Pioglitazone May Be Effective in Reducing Progression of Atherosclerosis in Patients with Diabetes

Although coronary artery disease (CAD) accounts for 75% of deaths in patients with diabetes, few studies have compared antidiabetic agents beyond their glucose-lowering efficacy. A prospective, randomized trial showed that an insulin-sensitizing drug (pioglitazone) may be more effective than a traditional insulin secretagogue (glimepiride) in stopping or reducing the progression of atherosclerosis.

The PERISCOPE trial was a multicenter, double-blind trial that included 543 patients with CAD and type 2 diabetes. All patients had intravascular ultrasonography (IVUS) at study entry and were randomly assigned to treatment with glimepiride (1-4 mg) or pioglitazone (15-45 mg), with the drug titrated to the maximally tolerated dose by 16 weeks. At 18 months, a second IVUS examination was performed to determine the change in percent atheroma volume (PAV), the primary endpoint. Other IVUS endpoints included the mean maximum atheroma thickness, the total atheroma volume, and the atheroma volume in the most diseased 10-mm segment. Changes in biochemical parameters (levels of glycohemoglobin, insulin, and lipoproteins) and blood pressure were also evaluated.

Steven Nissen, MD, Cleveland Clinic, Cleveland, OH, reported that at 18 months, the change in PAV from baseline indicated highly significant progression of atherosclerosis among the patients treated with glimepiride (increase of 0.73%; p<0.001); in contrast, the PAV was essentially unchanged from the baseline (decrease of 0.16%; p=0.44) among patients treated with pioglitazone (Figure 1). The difference in the primary endpoint of the study between the two groups was highly significant (p=0.002). In contrast, there were no significant differences in the secondary IVUS endpoints between the two groups, with the exception of maximum atheroma thickness (increase of 0.011 mm for glimepiride vs decrease of 0.011 mm for pioglitazone; p=0.006).

Mean (SD) baseline glycosylated hemoglobin levels were 7.4% (1.0%) in both groups and declined during treatment by an average of 0.55% (95% CI, -0.68% to -0.42%) with pioglitazone and 0.36% (95% CI, -0.48% to -0.24%) with glimepiride (between-groups p=0.03). Pioglitazone also had a greater effect on metabolic parameters, inflammation, and blood pressure (Table 1).

Figure 1. Change in PAV (%).

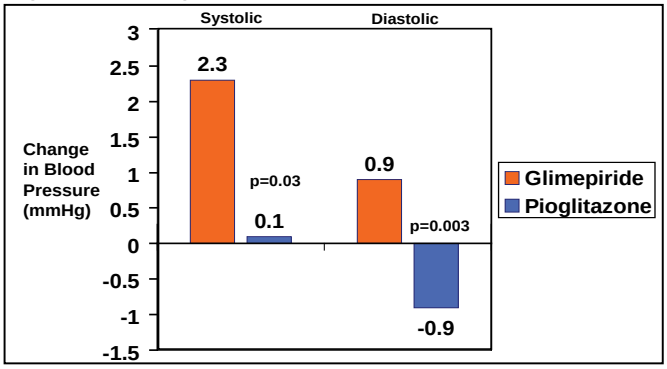


Table 1. Comparison of Pioglitazone and Glimepiride on Biochemical Parameters and Blood Pressure.

	Pioglitazone	Glimepiride	p Value
Change in HDL cholesterol level (%)	+16.0	+4.1	<0.001
Change in triglyceride level (%)	-15.3	+0.6	<0.001
Change in hsCRP level (%)	-44.9	-18.0	<0.001
Change in LDL cholesterol (%)	-6.6	-6.9	0.69
Change in fasting insulin levels (%)	-28.3	+8.5	<0.001
Change in systolic BP (mm Hg)	+0.1	+2.3	0.03
Change in diastolic BP (mm Hg)	--0.9	+0.9	0.003

With respect to safety, edema, fractures, and decreased hemoglobin levels occurred more frequently with pioglitazone, while hypoglycemia was more common with glimepiride.

Dr. Nissen compared the results of PERISCOPE with those of several other recent similar trials and noted that the collective findings suggest that glimepiride has a neutral effect on coronary disease progression. "However," he added, "the pioglitazone group had substantially less progression than would have been predicted for the LDL level achieved, suggesting an anti-atherosclerotic effect."

Celecoxib Cross Trial Safety Analysis

Long-term use of celecoxib is associated with an increase in cardiovascular (CV) risk for some patients, according to findings from a pooled analysis of 6 placebo-controlled, randomized clinical trials. The degree of risk is associated with both baseline CV risk and celecoxib dose.

"These data should provide comfort in prescribing celecoxib to patients with very low [baseline] cardiovascular risk," said Scott D. Solomon, MD, Brigham and Women's Hospital, Boston, MA. "Similarly, we should be cautious in prescribing celecoxib to patients who have elevated baseline risk," he said.

Conducted in partnership with the National Cancer Institute, the Cross Trial Safety Analysis was designed to characterize the long-term CV risk associated with celecoxib, a cyclooxygenase-2 (COX-2) inhibitor. Results of the analysis were published immediately following the late breaking trials session in an online version of the journal *Circulation* [Solomon et al. *Circulation* 2008].

Together, the 6 participating trials enrolled 7950 patients and provided the equivalent of 16,070 years of patient follow-up for analysis. Patients with no CV risk factors at baseline were described as low-risk for future cardiac events. Moderate-risk patients had at least one of the following risk factors: age >75 years, hypertension, hyperlipidemia, current tobacco use, or concurrent use of low-dose aspirin. Patients with 2 or more risk factors, and those with diabetes or previous CV disease, were classified as high-risk.

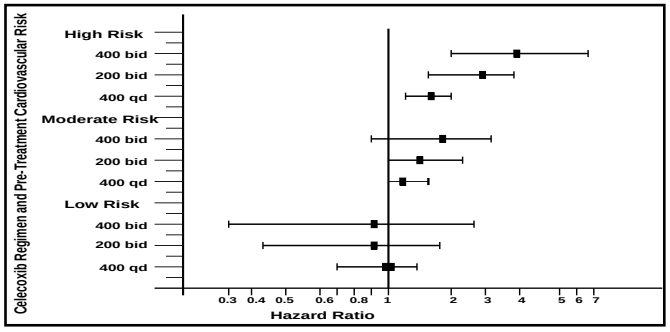
Across all patient groups (median follow-up of 31 months) and dosing regimens, the risk of CV events was elevated with celecoxib use compared with placebo [HR 1.6; 95% CI, 1.1-2.3; p=0.034].

The risk of CV events varied across the different dosing regimens that were evaluated in the trial (p value for dose regimen effect = 0.0005). Hazard ratios for the primary endpoint—a composite of CV death, myocardial infarction, stroke, heart failure, or thromboembolic event—were 1.1, 95% CI, 0.6-2.0 for the once-daily 400 mg dose, 1.8, 95% CI, 1.1-3.1 for the 200 mg dose given twice a day, and 3.1, 95% CI, 1.5-6.1 for the twice-daily 400 mg dose.

Dr. Solomon and colleagues also observed an interaction between baseline CV risk and celecoxib regimen (interaction p=0.034). For patients with the lowest baseline CV risk, the risks associated with the 400 mg once daily, 200 mg twice daily, and 400 mg twice daily regimens were roughly equivalent, with hazard ratios of 1.0, 0.9, and 0.9, respectively. However, for patients with the highest baseline CV risk, the differences across doses were pronounced. The hazard ratios for the primary endpoint were 1.5, 95% CI, 1.2-1.9, 2.3, 95% CI, 1.5-3.4, and 3.5, 95% CI, 1.9-6.4, respectively (Figure 1).

Dr. Solomon noted that the Celecoxib Cross Trial Safety Analysis findings support the American Heart Association position on celecoxib prescribing, which states that the lowest possible doses of celecoxib should be prescribed, especially in patients who are at highest risk of developing CV disease.

Figure 1. Risk of Celecoxib-Related CV Events by Celecoxib Dose and Baseline CV Risk.



Two Drugs Have Potential to Slow Progression of Atherosclerosis

Two trials explored the potential for pharmacologic therapy to slow the progression of atherosclerosis or even cause plaque regression in patients with coronary artery disease (CAD). The studies involved different classes of drugs and different imaging modalities to evaluate the change in the degree of stenosis caused by the atherosclerotic plaque.

In the ASTEROID trial, 507 patients with angiographic evidence of CAD were treated with rosuvastatin 40 mg/day for 24 months in an uncontrolled observational study. The initial results, first presented in 2006, demonstrated that the drug reduced plaque volume, as measured by intravascular ultrasound (IVUS), in arteries with less than 50% stenosis. Rosuvastatin 40 mg was well tolerated, with low rates of elevated ALT (1.8%) and CK (1.2%) observed, and only 12% of patients discontinuing due to adverse events. The current analysis was performed to evaluate changes in vascular lumen by quantitative coronary angiography (QCA) in arteries with more than 25% stenosis.

Christie Ballantyne, MD, Baylor College of Medicine, Houston, TX, reported that the coronary angiograms of 292 patients were evaluated at baseline and at 24 months. QCA showed that treatment with rosuvastatin led to an increase in the mean minimal lumen diameter from 1.65 ± 0.36 mm to 1.68 ± 0.38 mm (p<0.001) and a decrease in the mean percentage diameter stenosis from 37.3 ± 8.4% to 36.0± 10.1% (p<0.001).

In STRADIVARIUS, 839 abdominally obese patients with CAD were randomly assigned to treatment with either rimonabant 20 mg daily (422 patients) or placebo (417 patients). Rimonabant, a cannabanoid type 1 (CB1) receptor inhibitor, is an experimental agent that is not yet approved in