The rise and fall of rosiglitazone

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This editorial refers to ‘Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial†, by M. Komajda et al. on page 824

Komajda et al. have described the increased incidence of congestive heart failure (CHF) in patients treated with rosiglitazone in the RECORD Trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes).1 This study is the latest chapter in the tortured saga of rosiglitazone, a drug that was once the largest selling diabetes therapy in the world.2 The rise and fall of rosiglitazone raises critical scientific and ethical questions about drug development and marketing, with profound consequences, including the recent decision by US regulatory authorities to require cardiovascular outcome studies for all new diabetes drugs.3

Rosiglitazone and related thiazolidinediones (TZDs) are modulators of nuclear receptor proteins known as peroxisome proliferator-activated receptors (PPARs) that function as transcription factors regulating expression of genes. Of the many subclasses of PPAR modulators, two types have been marketed, PPARα agents, such as fenofibrate, that affect lipid metabolism, and PPARγ agents, such as rosiglitazone, that act as insulin sensitizers. One marketed TZD, pioglitazone, is considered a dual PPAR agonist, with modest α effects and strong γ effects. PPARs influence a large number of genes, perhaps 100 or more, most of which have unknown biological effects. Accordingly, the effects of these agents are unpredictable and can result in unusual toxicities. Indeed, during the past decade, >50 PPAR agonists have failed during clinical development, some due to cardiotoxicity,4 although few publications have detailed the precise toxicity encountered. One agent, muraglitazar, was recommended for approval by a US Food and Drug Administration (FDA) advisory panel, but ultimately not approved after a meta-analysis of clinical trials obtained from FDA documents revealed an approximate doubling of adverse cardiovascular outcomes.5

Development of rosiglitazone

In 1998, the only marketed TZD was troglitazone, a drug that had come under intense scrutiny for rare, but potentially fatal hepatotoxicity. The FDA appeared eager to approve a ‘safer’ alternative to troglitazone. Since both rosiglitazone and pioglitazone appeared to lack hepatotoxicity, the FDA moved swiftly to approve these agents. The rosiglitazone development programme was small, although typical of diabetes drugs in that era, consisting of five trials involving 2902 patients, mostly short-term (26 week) glycaemic control studies.6 In three pivotal studies (011, 024, and 020), rosiglitazone substantially increased LDL cholesterol (LDL-C), averaging 24, 20, and 13%, respectively. Of greater concern, in all five trials, ischaemic cardiovascular events occurred in 36/2902 patients receiving rosiglitazone and 10/1452 patients receiving comparators, a relative risk of 1.80 (P = NS), with confidence intervals not reported by the FDA statistician.5 There was no evidence of serious hepatotoxicity.

On 22 May 1999, an FDA advisory panel recommended approval of rosiglitazone, and 3 days later the Agency sent an approval letter (Table 1). Two months later, the FDA approved pioglitazone. With two available alternatives, in March 2000, the FDA ordered the removal of troglitazone from the market. In the rosiglitazone review, the FDA officer expressed concern about ‘EKG changes, chest pain, etc., even if not statistically different from comparators’ and commented that ‘based upon animal findings of cardiomegaly, and edema in clinical trials, RSG should be used with caution in patients with heart failure’.6 The reviewer further opined that ‘undesirable’ changes in weight and lipids were a ‘cause for concern’. He wrote that ‘heart disease due to atherosclerosis is a major cause of morbidity and mortality in patients with Type 2 diabetes, and it cannot be assumed that RSG will decrease the risk’. Finally, the reviewer recommended that a post-marketing study designed to address these issues should be a condition for approval.

Rosiglitazone was successfully launched and marketed, quickly capturing a major share of the diabetes market. The company emphasized the favourable effects of the drug on biomarkers such as high sensitivity C-reactive protein and HDL-C. The effect on LDL-C was largely dismissed, with the claim that rosiglitazone favourably affected LDL particle size, shifting unhealthy ‘small dense’ LDL to more favourable, ‘large fluffy’ LDL.7 However, a study comparing the lipid effects of pioglitazone and rosiglitazone...
demonstrated strikingly different patterns, with unfavourable effects for rosiglitazone on LDL-C and triglycerides, and less favourable increases in HDL-C.8 Following drug launch, many review articles advocated the potential of rosiglitazone to affect cardiovascular disease favourably through its insulin-sensitizing mechanism of action and effects on biomarkers.9 However, one prominent diabetes expert was not convinced and began to raise questions in public forums about the cardiovascular safety of rosiglitazone. Many years later it was revealed that this physician was visited by a delegation from the makers of rosiglitazone, who threatened to sue him for damages because of the fall in the company’s stock price (a loss of US$4 billion).10 He was persuaded to sign an agreement barring him from publicly expressing concerns about the safety of the drug.

Concerns emerge

During the 2 years follow drug launch, spontaneous reports associated rosiglitazone with fluid retention and CHF.11 In December 2002, the FDA ordered a revision of the rosiglitazone label noting ‘rare reports of unusually rapid increases in weight’ and recommending that such patients ‘should be assessed for fluid accumulation’ and ‘excessive edema and congestive heart failure’. Earlier in 2002, a warning had been added to the rosiglitazone label. Eventually, with accumulating evidence, the FDA greatly strengthened the heart failure warning for rosiglitazone, moving it to the ‘warnings’ section of the drug label. Despite these concerns, the market share of rosiglitazone (and pioglitazone) continued to grow. By 2006, rosiglitazone had annual sales of US$3.3 billion and pioglitazone reached sales of US$2.8 billion.

What became of the initial concerns expressed by the FDA reviewer related to the increase in LDL-C and ischaemic cardiovascular events? The FDA approval letter reminded the manufacturer of a Phase IV commitment ‘to conduct a long-term (4-year) safety and efficacy study (titled ADOPT study)’ to address ongoing safety concerns, including cardiovascular effects. Although the ADOPT study was actually performed, it was not powered to assess cardiovascular outcomes and did not adjudicate cardiovascular events. Instead, the study was designed to show that rosiglitazone achieved more persistent control of hyperglycaemia. The company did perform a large number of ‘marketing’ and ‘seeding’ trials, such as the ‘Avandia in Daily Practice’ study, which enrolled nearly 23,000 patients in Germany, described on the company website as a ‘multicentre, open-label, non-randomized, observational’ study.12 Two other large randomized trials were conducted, the DREAM study (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), a placebo-controlled trial designed to determine whether rosiglitazone could prevent diabetes in high risk individuals, and the RECORD Trial, an open label, active-control, randomized cardiovascular outcome trial.

When the results of these trials were first reported in 2006, the findings were worrisome. Although the DREAM trial demonstrated that rosiglitazone delayed the new onset of diabetes, a broad composite of adverse cardiovascular outcomes showed 75 events in the rosiglitazone treatment group and 55 in the placebo group, hazard ratio (HR) 1.37, 95% confidence interval (CI) 0.97–1.94, P = 0.08.13 There were 14 adjudicated CHF events in the rosiglitazone arm and two in the control group, P = 0.01. Three months later, the ADOPT trial reported results demonstrating, as postulated, that rosiglitazone produced more persistent reduction on blood glucose.14 Although cardiovascular events were not adjudicated, the ADOPT study disclosed the incidence of investigator-reported myocardial infarction. There were more events in the rosiglitazone treatment group, compared with metformin or glyburide, resulting in a crude odds ratio of 1.33 with 95% CI ranging from 0.80 to 2.21 (my calculations). An addendum added while the manuscript was in ‘proof’ reported a statistically significant increase in fractures.14

Rosiglitazone meta-analysis

In January 2007, concerned about the cardiovascular safety of the TZD class, we requested access to patient-level data from the manufacturers of both rosiglitazone, Glaxo Smith Kline (GSK), and pioglitazone, Takeda. The makers of pioglitazone agreed, but the manufacturer of rosiglitazone declined. Then serendipity intervened. In 2004, the state of New York had sued GSK alleging that the company had failed to publish the results of unfavourable studies of their antidepressant, paroxetine that demonstrated lack of efficacy and increased risk of suicidality in children and adolescents. In a negotiated settlement, GSK agreed to establish a ‘clinical trial register’ revealing the results of all clinical trials conducted after 27 December 2000. In April 2007, we became aware of this website and quickly identified 42 randomized clinical trials involving rosiglitazone, 35 of which were unpublished.15

On 1 May 2007, we completed our cardiovascular meta-analysis and submitted the manuscript. Within 24 h of submission, the manuscript was sent to reviewers; one of whom immediately faxed a copy to GSK.15 The company commenced an internal statistical review of the manuscript that confirmed the findings.16 According to Emails later obtained by the Wall Street Journal, one senior GSK official wrote ‘The numbers are the numbers, the analysis is very similar to our own’. The director of GSK research wrote ‘FDA, Nissen, and GSK all come to comparable conclusions regarding increased risk for ischemic events, ranging from 30% to 43%!’ Eventually, it was revealed that the company had conducted its own meta-analysis much earlier, first in the autumn of 2005, updated in the autumn of 2006. Both GSK analyses revealed an increased risk of ischaemic myocardial events and were quietly posted on the company’s clinical trials register and actually shared with the FDA.15 Subsequently, the FDA conducted its own analysis and concluded that rosiglitazone was associated with a statistically significant 40% increase in ischaemic events.17 However, throughout this period, neither the company nor the FDA revealed these findings to the medical community, nor to the public.

On 21 May, the results of the meta-analysis were published online, indicating an RR of 1.43 for myocardial infarction (95% CI 1.03–1.98) and an RR for cardiovascular death of 1.64 (95% CI 0.98–2.74).18 GSK, forewarned by the leak of the manuscript, hastily arranged partially to unblind the ongoing RECORD Trial, which enabled publication online only 16 days after the rosiglitazone meta-analysis. With the RECORD Trial still underway, there were too few events to reach any reasonable conclusions.
Following publication of the meta-analysis, sales of rosiglitazone plummeted, eventually falling to about a quarter of their highest levels. Later, a similar meta-analysis of pioglitazone was published, actually showing a reduction in ischaemic events, which further accelerated the decline in rosiglitazone usage.19

Rosiglitazone epilogue

The FDA finally added a ‘black box warning’ about the risk of ischaemic myocardial events to the label of rosiglitazone in October 2007. In December 2008, the FDA issued a new guidance for development of drugs to treat diabetes, requiring cardiovascular outcomes trials, sufficient to rule out a upper 95% CI for the HR of 1.8 prior to approval and 1.3 in a Phase IV trial.3 In January 2009, a consensus treatment algorithm issued by the American Diabetes Association and European Association for the Study of Diabetes ‘unanimously advised against using rosiglitazone’.20 More recently, final results of the RECORD Trial were published, which showed no significant increase in death or hospitalization for rosiglitazone compared with metformin or sulfonylurea, but the study was seriously underpowered for cardiovascular events of interest.21 This study postulated an 11% annual event rate, but observed only a 2.5% rate. The HR for myocardial infarction was 1.14, but upper 95% CIs reached 1.63. About 40% of patients were no longer taking rosiglitazone by the end of the trial, further diluting any safety signals. Eventually, the FDA mandated a study comparing rosiglitazone and pioglitazone with placebo, known as TIDE (Thiazolidinedione Intervention with Vitamin D Evaluation). However, results are not expected until 2015, an astonishing 16 years after the introduction of rosiglitazone.

What were the key mistakes and lessons learned from the rosiglitazone affair?

(i) The FDA rushed to approve rosiglitazone because of hepatotoxicity concerns about troglitazone, resulting in failure to consider the ‘signals’ suggesting cardiovascular toxicity.

(ii) An early critic of rosiglitazone was intimidated by company representatives and effectively silenced, a process antithetical to the principals of open scientific discourse.

Table I  Timeline: the rise and fall of rosiglitazone

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>May 1999</td>
<td>The FDA approves rosiglitazone despite concerns expressed by its reviewer about adverse lipid effects, oedema, and myocardial ischaemia.6</td>
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<td>July 1999</td>
<td>A prominent endocrinologist publicly raises concerns about the CV safety of rosiglitazone. The drugmaker forces him to sign an agreement promising not to express his safety concerns about the drug.10</td>
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<td>March 2000</td>
<td>Following approval of rosiglitazone and pioglitazone, the FDA withdraws troglitazone from the market.</td>
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<td>January 2001</td>
<td>Reports emerge suggesting that thiazolidinediones such as rosiglitazone may induce heart failure.11</td>
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<tr>
<td>December 2002</td>
<td>The FDA adds a precaution regarding ‘rare reports’ of rosiglitazone-induced congestive heart failure.</td>
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<tr>
<td>August 2004</td>
<td>GSK settles a lawsuit with the New York State alleging the company concealed paroxetine studies that showed lack of efficacy or increased suicidal in children and adolescents. The settlement requires the company to disclose all clinical trial results.</td>
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<td>September 2005</td>
<td>The company performs an analysis of all 37 randomized trials of rosiglitazone, showing an increase in the risk of myocardial ischaemic events. The trial results appear on the company website, are shared with the FDA, but not published.12</td>
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<td>September 2006</td>
<td>The DREAM study is published, showing that rosiglitazone reduces the new onset of diabetes. Numerically more CV events are observed in the rosiglitazone group (P = 0.08) with a statistically significant increase in CHF (P = 0.01).13</td>
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<tr>
<td>October 2006</td>
<td>The company updates their 2005 integrated analysis to include 42 trials, showing stronger evidence of adverse CV outcomes. The trial result appears on the company website, are shared with the FDA, but not published.12</td>
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<tr>
<td>December 2006</td>
<td>The ADOPT Trial is published, showing greater durability in glycaemic control with rosiglitazone, but a numerical excess of myocardial infarctions (P = NS).14</td>
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<tr>
<td>December 2006</td>
<td>Rosiglitazone reaches peak sales of US$3.3 billion annually.</td>
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<tr>
<td>January 2007</td>
<td>We request patient-level data to enable a meta-analysis of CV outcomes with rosiglitazone (which is declined) and pioglitazone (which is accepted).</td>
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<td>1 May 2007</td>
<td>We submit a manuscript reporting a meta-analysis of CV outcomes for 42 clinical trials of rosiglitazone.</td>
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<td>3 May 2007</td>
<td>One of the reviewers of the manuscript faxes a copy to GSK. An internal statistical analysis by the company review confirms the findings.16</td>
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<tr>
<td>21 May 2007</td>
<td>The meta-analysis of CV outcomes is published online.18</td>
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<td>6 June 2007</td>
<td>The company publishes an unblinded interim analysis of the RECORD Trial.</td>
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<td>30 July 2007</td>
<td>The FDA reveals its own meta-analysis of CV events with rosiglitazone, showing a statistically significant increase in risk (RR = 1.4).17</td>
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<tr>
<td>October 2007</td>
<td>The FDA adds a ‘black box warning’ to the rosiglitazone label for ischaemic events.</td>
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<tr>
<td>December 2008</td>
<td>The FDA issues a guidance requiring CV outcomes trials for diabetes drugs.3</td>
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<tr>
<td>January 2009</td>
<td>The ADA and EASD recommend that practitioners not use rosiglitazone.20</td>
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<tr>
<td>June 2009</td>
<td>The final RECORD results are published, but the study is underpowered.11</td>
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<tr>
<td>June 2009</td>
<td>The FDA mandates an adequately powered CV outcomes study for rosiglitazone, scheduled to complete in 2015.</td>
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ADA, American Diabetes Association; ADOPT, A Diabetes Outcome Progression Trial; CHF, congestive heart failure; CV, cardiovascular; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; EASD, European Association for the Study of Diabetes; FDA, Food and Drug Administration; GSK, Glaxo Smith Kline; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes.
(iii) Although early warnings were issued for the risk of heart failure, these warnings went largely unheeded in the face of aggressive marketing and promotion suggesting cardiovascular benefits.

(iv) No well-designed cardiovascular outcome trials were ever conducted for rosiglitazone, despite evidence suggesting increased cardiovascular risks. The only cardiovascular outcome trial was an open label study driven by a soft endpoint (hospitalization) with low adherence to randomized medications, seriously underpowered, and not completed until 10 years following launch.

(v) Although both the FDA and the company were aware of evidence of an increased risk of adverse cardiovascular outcomes, certainly by 2005, neither warned physicians nor the public.

(vi) When a meta-analysis of rosiglitazone was eventually submitted for publication, the company subverted the editorial review process by stealing a copy of the manuscript and used this advance knowledge inappropriately to unblind an ongoing randomized trial.

(vii) Approval of diabetes drugs exclusively upon their glycemic effects has been short-sighted and scientifically unwise. Drugs that lower blood sugar may have other adverse effects that overcome any inherent benefits.

(viii) The failure of >50 other PPARs, many for adverse cardiovascular effects, went largely unreported because of negative publication bias. Such knowledge might have warned the medical community about the potential risk of these agents.

**Conflict of interest:** S.E.N. consults with many pharmaceutical companies, but requires them to pay any honoraria directly to charity so that he receives neither income, nor a tax deduction.

**References**


2. Glaxo dodges FDA bullet, but Avandia sales unclear http://www.reuters.com/article/idUSL15728320071115


