ACS Event Rate Lowered 37%

Pioglitazone *from page 1*

based medicine for preventing cardiovascular events. This is the first prospective trial of any oral glucose-lowering drug to show evidence of reduced MI and ACS [acute coronary syndrome], so I think it is of utmost 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 said in an interview.

"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 new MIs, he 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, 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.

Although validation studies are needed, adding a glitazone has merit for patients whose glycemic control isn't optimal.

DR. ECKEL

As an outsider not involved in PROactive, the cardiologist said he has been surprised by the animated and sometimes heated discussion generated 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.

"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," said 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.

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

Iodixanol Unexpectedly Linked to Higher Renal Failure Rates

BY JANE SALODOF MACNEIL
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NICE, FRANCE — A study of 77,000 Swedish cardiac patients found rates of renal failure were about twice as high following the use of iodixanol, an iso-osmolar contrast medium promoted as less toxic to the kidneys than competing low-osmolar products, Pontus B. Persson, M.D., Ph.D., reported at the annual meeting of the Cardiovascular and Interventional Radiological Society of Europe.

"From these data we conclude there is absolutely no indication that iodixanol is less harmful for kidney function than ioxaglate or iohexol," Dr. Persson said.

"Actually, the contrary may be the case, but further studies are required to test if the contrary really may hold true," concluded Dr. Persson, a renal physiologist at Humboldt University's Campus Charité Mitte in Berlin.

Dr. Persson and colleagues in Sweden compared patients in the Swedish Coronary Angiography and Angioplasty Registry to rehospitalizations with a diagnosis of renal failure in a Swedish hospital discharge register. The follow-up stretched as long as 12-14 years after percutaneous coronary interventions (PCI) and coronary angiography.

Within 1 year of coronary angiography or PCI, 70 of 5,728 patients given iohexol (Omnipaque) and 291 of 24,577 patients given ioxaglate (Hexabrix) returned to a hospital with a renal failure diagnosis. For both agents the proportion was 1.2%, Dr. Persson reported.

Among 47,543 patients for whom iodixanol (Visipaque) was used, rehospitalization with renal failure was about twice as common: 1,108 patients or 2.3%. The difference was statistically significant.

With attribution of a hazard ratio of 1 to the diagnosis of primary or secondary renal failure with iodixanol, the investigators calculated hazard ratios of 0.84 for iohexol and 0.77 for ioxaglate.These varied only slightly in subgroup analyses for patients with and without a prior history of renal failure, Dr. Persson said.

'From these data we conclude there is absolutely no indication that iodixanol is less harmful for kidney function than ioxaglate or iohexol.'

Two-thirds of the Swedish market is now using iodixanol, according to Dr. Persson, so the investigators also did a subgroup analysis of patients treated during the last 4 years to rule out a "time effect" on the findings.

"Again the data are rather clear," he said. "Again we see a much higher risk for developing renal failure in the iodixanol group."

In an interview at the meeting, he said that iodixanol is gaining a large share of the global market because it is thought to be less harmful to the kidneys. Low-osmolar contrast media were developed, he said, in an attempt to reduce significant side effects with the first generation of high-osmolar media. The low-osmolar media were much better tolerated, so biotechnology companies sought to reduce the osmolarity even further.

The strategy did not make sense to Dr. Persson for two reasons. First, he did not believe osmolarity was a problem. "Actually we [have been] giving diuretics with high osmolarity for decades, and nothing has happened," he said.

Second, in reducing osmolarity, the new products increased the viscosity, "so it's more like syrup and not like water," he said.

The higher viscosity can cause severe damage to the kidney because it clots the tubules, Dr. Persson said.

As a result of the changes, he contended, "Those contrast media that today are thought to be [safer] for the kidney lead to a twofold higher increase in renal failure diagnosis."

Representatives of iodixanol's parent company, GE Healthcare Ltd. in Buckinghamshire, England, disputed Dr. Persson's findings in an interview after attending his presentation.

European medical director Hervé Lemaignen, M.D., and European brand manager Pamela McCord questioned whether nephropathy that was diagnosed long after use of iodixanol could be attributed to the dye.

They emphasized that the evidence in support of iodixanol being less neurotoxic comes from a randomized, double-blind, prospective, multicenter study (N. Engl. J. Med. 2003;348:491-9). It found that serum creatinine levels increased significantly less 3 days after angiography with iodixanol, compared with iohexol.

Dr. Persson said creatinine levels are only a surrogate measure for renal damage. He also contended that the published study was flawed because the patients in the iohexol group had diabetes for a mean of 18 years and therefore likely had more kidney damage than the iodixanol group, for whom the mean duration of diabetes was only 12.8 years.

The GE Healthcare officials maintained in turn that Dr. Persson's study was flawed, as the original database did not specify which contrast medium was used. "What they did was send out a questionnaire asking, 'Which contrast medium did you use in this year in your hospital?' So it is stretching it quite a little bit," Ms. McCord said.

Dr. Lemaignen also challenged Dr. Persson's argument that increased viscosity makes iodixanol harmful to the kidneys. It is more viscous in the vial, he said, but it becomes thinner when mixed with blood. ■

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