

# Commentary on the Results and Clinical Implications of the PROactive Study

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**T**hiazolidinediones (TZDs), or glitazones, are a relatively new class of oral drugs that are used to treat type 2 diabetes.<sup>1–4</sup> They lower blood glucose by targeting insulin resistance, one of the major underlying causes of the disease. In addition to their ability to lower blood glucose, TZDs also display a wide range of effects on lipids, blood pressure, weight, and other cardiovascular and metabolic risk factors. As with all other drugs, they can be associated with undesirable side effects.

By virtue of their glucose-lowering properties, all such agents will significantly reduce the risk of the microvascular complications associated with diabetes. On the other hand, no glucose-lowering agent has clearly been shown to significantly reduce macrovascular disease.

Since TZDs, in general, have a net favorable impact on blood lipid levels, may be associated with a reduction in blood pressure, and have positive effects on other physiological parameters associated with vascular disease (e.g., decreasing vascular inflammation, reducing insulin resistance), they have the potential to slow the progression of cardiovascular disease (CVD) in addition to lowering blood glucose.

Because of the above favorable actions of TZDs, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was initiated to assess the effects of pioglitazone (Actos; Takeda Pharmaceuticals and Eli Lilly) on the secondary prevention of macrovascular events in type 2 diabetic patients.

## Study design

PROactive was a randomized, double-blind, placebo-controlled study in 5,238 patients with type 2 diabetes who were managed with diet and/or glucose-lowering medications and who had a history of macrovascular disease.<sup>5</sup>

Male or female patients, aged 35–75 years, were randomized to receive placebo or pioglitazone titrated over 2 months to its maximally approved dosage (45 mg/day). Because study participants had preexisting CVD and diabetes of long duration (average 8 years), virtually all subjects at the time of enrollment were taking a glucose-lowering drug and other agents that help reduce the risk of CVD events.

The patients were followed for ~ 3 years, during which the incidences of a wide variety of macrovascular end points were tabulated. Of particular interest, however, was the incidence of all-cause mortality, nonfatal myocardial infarction, and stroke.

## What were the results of the PROactive study?

The addition of 45 mg pioglitazone to conventional therapy for ~ 3 years reduced the primary end point (comprised of many adverse macrovascular outcomes) by 10% ( $P = 0.095$ ) and a prespecified secondary composite event rate consisting of all-cause mortality, nonfatal myocardial infarction (excluding silent myocardial infection), and stroke by 16% ( $P = 0.027$ ) compared with placebo.<sup>6</sup> This represented an absolute risk reduction of ~ 2% after 3 years of therapy and was primarily due to reductions in stroke and nonfatal

myocardial infarction. After adjustment by multivariate analysis for entry characteristics, pioglitazone therapy was associated with a reduced hazard ratio of 0.84 (95% CI 0.72–0.98).

Pioglitazone treatment also was associated with a significant A1C absolute reduction of 0.5%, a relative reduction of 13% in serum triglycerides, a relative increase of 2% in LDL cholesterol and 9% in HDL cholesterol levels, and a reduction of 3 mmHg in systolic blood pressure. This resulted in a greater decrease in the LDL-to-HDL cholesterol ratio in the pioglitazone group compared with placebo. The proportion of patients using either metformin or insulin also was reduced with pioglitazone treatment.

## Are the results of the PROactive study clinically meaningful?

There appeared to be a clear clinical benefit of adding pioglitazone to type 2 diabetic patients already using most of the conventional classes of glucose-lowering agents. With an absolute event reduction in the secondary composite end points of ~ 2%, one would need to treat ~ 50 patients for 3 years to prevent one such event. Thus, in view of the substantial and well-established CVD risk reduction following cholesterol and blood pressure-lowering therapy, emphasis should first be directed at the aggressive use of other conventional cardiovascular risk reduction therapy.

## What adverse events were observed in the trial, and should they influence decisions regarding therapy?

Heart failure both requiring and not requiring hospitalization was significantly

increased in the pioglitazone group (10.8% for pioglitazone vs. 7.5% for placebo,  $P > 0.0001$ ), despite the fact that individuals with New York Heart Association Class II (i.e., symptoms with moderate activity), heart failure, or above were excluded from study. Since the criteria for heart failure were not clearly defined, it remains unclear as to whether the frequency of this diagnosis was skewed by an increased presence of peripheral edema in the pioglitazone group. Nevertheless, these data suggest that in the absence of extenuating circumstances, pioglitazone should not be used in individuals with a history of clinically significant heart failure.<sup>7</sup>

Consistent with previous studies, subjects in the pioglitazone group experienced greater weight gain (~ 3.6 kg) than subjects in the placebo group (0.4 kg decrease). The long-term effects of this degree of weight gain on patient compliance and vascular risk remains unknown. However, the fact that a reduction in vascular end points was observed in the pioglitazone group despite weight gain is reassuring. Nevertheless, it is prudent to help patients avoid weight gain through diet and lifestyle modification.

Symptoms of hypoglycemia and hypoglycemia requiring hospital admission were greater in the pioglitazone arm than in the placebo group. This observation is consistent with numerous previous studies in which an increased frequency of hypoglycemia is observed whenever glycemic control improves. Patients, therefore, should be instructed how to recognize and treat hypoglycemia and how to modify their lifestyle and other glucose-lowering agents so as to minimize the frequency and severity of hypoglycemic events.

### Can the results of PROactive be extrapolated to all people with diabetes?

There are many unanswered questions that preclude the assumption that pioglitazone would be an effective CVD intervention therapy in other patients with diabetes. First, subjects who participated

in PROactive had both diabetes and documented extensive macrovascular disease. They were at high risk of having another vascular event and, therefore, were an appropriate group to determine if treatment with pioglitazone reduced the probability of having a subsequent CVD event. The PROactive trial design, however, leaves uncertain the question of whether people with diabetes who do not have documented macrovascular disease would also benefit, and if so, whether the benefits would outweigh the risks.

Second, in excess of 98% of the subjects who participated in the study were Caucasian. Therefore, it is not known whether the risks and benefits would be the same in other ethnic groups.

Third, over 95% of the participants were involved with some other form of diabetes therapy. Additional studies will be required to determine whether a comparable CVD risk reduction would be observed if pioglitazone was used as monotherapy.

Last, A1C averaged ~ 7.8% at entry and decreased by ~ 0.5% more in the pioglitazone than placebo group, despite efforts to optimize glycemic control in both groups. A difference of this magnitude has not resulted in a reduction of macrovascular events in other trials, suggesting that the benefit of treatment relates to the non-glucose-lowering effects of the drug that are outlined above. It is not known whether individuals who have optimal glycemic control before pioglitazone therapy will have a comparable benefit. Similar uncertainty applies if patients were first optimally treated for any lipid and blood pressure abnormality. Of note, at the end of the study, nearly half of these high-risk subjects were still not taking statins, and the mean systolic pressure of the population was in the hypertensive range.

Thus, the data from the PROactive study indicate that people with type 2 diabetes of Caucasian heritage who have extensive macrovascular disease, suboptimal glycemic control despite treatment with other diabetes therapies

and suboptimal blood pressure and LDL cholesterol values, and no history of heart failure are likely to have reduced CVD events from the addition of pioglitazone to their current glucose-lowering therapy. Additional studies are required to determine whether comparable benefits and risks will be observed in people with type 2 diabetes from other ethnic groups, in individuals who do not have documented macrovascular disease, in patients whose CVD risk factors are optimally managed with respect to current guidelines, or when pioglitazone is used as the only glucose-lowering therapy.

### Do the results of PROactive apply to all TZDs?

The TZD class of drugs are all agonists of peroxisome proliferator-activated receptor- $\gamma$ , which is found in a wide variety of tissues and is known to regulate a number of genes involved in glucose and lipid homeostasis. In addition, these drugs exert other effects of uncertain etiology, such as improved vessel wall biology and the mitigation of many inflammatory factors. Their glucose-lowering effect, for which they have received drug approval, appears to act in part by increasing insulin-stimulated glucose disposal. Despite similar mechanisms of action, and equivalent reductions in blood glucose, currently available TZDs do not equally affect the various risk factors that might reduce CVD morbidity and mortality.<sup>8</sup> For example, the magnitude of triglyceride level reduction, increase in HDL cholesterol, and effect on LDL cholesterol can vary widely.

Because of these disparate effects on important CVD risk factors, it is premature to assume that the results of PROactive would hold for any other TZD or even for those drugs that are dual peroxisome proliferator-activated receptor- $\alpha$  and - $\gamma$  agonists. This conclusion is also supported by the fact that the design of the PROactive trial precluded the ability to ascertain which of the many effects of pioglitazone were key to the results

observed. Thus, at this time, clinicians should view the results of this trial to be drug specific.

In addition, again because of its numerous effects on CVD risk factors, it would be unwarranted to conclude that the insulin-sensitizing action of pioglitazone led to the results observed. It is still not known whether a reduction in insulin resistance per se has any effect on CVD mortality or morbidity. Consequently, this trial does not provide evidence for this drug, or any other glucose-lowering agent, as an effective treatment for the so-called insulin resistance (metabolic) syndrome.

#### Uncertainties and areas that require future research

PROactive was a carefully designed and well-executed clinical trial. Inclusion and exclusion criteria were carefully defined and end points appropriately specified. The fact that only two subjects were lost to follow-up is a testimony to the dedication and skill of the investigators. However, as with all studies, additional research questions arise, including the following.

1. To what extent do the results observed in these Caucasian subjects apply to other ethnic groups?
2. Would similar effects be observed when people with underlying vascular disease are treated with pioglitazone alone (i.e., monotherapy)?
3. Does pioglitazone reduce vascular events in people with diabetes who

have not had antecedent vascular events?

4. Does treatment with pioglitazone reduce vascular events when blood lipid, pressure, and glucose levels are all optimally treated?
5. Does treatment with pioglitazone increase, decrease, or have no effect on the natural history of postischemic myocardial function?
6. Among the beneficial effects of pioglitazone on CVD risk factors, which one(s) is more/less important?
7. Would comparable benefits and risks be observed with lower doses of pioglitazone (e.g., 15 or 30 mg/day).
8. Do pioglitazone or other TZDs reduce CVD or non-CVD mortality per se?
9. Do other TZD agents provide similar benefits and risks?

#### REFERENCES

- <sup>1</sup>Chilcott J, Tappenden P, Jones ML, Wight JP: A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. *Clin Ther* 23:1792–1823, 2001
- <sup>2</sup>Gegick C, Alheimer M: Thiazolidinediones: comparison of long-term effects on glycemic control and cardiovascular risk factors. *Curr Med Res Opin* 20:919–930, 2004
- <sup>3</sup>Yki-Jarvinen H: Thiazolidinediones. *N Engl J Med* 351:1106–1118, 2004
- <sup>4</sup>Del Prato S, Marchetti P: Targeting insulin resistance and beta-cell dysfunction: the role of thiazolidinediones. *Diabetes Technol Ther* 6:719–731, 2004
- <sup>5</sup>Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A, the PROactive Study Group: The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive):

can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes Care* 27:1647–1653, 2004

<sup>6</sup>Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray, GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golya A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J, the PROactive Investigators: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomised controlled trial. *Lancet* 366:1279–1289, 2005

<sup>7</sup>Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R, American Heart Association, American Diabetes Association: Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association: October 7, 2003. *Circulation* 108:2941–2948, 2003

<sup>8</sup>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

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**Note of disclosure:** Dr. Rizza and Dr. Henry have served as consultants for Takeda and GlaxoSmithKline, both of which are manufacturers of thiazolidinedione agents.