% confidence interval for major adverse cardiovascular events (MACE) of less than 1.80 and less than 1.30, respectively.³ Regardless of the presence or absence of preclinical or clinical signals of cardiovascular risk, the guidance has been applied broadly to all new diabetes drugs, creating substantial challenges in the drug development and approval process.

On June 5 and 6, 2013, the FDA held a joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (on which we serve) and the Drug Safety and Risk Management Advisory Committee to further evaluate the cardiovascular safety of rosiglitazone. When rosiglitazone was approved in Europe, the European

Medicines Agency raised concern about the cardiovascular risks of the thiazolidinedione class, including fluid retention, heart failure, and increased levels of low-density lipoprotein cholesterol. This concern led to a postmarketing requirement that cardiovascular-outcome trials be conducted for both pioglitazone and rosiglitazone, and these were reviewed at subsequent FDA meetings. Although the results of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study (NCT00379769) did not suggest an increased risk of MACE,⁴ issues with trial design and data integrity led the FDA to require the sponsor to perform an independent readjudication of the data. This extensive exercise, performed by the Duke Clinical Research Institute, had a minimal effect on the overall point estimates and confidence intervals for MACE, which remained at less than 1.30. The result was consistent with the FDA guidance and provided reassurance that rosiglitazone was not associated with excess cardiovascular risk.

Two groups of authors (Scirica et al. and White et al.) now report in the *Journal* the results of large, placebo-controlled, cardiovascular-outcome trials, these involving saxagliptin and alogliptin, members of the incretin drug class. Neither of these drugs had shown increased cardiovascular risk in its development program. Both trials were designed to first rule out excess cardiovascular risk by means of noninferiority testing; if that was shown, superiority testing followed, on the assumption that better glycemic control might yield cardiovascular benefit. Both trials clearly met the FDA 2008

guidance for cardiovascular safety, but neither showed a reduction in cardiovascular events. Saxagliptin was associated with an unexpected increased risk of hospitalization for heart failure and a high frequency of hypoglycemia. Neither trial showed any increased risk of pancreatic adverse events, including cancer.

Before rosiglitazone, the cardiovascular safety of diabetes drugs had not been well studied. The initial concern with rosiglitazone arose from observational and case-control epidemiologic studies that generated a legitimate signal of possible cardiovascular harm, but every study had substantial methodologic shortcomings, including multiplicity, which meant that a statistically positive finding might be a false positive result.⁵ Meta-analyses were also performed with preapproval studies that had been designed to show a positive glycemic effect as the primary end point. These studies enrolled patients at low cardiovascular risk, were short in duration, used both placebo and active controls, and did not prospectively adjudicate cardiovascular safety events. In such situations, comparison of a new drug with an active agent is challenged by the uncertain cardiovascular risk of the active comparator. In contrast, a placebo-controlled design may lead to imbalances in background therapy (as was the case with saxagliptin) that could influence the cardiovascular outcomes. Meta-analyses of these premarketing trials from phase 3 development programs were therefore relatively insensitive in assessing cardiovascular risk, making dedicated postmarketing cardiovascular-outcome trials such as the RECORD study necessary to substantiate any risk signals. But

the design of the RECORD study had substantial limitations that precluded a complete assessment of the cardiovascular safety of rosiglitazone.

In 2010, the FDA took a cautious stance and limited exposure to rosiglitazone, given the numerous alternative therapies that were available. But this position did not acknowledge the uncertainty of cardiovascular risk associated with other diabetes drugs on the market, and the FDA decision may have had unintended consequences. The intense publicity about the ischemic cardiac risk of rosiglitazone may have diverted attention from the better-established risk of heart failure that is common to the drug class. Restricted access led patients to switch from rosiglitazone to other diabetes drugs of unproven cardiovascular safety. Patients who had a myocardial infarction while taking rosiglitazone may have concluded that the drug was the cause, adversely affecting their perceptions of their doctor, drug companies, and the FDA. And placing a hold on the TIDE trial, although arguably justifiable, prevented any further clarification of the cardiovascular risks or benefits of the thiazolidinedione drug class. The rosiglitazone experience also raises the question of how to define a regulatory standard for withdrawing drugs from the market. New drug approvals are based on "substantial evidence" of drug safety and efficacy. But there is little guidance on what constitutes substantial evidence of harm that is sufficient to justify market withdrawal or the imposition of severe market restrictions.

What have we learned from the rosiglitazone experience? Clearly, the presumed cardiovas-

cular risks of rosiglitazone led to a major change in FDA policy regarding the approval of all new diabetes drugs. From a cardiovascular perspective, rosiglitazone, saxagliptin, and alogliptin appear to be relatively safe. It is disappointing, however, that neither intensive glycemic control nor the use of specific diabetes medications is associated with any suggestion of cardiovascular benefit. Thus the evidence does not support the use of glycated hemoglobin as a valid surrogate for assessing either the cardiovascular risks or the cardiovascular benefits of diabetes therapy.

Patients with type 2 diabetes and their physicians currently have numerous treatment options, and additional drugs are in development. Perhaps the recent experience with rosiglitazone will allow the FDA to become more targeted in its adjudication of the car-

diovascular safety of new diabetes drugs, focusing the considerable resources needed to rule out a cardiovascular concern only on drugs with clinical or preclinical justification for that expenditure. New therapies targeting glycemic control may have cardiovascular benefit, but this has yet to be shown. The optimal approach to the reduction of cardiovascular risk in diabetes should focus on aggressive management of the standard cardiovascular risk factors rather than on intensive glycemic control.

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The Dead-Donor Rule and the Future of Organ Donation

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The ethics of organ transplantation have been premised on “the dead-donor rule” (DDR), which states that vital organs should be taken only from persons who are dead. Yet it is not obvious why certain living patients, such as those who are near death but on life support, should not be allowed to donate their organs, if doing so would benefit others and be consistent with their own interests.

This issue is not merely theoretical. In one recent case, the parents of a young girl wanted to donate her organs after an accident had left her with devastating brain damage. Plans were made to withdraw life support

and to procure her organs shortly after death. But the attempt to donate was aborted because the girl did not die quickly enough to allow procurement of viable organs. Her parents experienced this failure to donate as a second loss; they questioned why their daughter could not have been given an anesthetic and had the organs removed before life support was stopped. As another parent of a donor child observed when confronted by the limitations of the DDR, “There was no chance at all that our daughter was going to survive. . . . I can follow the ethicist’s argument, but it seems totally ludicrous.”¹

In another recent case de-

scribed by Dr. Joseph Darby at the University of Pittsburgh Medical Center, the family of a man with devastating brain injury requested withdrawal of life support. The man had been a strong advocate of organ donation, but he was not a candidate for any of the traditional approaches. His family therefore sought permission for him to donate organs before death. To comply with the DDR, plans were made to remove only nonvital organs (a kidney and a lobe of the liver) while he was under anesthesia and then take him back to the intensive care unit, where life support would be withdrawn. Although the plan was endorsed by the