

# Pioglitazone Appears to Stop Progression of Carotid Artery Atherosclerosis

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REVIEWED BY THEODORE MAZZONE, MD

In an 18-month study that compared the effects of pioglitazone (Actos; Takeda Pharmaceuticals North America, Deerfield, Ill) and glimepiride among patients with type 2 diabetes, pioglitazone appeared to stop progression of artery narrowing, according to researchers at the American Heart Association's (AHA) Scientific Sessions 2006 in Chicago.

Theodore Mazzone, MD, chair of the trial and chief of endocrinology, diabetes and metabolism in the department of medicine at the University of Illinois at Chicago presented results of the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) study in a late-breaking clinical trials session. The study will be simultaneously published in the *Journal of the American Medical Association*, according to an AHA news release.

"The CHICAGO study is another interesting piece of the puzzle, adding to the understanding of how pioglitazone may confer benefits beyond glycemic control," said Dr. Mazzone. "Although physicians have aggressively treated cardiovascular risk, people living with diabetes are still at a higher risk for heart disease. And while additional studies are needed to determine how reductions in [carotid intima-thickness] (CMT) with pioglitazone might prevent cardiovascular events, we do know that new approaches to addressing cardiovascular risk factors in diabetes are critical."

## LARGEST AND LONGEST STUDY OF ITS KIND

CHICAGO, a phase 3b multicenter, double-blind, randomized, placebo-controlled two-arm study, is the



Figure 1. A type A carotid lesion showing short, concentric stenosis without ulceration.



Figure 2. A type C lesion with an ulceration 1.5 cm in length, bifurcation involvement and 95% stenosis.

largest and longest study to examine the effects of pioglitazone on measures of the atherosclerotic disease process in patients with type 2 diabetes, most of whom had no clinical evidence of heart disease. CHICAGO compared pioglitazone, a thiazolidinedion, to glimepiride, a sulfonylurea. Figures 1 through 3 show various types of carotid artery lesions.

Photos courtesy of Mark H. Wholey, MD

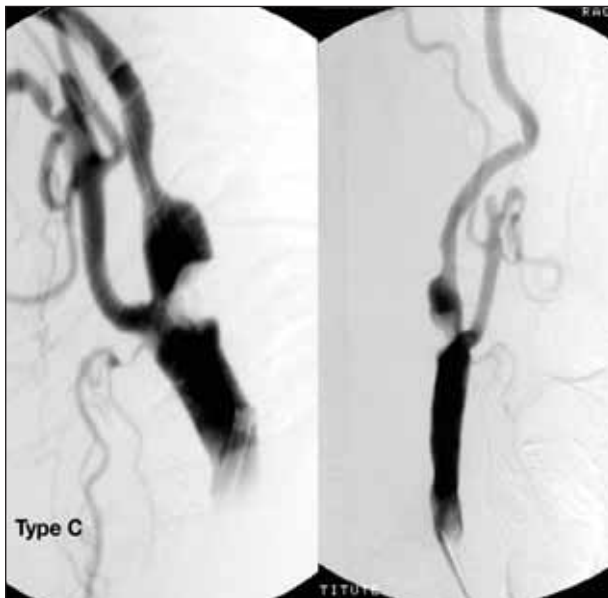


Figure 3. A type C lesion. Note the polypoid-like defect with extrinsic compression.

“From baseline to the final visit, there was a significant difference in CIMT in favor of the pioglitazone group,” Dr. Mazzone said. “Over the 18-month treatment period, the glimepiride group’s CIMT continued to progress whereas progression was virtually arrested in the pioglitazone group.”

Included in the study were 462 patients with type 2 diabetes, aged 45 to 85 years, who were recruited from the multiracial/ethnic population of the Chicago area. Doctors in this study could add insulin or metformin in addition to the investigation drugs, if necessary, Dr. Mazzone said.

### CIMT MEASURED BY ULTRASOUND

Patients were randomized to receive one of three doses of pioglitazone or one of three doses of glimepiride. After 18 months, the researchers measured the absolute change in CIMT using ultrasonography. The study also looked at cardiovascular endpoints, glycemic control, lipid profiles, blood pressure and other atherosclerotic markers.

“If supported by additional research, these findings would indicate that pioglitazone can delay the progression of atherosclerosis in patients with diabetes,” Dr. Mazzone said. The findings are particularly significant because the benefits were found in patients whose blood sugar, blood pressure and cholesterol levels were at or near American Diabetes Association/AHA targets, he said. This suggests a potentially novel mechanism for managing cardiovascular risk in

patients with diabetes.

“Diabetes is a huge public health problem,” Dr. Mazzone said. “It is estimated that one out of every three babies born in the United States this year will develop diabetes at some time in his or her life. Diabetes is a major risk factor for myocardial infarction (MI), and [patients with diabetes] have a poorer prognosis after [MI] than [those who do not have diabetes].”

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### BENEFITS APPLIED ACROSS THE BOARD

Patients taking pioglitazone should have their liver enzymes evaluated before starting this therapy, he said. The thiazolidones also carry a risk of fluid retention that can lead to or worsen heart failure. In this study, one patient taking pioglitazone was hospitalized for heart failure, which was reversed when the drug was discontinued.

Although the study was not large enough to measure a significant difference in cardiovascular events, researchers reported 10 cardiovascular events in the glimepiride group and four in the pioglitazone group.

The researchers found that the benefits of pioglitazone over glimepiride applied across the board: to the less obese and more obese patients, to those whose blood sugar was in good control and those for whom it was poorly controlled, and to younger and older patients.

“People with diabetes do much worse after a [MI] or stroke than those without diabetes, and they die more frequently,” Dr. Mazzone said. “We have learned a lot about managing cardiovascular risk in people with diabetes using blood pressure and lipid medications but still more needs to be done. So we need to evaluate novel approaches like this one.” ■

*Theodore Mazzone, MD, is chief of endocrinology, diabetes and metabolism in the department of medicine at the University of Illinois at Chicago. He may be reached at [Tmazzone@uic.edu](mailto:Tmazzone@uic.edu). Dr. Mazzone is a consultant for and has received speaking honoraria from Takeda Pharmaceuticals North America, Merck, Amlyn, Novartis Pharmaceuticals and Pfizer.*

Mazzone T, Meyer PM, Feinstein SB, et al. Effects of pioglitazone compared to glimepiride on carotid intima-media thickness (CIMT) in type 2 diabetes - Results of the CHICAGO Study. Presented at the American Heart Association's Scientific Sessions 2006. Nov. 12-15. Chicago.