

# Pioglitazone Reduced MI, Stroke and Death in Diabetic Patients

Added to best standard therapy, this agent could help patients avoid major cardiovascular events. Questions linger about possible heart failure risk, however.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

**P**ioglitazone (Actos, Takeda, Lincolnshire, Ill) significantly reduced the combined risk of myocardial infarction (MI), stroke and death by 16% in high-risk patients with type 2 diabetes.

Data from PROACTIVE (PROspective pioglitAZone Clinical Trial In macroVascular Events), a randomized, double-blind, placebo-controlled outcome study, was presented at the 41st Meeting of the European Association for the Study of Diabetes in Athens.<sup>1</sup>

"The PROACTIVE study is the first in the world to prospectively show that a specific oral glucose-lowering medication, namely pioglitazone, can significantly improve cardiovascular outcomes by helping to delay or reduce [MI], strokes and death in high-risk patients," said John Dormandy, MD, professor of vascular sciences at St. George's Hospital, London, and chairman of the PROACTIVE Study Steering Committee. "This groundbreaking study gives new hope to people with type 2 diabetes who, despite their attempts to control blood glucose and take medications, fear these life-threatening events."

## 19 COUNTRIES

Prof. Dormandy and colleagues undertook PROACTIVE to determine the effects of pioglitazone on mortality and morbidity associated with the progression of cardiovascular disease in 5,238 high-risk patients with type 2 diabetes. Patients were enrolled from 19 European countries and had experienced one or more cardiovascular events such as MI, coronary artery bypass surgery or stroke. They were followed for an average of 2.8 years.

Patients were randomized to the highest tolerated dose of pioglitazone (up to 45 mg/day) or matched placebo in addition to the best standard of care treatment. This included angiotensin-converting enzyme

The trial did not meet its primary outcome of a 20% improvement in time from randomization to next cardiovascular event.

inhibitors and beta-blockers; metformin, sulphonylureas and insulin; aspirin; and statins and fibrates.

At baseline, 75.4% of patients had hypertension, 57.5% angina, 23.6% claudication, 23.2% retinopathy, 14.1% nephropathy and 5.7% had a history of transient ischemic attacks.

## PRIMARY OUTCOME NOT MET

The trial failed to meet its primary outcome of a 20% improvement in time from randomization to next cardiovascular event, defined as a composite of seven macrovascular events of varying clinical importance (all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, coronary revascularization, limb revascularization or amputation above the ankle). While this primary endpoint was reduced by 10%, it had not reached statistical significance by the end of the study ( $P=.095$ ).

The principal secondary combination outcome was life-threatening events including death, MI and stroke. Pioglitazone significantly reduced the risk of MI, stroke and death by 16% ( $P=.027$ ), the principal secondary endpoint of life-threatening events.

Prof. Dormandy said that these results predict that 21 first MIs, strokes or deaths would be prevented for every 1,000 patients at high-risk who are treated with pioglitazone – in addition to other medications – over a 3-year period. He called the results a breakthrough for patients

## INTENSIVE DIABETES CONTROL REDUCED LONG-TERM CVD IN TYPE 1 DIABETES PATIENTS

The 17-year Diabetes Control and Complications Trial (DCCT) has found that intensive therapy can reduce the risk of myocardial infarction (MI) and stroke in type 1 diabetes by about half.

Reporting in *The New England Journal of Medicine*, the investigators wrote that intensive diabetes therapy aimed at achieving near normoglycemia reduced the risk of microvascular and neurologic complications of type 1 diabetes. The DCCT studied whether the use of intensive versus conventional therapy affected the long-term incidence of cardiovascular disease (CVD).

"This is a truly important study, and I don't usually say that," Robert Rizza, MD, told *The New York Times*. Dr. Rizza is a professor of medicine at the Mayo Clinic and president of the American Diabetes Association.

In the DCCT, 1,441 patients with type 1 diabetes were randomized to intensive or conventional therapy and treated for a mean of 6.5 years between 1983 and 1993. During the observational portion of the trial, called Epidemiology of Diabetes Interventions and Complications (EDIC) study, 93% of the patients were followed until February 1, 2005. An independent committee then assessed CVD, defined as nonfatal MI, stroke, death from CVD, confirmed angina or the need for coronary artery revascularization.

During the mean 17-year follow-up, 46 CVD events

occurred in 31 patients who had received intensive treatment in DCCT as compared with 98 events in 52 patients who had received conventional treatment. According to the report, intensive treatment reduced the risk of any CVD event by 42% (95% CI, 0.09-0.63;  $P=.02$ ) and the risk of MI, stroke or death from CVD by 57% (95 CI 0.12-0.79;  $P=.02$ ).

"The decrease in glycosylated hemoglobin values during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of CVD," the investigators wrote. "Microalbuminuria and albuminuria were associated with a significant increase in the risk of CVD, but differences between treatment groups remained significant ( $P\leq.05$ ) after adjusting for these factors."

John B. Buse, MD, director of the diabetes care center at the University of North Carolina told *The New York Times* that the results are likely to affect clinical practice, encouraging physicians to put more effort into helping patients attain optimal blood sugar control. He said the study is "the most rigorously conducted to date and its authors are exceptionally well known in the diabetes and medical world."

Researchers suspect that the same results will hold true for patients with type 2 diabetes. ■

The DCCT/EDIC Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.

who are at high risk from MI, stroke or premature death because it is the first time an oral diabetes agent has been shown to have this benefit in a prospective study.

### OTHER PROACTIVE FINDINGS

The study also found that patients taking pioglitazone had a significant reduction in HbA1c levels versus placebo ( $P<.001$ ). Lipid profiles significantly improved, with an HDL cholesterol increase of 9% over placebo ( $P<.001$ ) and a 13% reduction in triglycerides over placebo ( $P<.001$ ). Additionally, the LDL/HDL cholesterol ratio significantly improved ( $P<.001$  in patients assigned pioglitazone). There was a significant decrease in systolic blood pressure ( $P=.03$ ). The number of patients who needed insulin permanently added to their treatment was 50% less than placebo ( $P<.001$ ).

Another aim of the PROACTIVE study was to further examine the safety of pioglitazone in this high-risk patient group. Prof. Dormandy and colleagues said that the adverse events reported were consistent with the known safety profile of pioglitazone. Known side effects

were observed more frequently in the treatment group versus placebo.

Investigators said the benefits seen in the study outweighed the risks, and importantly there were no reports of acute liver toxicity.

### EDEMA OR HEART FAILURE?

More patients taking pioglitazone were diagnosed with heart failure (HF), although there was little difference in the hospitalizations for HF and no difference in HF mortality. "My feeling is that the edema that may have occurred was falsely considered as [HF]," said investigator Erland Erdmann, MD, from the Medizinische Klinik III der Universität zu Köln, Germany. At least 10% of the patients taking pioglitazone developed edema.

"Until we know how pioglitazone works to provide these life-saving benefits, the beneficial results of PROACTIVE should not be generalized to any other oral glucose-lowering medication," Prof. Dormandy said in a news release.

Richard Kahn, MD, chief scientific and medical officer

of the American Diabetes Association said that the results were encouraging, but on balance, "it leads you to conclude that it is not a slam dunk."

At press time, the PROACTIVE study was published in *The Lancet*.<sup>2</sup> In a related editorial, Hannele Yki-Jarvinen, MD, from the University of Helsinki, Finland said that the findings provide "some good news, some bad news, and some unknowns." Pioglitazone reduced the risk of the secondary endpoint, that was the good news. The bad news was that it increased the risk of HF and weight gain, he wrote. And the unknowns include the prognosis of the HF and whether the drug can be safely used with insulin.

### SECONDARY ANALYSIS

A secondary analysis from the PROACTIVE study, presented at the American Heart Association's 2005 Scientific Sessions, found that pioglitazone reduced the occurrence of fatal and nonfatal MI and acute coronary syndromes (ACS) in high-risk patients with type 2 diabetes and previous MI.<sup>3</sup>

Prof. Erdmann gave data on 2,445 patients with type 2 diabetes and preexisting MI. According to this analysis, patients taking pioglitazone on top of standard treatment had a 28% reduction in the recurrence of fatal or nonfatal MI ( $P=.045$ ). The risk of ACS was reduced by 37% ( $P=.035$ ) and there was a 19% risk reduction ( $P=.034$ ) in the cardiac composite endpoint of nonfatal MI, coronary revascularization, ACS and cardiac death.

"This study includes one of the largest groups of patients with type 2 diabetes and a previous [MI] to be studied in a randomized placebo-controlled trial," said Prof. Erdmann. ■

*John Dormandy, MD, is professor of vascular sciences in the Department of Clinical Vascular Research, St. George's Hospital, London. He is chairman of the PROACTIVE Study Steering Committee. He can be reached at john.dormandy@btinternet.com.*

*Erland Erdmann, MD, is professor of medicine at the University of Koeln and director for the Third Clinic for Internal Medicine in Germany. He can be reached at erland.erdmann@uni-koeln.de.*

1. Dormandy J, et al. PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROACTIVE). Presented at the 41st meeting of the European Association for the Study of Diabetes. September 12-15, 2005. Athens.

2. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet*. 2005;366:1279-1289.

3. Erdmann E. The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2445 Patients With Type 2 Diabetes and Preexisting Myocardial Infarction - Data from the PROACTIVE Study. Presented at the American Heart Association's 2005 Scientific Sessions. November 13-16, 2005. Dallas.

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

DiabeticMCToday.com

visit [www.diabeticmctoday.com](http://www.diabeticmctoday.com) for the current issue and complete archives

DiabeticMCToday.com

DiabeticMCToday.com