

The Heart of the Matter: The Data Behind the Rosiglitazone Controversy

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In 2007, the *New England Journal of Medicine* published a meta-analysis by Nissen and Wolski indicating that rosiglitazone (Avandia®), a popular medication for the treatment of type 2 diabetes mellitus, may increase the risk of myocardial infarction and cardiovascular death.¹ The conclusion sparked widespread media coverage, confusion among patients, and intense debate among providers. The Food and Drug Administration (FDA) and GlaxoSmithKline (GSK), rosiglitazone's manufacturer, came under fire for withholding data, while Nissen and Wolski faced criticism for their study's design. The uproar surrounding rosiglitazone is understandable. Diabetes is already associated with increased cardiovascular risk, and more than one million diabetics were taking rosiglitazone at the time. Understanding the controversy is necessary in order to appropriately prescribe rosiglitazone.

BACKGROUND

In 1999, the FDA approved the thiazolidinediones, rosiglitazone and pioglitazone (Actos®). Since then, they have found a niche in the treatment of type 2 diabetes, as they do not cause significant hypoglycemia but still improve glycemic control.⁴ Upon failure of metformin monotherapy, the American Diabetes Association (ADA) recommends the addition of insulin, a sulfonylurea, or a thiazolidinedione.² Rosiglitazone and pioglitazone, however, are associated with weight gain, edema, and heart failure. They are contraindicated in patients with New York Heart Association Class III and IV heart failure and carry a "Black Box" warning stating that they may cause or exacerbate the condition. While it is unclear if thiazolidinediones increase the risk of mortality due to heart failure, they have been associated with increased heart failure signs and symptoms and rate of hospitalization due to cardiovascular causes.^{3,4} Since the controversy emerged, the ADA's clinical practice recommendations have been updated with a cautionary statement that "rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction."⁵ Neither the ADA nor the American Association of Clinical Endocrinologists changed the recommended role of thiazolidinediones in their published guidelines, as they deemed the data to be inconclusive.^{2,6}

Thiazolidinediones activate the peroxisome proliferator-activated receptor- γ (PPAR- γ), which activates genes that regulate carbohydrate and lipid metabolism. Free fatty-acid storage shifts from the plasma, viscera, and liver to the subcutaneous tissue, where it is more sensitive to insulin. While the overall clinical effects of rosiglitazone and pioglitazone are similar, the drugs activate different gene groups and warrant separate adverse effect consideration. Thus, it is conceivable that pioglitazone may not have the same cardiovascular effects as rosiglitazone. Rosiglitazone has been found to increase low-density lipoprotein (LDL) cholesterol by approximately 7% to 14%, though it also decreased triglycerides by 8% to 22% and increased high-density lipoprotein (HDL) cholesterol by 3% to 10%.⁴ Pioglitazone is not known to change LDL cholesterol, but trials have shown a reduction in triglycerides by 9% and an increase in HDL cholesterol by an average of 12% to 19%.³ Rosiglitazone's less favorable lipid profile when compared to pioglitazone was an early sign that it could have adverse macrovascular effects.

Interestingly, thiazolidinediones are associated with increased bone loss and fracture risk.^{4,7} This effect may be due to PPAR- γ stimulation of bone marrow stem cells to preferentially differentiate into adipocytes over osteoblasts. There is concern that bone loss may be linked to vascular calcification, a clinical marker of atherosclerosis.⁸ While still a theory, the mechanism by which rosiglitazone exerts its suspected adverse cardiovascular effects may be more complex than alteration of lipids and blood glucose levels.

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Rosiglitazone and pioglitazone activate different sets of genes, indicating that they might have different side-effect profiles.

Thiazolidinediones carry a Black Box warning stating they may exacerbate heart failure, and they are contraindicated in NYHA Class III and IV heart failure.

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The FDA meta-analysis showed a significant risk of serious or non-serious myocardial ischemic events with rosiglitazone versus comparators, although serious events alone did not reach significance.

WHAT IS THE EVIDENCE BEHIND THE CONTROVERSY?

In response to adverse event reporting by the World Health Organization, GlaxoSmithKline pooled data from 42 randomized controlled Phase 2 and 3 clinical trials for assessment of cardiovascular risk with rosiglitazone.^{9,10} Completed in August 2006, this meta-analysis included 14,237 patients with type 2 diabetes mellitus. GSK had access to patient-level data, allowing for closer evaluation of individual events. Rosiglitazone was evaluated as monotherapy and in combination with sulfonylureas, metformin, and/or insulin, with a comparator group of placebo or combinations of sulfonylureas, metformin, and/or insulin. The GSK meta-analysis found a statistically significant increase in cardiac ischemic events in rosiglitazone groups versus non-rosiglitazone groups (1.99% vs. 1.51%, HR 1.31, 95% CI 1.01 - 1.70, $p = 0.04$). Though not significant, a subgroup analysis showed a higher risk of myocardial ischemia-related adverse events in patients who were taking both rosiglitazone and insulin (2.77% vs. 1.36%, OR 2.02, 95% CI 0.90 - 4.94). After reviewing the preliminary results of the GSK meta-analysis, the FDA decided to conduct its own.

The FDA's meta-analysis used much of the data used by GSK, but it combined endpoints due to low event rates.¹⁰ It showed a significant risk of serious or non-serious myocardial ischemic events with rosiglitazone versus comparators (2% vs. 1.5%, OR 1.38, 95% CI 1.1 - 1.8, $p = 0.02$), although serious myocardial ischemic events alone did not reach significance (1% vs. 0.8%, OR 1.44, 95% CI 0.98 - 2.1, $p = 0.06$). There was no evidence to indicate that rosiglitazone was associated with a higher risk of myocardial ischemia than metformin or sulfonylureas, but subgroup analyses noted that the highest odds ratios occurred when rosiglitazone was combined with metformin or insulin. The FDA planned an Advisory Committee meeting to determine the appropriate action to be taken in response to these results.

After the initiation of the meta-analyses by GSK and FDA, several clinical trials of longer durations released their results. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, published in September 2006, was a diabetes prevention trial of 3 years duration in which 5,269 patients with impaired fasting glucose or glucose intolerance were randomized into rosiglitazone or placebo groups.¹¹ Given that these patients were treatment-naïve, they might have had a lower cardiovascular risk than patients in other trials. The secondary endpoint, a composite of multiple cardiovascular outcomes, occurred more frequently with rosiglitazone than placebo but was not significant (2.9% vs. 2.1%, HR 1.37, 95% CI 0.97 - 1.94, $p = 0.08$). The incidence of myocardial infarction alone was also not significantly higher with rosiglitazone (0.6% vs. 0.3%, HR 1.66, 95% CI 0.73 - 3.80, $p = 0.2$).

Contingent upon rosiglitazone's approval, GSK conducted a 4-year safety and efficacy study of rosiglitazone versus metformin or glipizide in drug-naïve patients with recently diagnosed type 2 diabetes ($n = 4,360$).^{12,13} The results of this randomized, double-blind, parallel group study, referred to as A Diabetes Outcome Progression Trial (ADOPT), were published in December 2006. Myocardial infarction occurred slightly more often in the rosiglitazone group versus the comparator groups (1.85% vs. 1.42%, OR 1.33, 95% CI 0.8 - 2.21, $p = 0.27$). All-cause mortality was similar between the treatment groups. However, ADOPT was not powered to assess cardiovascular outcomes and did not adjudicate cardiovascular adverse events.

After the FDA completed its meta-analysis, Nissen and Wolski attracted extensive attention from the press by publishing their meta-analysis in June 2007.¹ The authors included trials of at least 24 weeks duration that evaluated rosiglitazone versus comparator groups. They also had limited access to the unpublished GSK data. Rosiglitazone was associated with a significantly increased risk of myocardial infarction versus comparators (OR 1.43, 95% CI 1.03 - 1.98, $p = 0.03$) and a non-significant risk of death from cardiovascular causes (OR 1.64, 95% CI 0.98 - 2.74, $p = 0.06$). The authors concluded that patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone. Of note, some trials were excluded because they did not contain reports of myocardial infarction or cardiovascular death. This exclusion was criticized for its potential to give false weight to included trials. Another criticism was that the analysis could only be hypothesis-generating, meaning that the results should prompt further investigation but not be taken as a firm conclusion. As with the FDA and GSK meta-analyses, interpretation was limited by inconsistent definitions of cardiovascular disease in patient-level data, short trial durations, and low event rates.

Diamond et al. critiqued the design of the Nissen and Wolski meta-analysis.¹⁵ They proposed that the use of the Cochran Q test to pool data may have artificially inflated the risk estimate and increased its perceived precision. Also, 3 of the included trials evaluated rosiglitazone in the treatment of diseases other than diabetes. The highest incidences of myocardial infarction ($n = 5$) and cardiovascular death ($n = 3$) occurred in a small trial evaluating the use of rosiglitazone in diabetic patients with congestive heart failure, and Diamond et al. questioned the inclusion of patients with a known contraindication to rosiglitazone. For the purposes of its regulatory decisions, the FDA relied on its own meta-analysis rather than the one conducted by Nissen and Wolski. Under pressure from the media and Congress, the FDA moved up the planned Advisory Committee meeting to July 2007. Ultimately, it was decided to alter rosiglitazone's product labeling to include a warning about cardiac adverse events, including ischemia, with a statement declaring that the data are still inconclusive.

In September 2007, Singh et al. published a fourth meta-analysis evaluating cardiovascular events with rosiglitazone.¹⁶ It differed from the others by limiting inclusion to randomized, clinical trials with at least 12 months of follow-up. Rosiglitazone was associated with a significantly higher risk of myocardial infarction compared to controls (RR 1.42, 95% CI 1.06 - 1.91, $p = 0.02$). Cardiovascular mortality and all-cause mortality due to rosiglitazone were not significantly higher with rosiglitazone.

In response to the controversy, the investigators of the ongoing Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD) trial performed an unplanned interim analysis.¹⁷ The RECORD trial is an open-label cardiovascular outcomes study of 6 years duration comparing the addition of rosiglitazone versus metformin or a sulfonylurea to existing therapy. Though RECORD focuses specifically on cardiovascular outcomes, it also suffers from unfortunate design flaws. The primary endpoint of death or hospitalization due to cardiovascular causes is broad and limits the interpretation of results. Also, the power calculation for the primary endpoint assumed an annual event rate of 11% in the diabetic patient population, but the observed rate has been only 2.5%. As a result, the power to detect a difference in the primary endpoint dropped substantially, and the interim analysis was inconclusive (HR 1.08, 95% CI 0.89 - 1.31). When myocardial infarction alone was evaluated as a secondary endpoint, the difference between rosiglitazone and comparators was not significant (HR 1.16, 95% CI 0.75 - 1.81). It is unlikely that the RECORD trial will be able to overcome its design flaws to provide a concrete answer.

Other ongoing trials may provide some insight when their results are released. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial is investigating the mortality rate in patients who are treated with either insulin-sensitizing or insulin-providing therapies, with or without coronary revascularization. Though the composite endpoint of death, myocardial infarction, and stroke is secondary, the trial limited its enrollment to patients with preexisting coronary heart disease, and approximately 90% of the patients treated with insulin-sensitizing therapy were using rosiglitazone at enrollment.^{10,18} Meanwhile, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study is comparing the effects of different hemoglobin A1c goals on cardiovascular outcomes.¹⁹ Its primary endpoint is a composite of nonfatal myocardial infarction, nonfatal stroke, or death due to cardiovascular disease. For reasons that are yet unclear, the trial arm with a goal hemoglobin A1c of $< 6\%$ was stopped due to increased all-cause mortality compared to less aggressive treatment. This alarming result could not be attributed to any one drug, including rosiglitazone. The Veterans Affairs Diabetes Trial (VA DT) is assessing the effect of glycemic control on cardiovascular outcomes in type 2 diabetes, with a primary endpoint evaluating a broad range of cardiovascular outcomes. Finally, the APPROACH study is evaluating the effect of rosiglitazone versus glipizide on the progression of atherosclerosis in type 2 diabetics with cardiovascular disease.¹⁰ The APPROACH trial and VA DT are expected to be completed by mid-2008, whereas the ACCORD and BARI 2D trials will likely not conclude until at least 2009.¹⁰

HAS PIOGLITAZONE BEEN ASSOCIATED WITH ADVERSE CARDIOVASCULAR EVENTS?

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) was a 4-year, randomized, double-blind, cardiovascular outcome trial designed to investigate cardiovascular risk with pioglitazone.^{20,21} The primary endpoint was a broad composite of all-cause mortality, non-fatal myocardial infarction, acute coronary syndrome, cardiac intervention including coronary artery bypass graft or percutaneous coronary intervention, stroke, major leg amputation above the ankle, bypass surgery, and revascularization of the leg, each of which were also evaluated individually as secondary endpoints. A total of 5,238 patients who had previously experienced a macrovascular complication were randomized to receive a forced titration of pioglitazone or placebo as an add-on to existing treatment. The primary endpoint occurred in 19.7% of patients in the pioglitazone group and 21.7% of patients in the placebo group (HR 0.90, 95% CI 0.80 – 1.02, $p = 0.095$). While not significant, the data trended toward a favorable effect of pioglitazone for this broad macrovascular endpoint. A composite of all-cause mortality, stroke, and non-fatal myocardial infarction was significantly lower in the pioglitazone group versus placebo (11.6% vs. 13.6%, HR 0.84, 95% CI 0.72 – 0.98, $p = 0.027$), though this was a secondary endpoint. As expected, the number of patients with reported heart failure was significantly higher with pioglitazone versus placebo, but mortality due to heart failure was not. While PROACTIVE could not rule out the possibility of increased myocardial infarction or cardiovascular death with pioglitazone, the results trended in the opposite direction.

Two meta-analyses published after the release of PROACTIVE also found encouraging results with pioglitazone. Lincoff et al. compiled data from 16,390 patients in 19 trials.²² A composite endpoint of death, myocardial infarction, and stroke was significantly lower in patients receiving pioglitazone versus comparators (4.4% vs. 5.7%, HR 0.82, 95% CI 0.72 – 0.94, $p = 0.005$), while myocardial infarction alone trended towards a favorable outcome (1.5% vs. 2%, HR 0.81, 95% CI 0.64 – 1.02). Meanwhile, Lago et al. evaluated seven trials consisting of 20,191 patients in order to evaluate heart failure and cardiovascular death with thiazolidinediones.²³ Interestingly, there was no association with risk of cardiovascular death for pioglitazone (RR 1.01, 95% CI 0.51 – 2.01, $p = 0.98$) or rosiglitazone (RR 0.91, 95% CI 0.63 – 1.32, $p = 0.63$) versus comparators. While these studies carry the limitations common to most meta-analyses, the results pertaining to pioglitazone do not contradict PROACTIVE.

CLINICAL APPLICATION

It is unclear from the available data if rosiglitazone increases the risk of myocardial infarction or cardiovascular death. The meta-analysis conducted by the FDA indicates a trend toward increased risk of these adverse events, but the significance of such a trend is in question. Nissen and Wolski's meta-analysis found a statistically significant increase in myocardial infarction, but there is debate as to whether or not its design may have inflated the results. All 3 meta-analyses mostly consisted of trials of six months duration or less. It is unlikely that the RECORD study will provide an answer due to its design limitations. Pioglitazone may be a better treatment option than rosiglitazone with respect to cardiovascular ischemia and mortality. However, there is not enough evidence to completely rule out the possibility that pioglitazone is similar in effect to rosiglitazone.

RECORD, a cardiovascular outcomes study of rosiglitazone, will not achieve its anticipated power. Its interim analysis was inconclusive.

PROACTIVE indicated that pioglitazone may not have the same association with cardiac ischemic events. Two meta-analyses have supported this conclusion.

The FDA altered rosiglitazone's product labeling to include a warning about cardiac adverse events, including ischemia, with a statement that the data are still inconclusive.

The American Diabetes Association and the American Association of Clinical Endocrinologists have not changed the role of thiazolidinediones in their treatment recommendations.

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Unfortunately, there is no end in sight to the rosiglitazone controversy, and providers must use their clinical judgment when prescribing thiazolidinediones. When considering oral antidiabetic agents, the patient's cardiovascular risk factors and history should be assessed. Thiazolidinediones should be avoided in patients with NYHA Class III and IV heart failure and used with caution in Class I and II heart failure. In light of recent data, it may be prudent to avoid rosiglitazone in patients at high risk for myocardial infarction and consider other agents, such as metformin, sulfonylureas, and/or insulin. If those options have been exhausted, newer treatment options have surfaced in recent years, including sitagliptin

(Januvia®), exenatide (Byetta®), and pramlintide (Symlin®), but clinical experience with these agents is still evolving. Providers should discuss the potential risks and benefits of continuing therapy with patients who are already taking rosiglitazone. The FDA has released a medication guide that must be dispensed to patients each time a rosiglitazone prescription is filled.²⁴ If a patient experiences cardiovascular adverse events while taking rosiglitazone, including chest pain, myocardial infarction, or signs or symptoms of heart failure, strong consideration should be given to the discontinuation of therapy.

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P&T COMMITTEE BRIEF SUMMARY March 18, 2008

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S)	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE
Insulin Glargine pen (Lantus® Solostar® pen)	3 ml per disposable insulin delivery device (100 units per ml)	Antidiabetic agent	Treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for control of hyperglycemia.	Adjust according to patient's need to a total daily dose ranging from 2 to 100 IU.
Sodium Hyaluronate (Healon5®)	0.6 ml single-use syringe 2.3% sodium hyaluronate	Viscoelastic agent	An aid in cataract surgery	0.6 ml
Trypan Blue (Vision Blue®)	2.25 ml prefilled syringe 0.06% solution	Intraocular stain	Enhance visualization of the anterior lens capsule during cataract surgery	0.5 ml