Pioglitazone Stalled Thickening of The Carotid in Type 2 Patients

BY CATHERINE HACKETT
Senior Editor

CHICAGO — Treatment with pioglitazone for 18 months halted progression of atherosclerosis in patients with early type 2 diabetes, Dr. Theodore Mazzone reported at the annual scientific sessions of the American Heart Association.

Carotid intima media thickness (CIMT), which continued to progress in patients treated with glimepiride, was “virtually arrested” in the pioglitazone group in the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial. The beneficial effect improved during the mean 18 months of treatment, said Dr. Mazzone of the endocrinology, diabetes, and metabolism section of the University of Illinois, Chicago.

CIMT was used as a surrogate for risk of stroke and MI in the diabetic patients. “The thicker the intima, the higher the risk of heart disease, or death, in 5-10 years,” Dr. Mazzone said in a press briefing. The CHICAGO trial was conducted from October 2003 to May 2006 in a multicentric, multiracial population of patients at 28 clinical sites in Chicago. The 462 patients, aged 45-85 years, were newly diagnosed with type 2 diabetes that was controlled by diet or treated with sulfonyureas, metformin, or insulin. Patients taking medicine for high blood pressure were eligible if their glycosylated hemoglobin A1c (HbA1c) values were at least 6.5% but less than 9%.

Exclusion criteria included symptomatic coronary artery disease, cerebrovascular disease, New York Heart Association class III or IV heart failure, and current use of ACE inhibitors or diuretics. “We wanted patients early in the disease process,” Dr. Mazzone said.

CIMT was measured using high-resolution, B mode carotid artery ultrasound. All images were taken by the same ultrasonographer at the same location.

The primary end point was the change in mean CIMT from baseline at 72 weeks. The CIMT reduction in the pioglitazone group was 0.16 mm, compared with an increase of 0.012 mm in the glimepiride group. This beneficial effect was present regardless of age, sex, presence of hypertension, duration of type 2 diabetes, body mass index, HbA1c value, and statin use, said Dr. Mazzone, who is a consultant for and has received speaking honoraria from Takeda Pharmaceuticals North America Inc., maker of pioglitazone (Actos).

Diabetes was well controlled in the study population. The mean HbA1c value of the pioglitazone group at baseline was 7.44%, and that of the glimepiride group was 7.36%. The glycemic effects of the two drugs differed over time in the study. With glimepiride, mean HbA1c values dropped rapidly in the beginning of the trial, but rose gradually back to nearly their original level by week 72. In pioglitazone-treated patients, HbA1c values decreased gradually over 48 weeks and remained steady until 72 weeks. At the final visit, the mean HbA1c level in the pioglitazone group was 0.12% lower than that of the glimepiride group, a highly significant difference, Dr. Mazzone said.

Lipid levels were also well controlled in the CHICAGO participants, with about 70% of the patients in each group taking lipid-lowering drugs. With pioglitazone, HDL cholesterol and triglyceride levels improved significantly. HDL levels were similar between the groups, while triglyceride levels fell by 9.3 mg/dL in the glimepiride group and 47.1 mg/dL in the pioglitazone group. By the final visit, the HDL level was 6.8% higher in the pioglitazone group than in the glimepiride group. Triglyceride levels decreased by 13.5% in the pioglitazone patients and rose by 2.1% with glimepiride.

The beneficial metabolic effects of pioglitazone were expected on the basis of previous trials of thiazolidinediones, said discussant Dr. Peter Wilson, an endocrinologist at Emory University, Atlanta. But the effects of pioglitazone in CHICAGO may not be generalizable to the other thiazolidinediones, he noted, because pioglitazone may be stronger than other drugs in the class.

Adverse effects of treatment with pioglitazone were similar to those with the sulfonylurea glimepiride, although treatment-limiting peripheral edema occurred in four pioglitazone patients and none of the glimepiride patients.

Weight gain also was more frequent with pioglitazone. These effects have been seen in other randomized trials of thiazolidinediones, and raise concerns about an increased risk of heart failure with pioglitazone. But Dr. Wilson noted that because of its prescience of patients who were not likely to get into heart failure concerns, CHICAGO “opens the window a little wider for when we can use these agents.” The results were published online simultaneously with the presentation (JAMA 2006;296:2572-81).

Apnea Seen as An Independent Heart Risk Factor

BY PATRICE WENDLING
Chicago Bureau

TUCSON, ARIZ. — High levels of anger and lower levels of self-control are independent predictors that prehypertension will progress to hypertension, coronary artery disease, and coronary artery-disease-related death, Dr. Marty Player said at the annual meeting of the North American Primary Care Research Group.

Dr. Player presented a secondary data analysis of the Atherosclerosis Risk in Communities (ARIC) study, a prospective study of 15,792 men and women aged 45-64 years at the time of enrollment in four communities across the United States. The analysis included 2,334 individuals free of cardiovascular disease with blood pressure in the prehypertension range of 120-139 mm Hg systolic BP of 80-89 mm Hg diastolic BP of 120-139 mm Hg.

First examinations were conducted from 1987 to 1989, with annual telephone interviews and three-trial visits through 1999.

Using a bivariate analysis, researchers found that the factors significant for progression from prehypertension to hypertension were advanced age, female gender, and black race, said Dr. Player, a research fellow, and colleagues in the family medicine department at the Medical University of South Carolina, Charleston. The research was presented as one of the meeting’s distinguished papers.

The investigators also evaluated progression to coronary heart disease as indicated by a history of MI, revascularization procedure, MI on electrocardiogram, or fatal coronary heart disease record at a triennial visit or annual follow-up interview.

Using a bivariate analysis, researchers found that age, gender, and nonblack race were significant factors for the progression of atherosclerosis disease. More men (17%) developed coronary heart disease or fatal CHD, compared with women (5.8%), as did nonblacks (12%), compared with blacks (7.6%).

In a multivariate analysis, high levels of prolonged psychological stress, as assessed by the M�astricht Questionnaire, were significantly associated with progression to CHD and fatal CHD in all participants (OR 1.68). The association was particularly strong in women (OR 2.63) than in men (OR 1.46). About 10% of participants had M�astricht Questionnaire score of 7 or less developed CHD or fatal CHD, compared with 9.5% of those with scores of 8-12, and 14% with a score of 12 or more.

High Spielberger anger scores were significantly predictive of progression to CHD or fatal CHD in men (OR 1.92) but not in women (OR 0.95), reported the authors, whose work was supported by grants from the U.S. Department of Health and Human Services’ Health Resources and Services Administration.

The findings provide new leads for investigation and possibly new strategies for intervention and prevention. Dr. Player said his research should evaluate common psychosocial variables, such as depression and anxiety, and include younger patients.