Risk of MI Reduced

Glitazones *from page 1*

most importance that this drug, with all of its cardiovascular effects, be used in those diabetic patients with the most serious prognosis," he said in an interview.

AHA President Robert H. Eckel, M.D., wasn't prepared to go quite so far as yet. "This is a first observation, and I do think with all first observations that we need validation studies," he told this newspaper.

"But I think if glycemic control is not optimal in a patient with type 2 diabetes who is treated with oral agents, the idea of adding a glitazone—specifically, pioglitazone—has merit. The lipid and glucose modifications are favorable, and I myself use glitazones in my practice in such patients," added Dr. Eckel, professor of medicine, physiology, and biophysics at the University of Colorado, Denver.

Dr. Erdmann reported on 2,445 PROactive participants with type 2 diabetes and a prior MI who were randomized in a double-blind fashion to 45 mg of pioglitazone once daily or placebo, in addition to optimal background antidiabetic and cardiovascular medications.

After 3 years of follow-up, the incidence of fatal or nonfatal recurrent MI was 5.3% in the pioglitazone group and 7.2% with placebo, for a highly significant 28% relative risk reduction. The 2.8% incidence of ACS events in the pioglitazone arm represented an even more robust 37% relative risk reduction.

On the basis of these data, treating 1,000 type 2 diabetic patients who had a previous MI with pioglitazone for 3 years would prevent 22 recurrent MIs, Dr. Erdmann added.

This was a prespecified subgroup analysis of the larger PROactive study, which involved 5,238 type 2 diabetic patients with macrovascular disease. In the overall study, presented in September at the annual meeting of the European Association for the Study of Diabetes and subsequently published (Lancet 2005; 366:1279-89), pioglitazone didn't achieve a significant reduction in the complex and controversial combined primary end point, although there was a significant 16% relative risk reduction in the secondary combined end point of death, nonfatal MI, or stroke.

Dr. Erdmann said pioglitazone was well tolerated. Although 92 patients in the pioglitazone arm of the secondary study were hospitalized for heart failure, compared with just 63 control subjects, this appears to be a red herring.

Because more than one-third of controls hospitalized for heart failure died during follow-up, compared with less than one-quarter of those on pioglitazone, Dr. Erdmann is convinced the excess hospitalizations in the pioglitazone arm represented misdiagnosis of heart failure in patients who actually had peripheral edema, a known side effect of the drug and one that a skilled clinician can readily differentiate from heart failure through physical examination. Supporting this view was the finding that mortality due to heart failure in the overall pioglitazone arm was 1.8%—virtually identical to the 1.7% rate in the placebo group.

Discussant Jorge Plutzky, M.D., agreed with this assessment, noting the glitazones, or thiazolidinediones, aren't known to cause myocardial dysfunction; in fact, animal studies suggest just the opposite—that these drugs improve left ventricular dysfunction in the post-MI setting.

As an outsider not involved in PROactive, Dr. Plutzky said he has been surprised by the animated and sometimes heated discussion generated in recent months by the full study's failure to meet its prespecified primary end point. To him, it's obvious the combined primary end point chosen by investigators was flawed and probably unachievable, since it included not only coronary events but lower-leg amputations and leg revascularization procedures.

'It is of utmost importance that this drug ... be used in those ... with the most serious prognosis.'

DR. ERDMANN

"Peripheral vascular disease and coronary disease are not the same and don't necessarily respond the same to therapy. For example, in the statin trials these same lower limb end points have been quite difficult to prove despite the drugs' efficacy in coronary disease," noted Dr. Plutzky, director of the vascular disease prevention program at Brigham and Women's Hospital, Boston.

The reduction in recurrent MIs seen in the new PROactive analysis was unlikely to be due chiefly to pioglitazone's glucose-lowering effect, which was rather modest: a mere 0.4% lower HbA_{1c} than in controls.

As in other studies, pioglitazone improved HDL cholesterol, blood pressure, and triglycerides in PROactive. But whether the reduction in MIs resulted indirectly from these favorable metabolic effects or from pioglitazone's proposed ability as a peroxisome proliferator-activated receptor (PPAR)–gamma-activating agent to directly affect inflammatory cells and the arterial wall remains unclear.

Either way, PROactive "does support the hypothesis that PPAR-gamma may be a central target in abnormal metabolism that underlies diabetes and cardiovascular complications," Dr. Plutzky said.

Dr. Erdmann has received honoraria from Takeda, which together with Eli Lilly funded PROactive.

A Takeda official said in an interview that no decision has yet been made as to whether the company will file for a new indication for pioglitazone for the prevention of cardiovascular events in diabetic patients. That will hinge in part on the results of a couple of ongoing clinical studies aimed at demonstrating the specific mechanisms involved in such a benefit.

Also, clinical trials of rosiglitazone for cardiovascular protection in high-risk diabetic patients are ongoing. ■

Central Pressure Changes May Drive Amlodipine's Advantage

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — Brachial blood pressure measurements may not be the best way to assess the effects that antihypertensive drugs have on blood pressure.

An amlodipine-based regimen was much better than atenolol-based treatment for lowering central aortic pressure in a substudy of a trial that involved a total of more than 19,000 patients, Bryan Williams, M.D., said at the annual scientific sessions of the American Heart Association.

The results show that BP-lowering drugs have different effects on central aortic pressures and hemodynamics, despite having a similar impact on brachial BP.

The results "demonstrate for the first time in a large, clinical-outcomes trial that blood-pressure lowering drugs have profoundly different effects on central aortic pressures and hemodynamics despite a similar impact on brachial blood pressure," said Dr. Williams, a professor of medicine at the University of Leicester (U.K.).

Amlodipine's ability to substantially reduce central aortic pressure is likely a major reason why the clinical results from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that patients treated with an amlodipine-based regimen had a 16% relative reduction in the incidence of total cardiovascular events and procedures, compared with patients treated with an atenolol-based regimen during an average follow-up of 5.5 years (Lancet 2005;366:895-906).

"It's remarkable that we're talking about what these drugs do in the central aorta after years of being completely blind" to these effects, said Dr. Williams.

Multiple measures of central aortic pressures were obtained for 2,199 of the patients who were enrolled in ASCOT.

These measures were obtained via a commercially available device that calculates central aortic pressures after it transcutaneously measures the radial artery waveform through an external transducer wand that is placed on a patient's wrist.

"Systolic pressure is not constant throughout the arterial tree, and clinically relevant changes may not be measured by brachial-cuff blood pressure," commented Joseph L. Izzo Jr., M.D., professor of medicine and pharmacology at the State University of New York at Buffalo. "We now have a mandate to look beyond blood-pressure cuff measurements."

The ASCOT substudy was done at five participating hospitals in the United Kingdom and Ireland.

Patients who participated had their central aortic pressures measured at baseline and during multiple follow-up examinations using the SphygmoCor Px system.

Like all participants in ASCOT, these hypertensive patients were randomized to treatment with either of two regimens: amlodipine, followed by perindopril when a second drug was needed to reach the goal brachial-artery pressure, or atenolol, with the diuretic bendroflumethiazide and potassium added when a second drug was needed.

Throughout treatment, patients on the amlodipine-based regimen maintained a central aortic systolic pressure that averaged 4.3 mm Hg lower than patients treated with the atenolol-based regimen. Central aortic pulse pressure averaged 3.0 mm Hg lower in the amlodipine group, reported Dr. Williams.

Both cuts in pressure were statistically significant. In contrast, systolic pressure measured by brachial cuff averaged 0.7 mm Hg lower in the amlodipine group, compared with the atenolol group, and diastolic blood pressure averaged 1.6 mm Hg lower with amlodipine.

Dr. Williams and his associates analyzed the role of central aortic pressure and other measured variables on the incidence of 305 cardiovascular events, procedures, or episodes of renal impairment that occurred among the 2,199 patients during follow-up. In a multivariate analysis, central aortic pulse pressure was the only factor that produced a significant, independent effect on the rate of these outcomes.

Central aortic pressure is produced by a combination of the main, outgoing pressure wave and a wave that's reflected back from the arms. Amlodipine causes peripheral vasodilation that reduces the reflected wave and shifts it away from the heart; atenolol causes peripheral vasoconstriction that boosts the reflected wave and brings it closer to the heart, said Dr. Williams.

The ASCOT study and substudy were sponsored by Pfizer Inc. which markets amlodipine (Norvasc).

Dr. Williams has been a consultant to and has received research grants from Pfizer. ■

Museum Features Healthy Heart Exhibit

The National Museum of Health and Medicine at Walter Reed Army Medical Center, Washington, is featuring a healthy heart exhibit through 2006. The exhibit examines human cardiovascular anatomy for both scientific and lay audiences. For more information, visit www.nmhm.washingtondc.museum or call 202-782-2200.