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 attack or stroke in 5-10 years," Dr. Mazzone said in a press briefing. The CHICAGO trial was conducted from October 2003 to May 2006 in a multiracial, multiethnic 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 sulfonureas, metformin, or insulin. Patients taking medicine for blood glucose control were eligible if their glycosylated hemoglobin A_{1c} (HbA_{1c}) values were at least 6.5% but less than 9%.

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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 0.001 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, HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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, HbA_{1c} values decreased gradually over 48 weeks and remained steady until 72 weeks. At the final visit, the mean HbA_{1c} level in the pioglitazone group was 0.32% 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 groups at baseline, at 47.6 mg/dL in the glimepiride group and 47.1 mg/dL in the pioglitazone group. By the final visit, the HDL level was 6.5% 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 would be 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 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 preselection of patients who were not likely to get into heart failure concerns, CHIGAGO "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

CHICAGO — Obstructive sleep apnea is associated with subclinical coronary artery disease independent of the traditional cardiovascular risk factors, Dr. Dan Sorajja reported at the annual scientific sessions of the American Heart Association.

Moreover, the severity of subclinical coronary artery disease as reflected by the extent of coronary artery calcium (CAC) on electron beam CT increases with obstructive sleep apnea severity. For this reason, the presence and severity of obstructive sleep apnea ought to be incorporated into coronary artery disease risk stratification and preventive cardiology efforts, said Dr. Sorajja of the Mayo Clinic, Rochester, Minn.

He reported on 202 consecutive patients with no history of coronary artery disease who underwent electron beam CT within 3 years of polysomnography at the Mayo Clinic. They were a median of 50 years old, with a mean body mass index of 33 kg/m^2. More than half were dyslipidemic and 44% had hypertension. CAC was present in 67% of patients with obstructive sleep apnea and in 31% without. Apnea, in turn, was present in 76% of those with CAC. The mean CAC score was 144 Agatston units in those with obstructive sleep apnea and 26 Agatston units in those without.

In a multivariate analysis, the adjusted odds ratio for CAC increased in stepwise fashion with each increasing quartile of obstructive sleep apnea severity as determined by the apnea-hypopnea index (AHI). The prevalence of coronary artery disease was 2.1-fold greater in patients in the second obstructive sleep apnea severity quartile, with an AHI of 5-13, than in those in the lowest quartile. The CAC prevalence was 2.4-fold greater among patients in the third quartile, with an AHI of 14-32, than in the first. And in individuals in the top quartile, where the mean AHI was 63, the prevalence of CAC was 3.3-fold greater than in the first quartile.

The chief limitation of a cross-sectional study such as this one is the potential for selection bias, he conceded.

Obstructive sleep apnea is a common medical condition. The prevalence of significant obstructive sleep apnea symptoms has been estimated at 4%-9% among middle-aged adults. Previous research data have shown that the condition is a cause of hypertension. It is also associated with an increased risk of MI and with elevated rates of several important risk factors for coronary artery disease, including dyslipidemia, diabetes, and obesity, Dr. Sorajja noted.

—Bruce Jancin

Stress and Anger Fuel Progression To Hypertension

BY PATRICE WENDLING
Chicago Bureau

TUCSON, ARIZ. — High levels of anger and long-term psychological stress 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, defined as a systolic BP of 120-139 mm Hg or diastolic BP of 80-89 mm Hg. First examinations were conducted from 1987 to 1989, with annual telephone interviews and three triennial visits through 1998.

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.

After the researchers adjusted for age, race, body mass index, diabetes mellitus, and exercise, the odds ratio of developing hypertension was 1.53 for any participant having a high score on the Spielberger Trait Anger Scale. High trait anger indicates anger that occurs frequently with high intensity and prolonged duration. The association was significant for men (odds ratio 1.71) but not for women (OR 1.34), he said.

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 recorded 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 Maastricht Questionnaire, were significantly associated with progression to CHD and fatal CHD in all participants (OR 1.68). The association was particularly stronger in women (OR 2.63) than in men (OR 1.54). About 10% of patients with a Maastricht 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 significant predictors 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. Further research should evaluate common psychosocial variables, such as depression and anxiety, and include younger patients. ■