

Dear Health Care Provider,

We have been asked by the University Hospital District to provide guidance to health care providers regarding the use of pioglitazone (Actos®) for patients with diabetes. Pioglitazone and rosiglitazone (Avandia®) are insulin-sensitizers of the thiazolidinedione (TZD) class. Only Actos® is available on the University Hospital District formulary. First, some background...

On May 21st, 2007 the June 14th issue of the *New England Journal of Medicine* was made available online. In the issue Nissen and Wolski published a meta-analysis which suggested a significant increase in the risk of myocardial infarction associated with rosiglitazone (Avandia®) treatment and an increase of similar magnitude, albeit nonsignificant, in the risk of death from cardiovascular causes. This publication created a furor in the press and has resulted in a quandary for physicians and their patients. In our opinion, the scientific merit of this meta-analysis is limited due to at least 14 major weaknesses of the “study”.

On June 5th, 2007 the July 5th issue of the *New England Journal of Medicine* was made available online. In this issue Home and colleagues reported an unscheduled interim analysis from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study — a multicenter, drug-company sponsored, open-label, non-inferiority trial. Whereas the 42 trials included in the published meta-analysis by Nissen and Wolski generally were directed at the treatment of hyperglycemia and were not designed or powered to study potential adverse events such as cardiovascular disease, the RECORD trial was specifically designed to examine the effect of rosiglitazone (in combination with oral agents and insulin) on cardiovascular outcomes. While the results of the interim analysis are underpowered to give a conclusive answer, the results show a very small, statistically insignificant increase in cardiovascular outcomes in the rosiglitazone treated patients. Considering the low power of the study, the use of multiple oral agents plus insulin in the rosiglitazone treated diabetic patients and the slight increased risk for cardiovascular events reported in the interim analysis, it is highly unlikely that the study ever will establish a cardiovascular benefit for rosiglitazone.

Unlike rosiglitazone, pioglitazone (ACTOS®) has been studied in a prospective, randomized trial of cardiovascular outcomes, called Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE).¹ The primary end point of PROACTIVE was a broad composite that included coronary/peripheral vascular events – demonstrated a trend toward benefit from pioglitazone (hazard ratio = 0.90; P=0.095). The second principal end point, consisting of myocardial infarction, stroke, and death from any cause, was significantly improved in the pioglitazone treated patients (hazard ratio = 0.84; P=0.027). We agree with Dr. Nissen’s conclusion about pioglitazone that this thiazolidinedione has been shown in a large, prospective double-blind study to reduce the risk of cardiovascular events in diabetic patients with a previous cardiovascular event.

Although pioglitazone and rosiglitazone belong to the insulin sensitizing thiazolidinedione class of antidiabetic drugs, there are significant differences between the two TZDs with respect to the genes which they turn on and off. From the clinical standpoint, one major difference relates to the effect of the two thiazolidinediones on the plasma lipid profile. Both a meta-analysis² (*Arch Int Med* 164:2097-2104, 2004) and a head-to-head comparison³ (*Diabetes Care* 28:1547-1554, 2005) have demonstrated that rosiglitazone tends to cause an increase in the plasma LDL cholesterol and triglyceride levels, whereas pioglitazone significantly reduces the plasma triglyceride concentration and has no significant effect on LDL cholesterol concentration while decreasing the number of LDL particles (apo B100). Although both TZDs raise the plasma HDL cholesterol concentration, pioglitazone is twice as effective as rosiglitazone in increasing HDL levels. These differences in plasma lipids may explain, in part, the observed reduction in cardiovascular risk in pioglitazone treated diabetic patients (PROACTIVE), and the failure to observe any decrease in cardiovascular events in diabetic patients treated with rosiglitazone.

As part of a separate issue (i.e., distinct from cardiovascular events), the FDA in April of 2007 determined that both rosiglitazone and pioglitazone should have black box warnings placed in their package inserts to highlight the increased risk of congestive heart failure. TZDs stimulate sodium reabsorption by the kidney and the increase in fluid volume may result in congestive heart failure in patients with underlying cardiovascular dysfunction. This fluid retention is a class effect of the thiazolidinediones (TZDs). There is no evidence that the TZDs have any direct negative effect on cardiac function. Fluid retention (edema) and CHF have been recognized as side effects of the TZDs since their introduction to the U.S. market and both drugs have prominent warnings regarding the increased risk of congestive heart failure in the Warnings Section of their package inserts. Despite this, patients with Class III-IV congestive heart failure continue to be started on TZDs and the FDA felt a stronger warning was warranted. It is important to note the decision to place a black box warning for congestive heart failure predated and is unrelated to the NEJM articles about the possible increased risk of cardiovascular events with rosiglitazone.

What do we recommend for our patients on Actos®? First, patients on Actos® can be reassured that Actos® is not associated with an increased risk of cardiovascular events. The recent NEJM study suggesting an increase in cardiovascular events is limited to Avandia and is poorly substantiated by the data presented in the article. Second, you should be aware of the increased risk of congestive heart failure in patients given Actos®. Patients who develop edema should be monitored closely for signs and symptoms of CHF, and excess fluid retention should be treated with a diuretic.

Sincerely,

Charles A. Reasner, M.D.
Professor of Medicine/Endocrinology
University of Texas Health Science Center at San Antonio
Medical Director, Texas Diabetes Institute

Ralph DeFronzo, M. D.
Professor of Medicine
Chief, Diabetes Division
University of Texas Health Science Center at San Antonio
Deputy Director, Texas Diabetes Institute

References:

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. Published at www.nejm.org May 21, 2007.
2. Chiquette E, Ramirez G, DeFronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. *Arch Intern Med* 164:2097-2104, 2004.
3. Goldberg GB, Kendall DM, Deeg MA. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 28:1547-1554, 2005.