Microalbuminuria Risk Drops With Carvedilol

BY MITCHEL L. ZOLER
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ORLANDO, FLA. — Treatment with carvedilol cut the incidence of new-onset microalbuminuria by 47%, compared with metoprolol, in a study of more than 700 patients with type 2 diabetes and hypertension.

Carvedilol's ability to prevent microalbuminuria is probably due to its antioxidant properties—an effect that gives carvedilol an advantage over other -blockers and perhaps over other classes of antihypertensive medications as well, George L. Bakris, M.D., said at the annual meeting of the American College of Cardiology.

"These findings should be taken into account when selecting an antihypertensive medication," especially for patients with type 2 diabetes, said Dr. Bakris, director of the Hypertension/Clinical Research Center at Rush University in Chicago.

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DR. BAKRIS

Even among hypertensive patients who do not have diabetes, carvedilol may be a good option if they have indications of impaired glucose control or if they have inflammatory markers, Dr. Bakris told this newspaper. However, he cautioned that this doesn't mean that a patient whose diabetes is currently well controlled and who is tolerant of another -blocker or other antihypertensive regimen should be switched to carvedilol.

The new findings came from a prespecified subanalysis of the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, sponsored by GlaxoSmithKline, the company that markets carvedilol (Coreg). Dr. Bakris has received research grants from and is a speaker and consultant for GlaxoSmithKline. He has also received research grants from and is a speaker and consultant for Novartis, which markets the trade formulation of metoprolol (Lopressor). Metoprolol is also available in several generic formulations.

The primary objective of the GEMINI trial was to compare the effects of carvedilol and metoprolol on glycemic and metabolic control in 1,235 patients with type 2 diabetes and hypertension. Virtually all patients in the study were on optimized treatment with an ACE inhibitor or an angiotensin-receptor blocker. The study results showed that after 5 months of -blocker treatment, patients treated with carvedilol had significantly better glycemic control and better improvements in measures associated with metabolic syndrome—insulin resistance, body weight, total cholesterol, and triglycerides—compared with metoprolol-treated patients (JAMA 2004;292:2227-36).

A prespecified subanalysis of the study focused on the 88% patients who had albuminuria at enrollment. The vast majority of these patients had a modest level, with a urinary albumin-to-creatinine ratio of less than 30 mg/g. A total of 191 patients had microalbuminuria, defined as a ratio of more than 30 mg/g but less than 301 mg/g. Microalbuminuria was the focus of this study because it reflects diffuse endothelial dysfunction in the renal vasculature and has been an independent predictor of cardiovascular events in patients with diabetes as well as in patients without diabetes. Microalbuminuria is also a marker of systemic inflammation that mirrors levels of high-sensitivity C-reactive protein.

Patients in the study were randomized to treatment with either carvedilol or metoprolol, and their dosages were up-titrated over a 7-week period. Carvedilol treatment began at a daily dosage of 6.25 mg b.i.d and was increased as tolerated to a daily maximum of 25 mg b.i.d. Metoprolol was begun at 50 mg b.i.d and was raised to a maximum dosage of 200 mg b.i.d. Patients who entered the study with a blood pressure of at least 140/90 mm Hg were treated to achieve a pressure of 135/85 mm Hg or less. Those who began at a pressure of 130-139/80-89 mm Hg were treated to reach a goal pressure of 130/80 mm Hg or less.

After 5 months of treatment, 388 patients treated with carvedilol had an average drop in their urinary albumin-to-creatinine ratio of 14%, compared with an average increase in the ratio of 2.5% among 542 patients treated with metoprolol—a statistically significant difference.

Among the patients who began the trial with a ratio of less than 30 mg/g, 6.6% of patients treated with carvedilol developed new-onset microalbuminuria during the 5-month follow-up, compared with 11.1% of the patients treated with metoprolol—a statistically significant difference. Treatment with carvedilol cut the risk of developing microalbuminuria by 47%, compared with patients treated with metoprolol. Carvedilol was also more effective than metoprolol for cutting urinary albumin levels in patients who were normoalbuminuric when they started treatment.

The protective effect of carvedilol, compared with metoprolol, was independent of the drugs' antihypertensive effects. The achieved blood pressures among the patients in both treatment groups were essentially identical. This led Dr. Bakris to speculate that carvedilol's ability to prevent microalbuminuria was due to the drug's antioxidant properties. He cautioned that reductions in microalbuminuria have not yet been proved to cut the rate of cardiovascular events. ■

CV Risk Persists in Atorvastatin Tx of Type 2 Diabetics on Dialysis

BY JERRY INGRAM
Contributing Writer

ST. LOUIS — Type 2 diabetic patients with kidney failure or end-stage renal disease had significant reductions in LDL cholesterol, but not cardiac death, MI, or stroke, after an average of 4 years of treatment with atorvastatin, Christoph Wanner, M.D., reported at the annual meeting of the American Society of Nephrology.

"We reached the goal of reducing LDL [cholesterol] by 41% in type 2 diabetic patients with kidney failure or end-stage renal disease. In addition, safety was excellent in this patient population," said Dr. Wanner, professor of medicine and head of nephrology at the University Clinic, Würzburg, Germany.

For this prospective, randomized, double-blind study, Dr. Wanner and his associates enrolled 1,255 patients at 178 dialysis centers in Germany between 1998 and 2004. They randomized patients to 20 mg of atorvastatin (619 patients) or placebo (636 patients) for a median of 4 years.

The trial, known as the Deutsche Diabetes Dialyse Studie, and also referred to as the 4D Trial, is the first examination of statin therapy in patients with type 2 diabetes and kidney failure. It also is the first study of cardiovascular outcomes among dialysis patients taking statins, Dr. Wanner said. All study participants had advanced-stage type 2 diabetes and were on maintenance hemodialysis. Some patients also had complications of diabetes including retinopathy, degenerative nerve disease, blindness, and diabetic gangrene, the researchers reported. Among the study participants, between 20% and 30% had a history of prior MI, revascularization, and/or heart surgery.

The investigators noted that the 41% reduction in LDL cholesterol in their study patients taking atorvastatin was consistent with data obtained previously in the general population.

But there was one important difference between the participants in their study and those in previous studies such as the Collaborative Atorvastatin Diabetes Study. Patients in the 4D Trial did not have statistically significant reductions in risk of cardiac death, myocardial infarction, and stroke.

"Importantly, this trial suggests that statins are not as effective in dialysis patients. Randomized trials will be necessary if we really want to begin to treat these patients appropriately," David Charytan, M.D., said in an interview with this newspaper. Dr. Charytan, who is a clinical and research fellow at Brigham and Women's Hospital, Boston, was another presenter at the meeting.

Because of this difference in response to statin drugs, patients with type 2 diabetes should be treated with statin therapy early on, before the onset of renal disease, Dr. Wanner concluded. ■

FDA Issues Public Advisory on Crestor Dose in Asian Patients

Evidence of a heightened risk of rhabdomyolysis in Asian Americans led the Food and Drug Administration to issue an alert and to require a label revision for the statin rosuvastatin last month.

According to the FDA Public Health Advisory, in a phase IV pharmacokinetic study "involving a diverse population of Asians residing in the United States, rosuvastatin [Crestor] drug levels were found to be elevated approximately twofold, compared with a Caucasian control group."

Because the risks of statin side effects have been shown to be dose dependent, a change to the Dosage and Administration section of the label was made to state that the 5-mg dose should be considered the starting dose for Asian patients, and any increase in dose should take into consideration the increased drug exposure in this patient population. The new label also emphasizes that 40 mg should not be used as a starting dose and should only be used in patients "who have not achieved their cholesterol goals with the 20-mg dose."

All statins are known to create a risk of myopathy/rhabdomyolysis, and the original Crestor product label included a warning that patients of advanced age (older than 65 years) or those who had hypothyroidism and/or renal insufficiency should be considered to be at greater risk of developing myopathy while receiving a statin and should be started at low doses and carefully monitored.

In 2004 the drug's maker, AstraZeneca Pharmaceuticals LP, found itself under attack by Public Citizen Health Research Group, which petitioned the FDA to have rosuvastatin removed from the market because of safety concerns regarding the risk of myopathy/rhabdomyolysis.

In June, the FDA issued a public health advisory alert to physicians emphasizing that physicians should pay close attention to the rosuvastatin label regarding dosage, "to cut the risk of myopathy."

Just days after the current advisory was released, Public Citizen renewed its call for the drug's withdrawal, citing its own analysis of adverse event reports in which the rate of rhabdomyolysis per million prescriptions filled for rosuvastatin was 6.2 times higher than the rate for all of the other statins combined.

The FDA denied the request, stating, "We do not believe that the adverse event reports on Crestor indicate the drug poses and unacceptable risk of rhabdomyolysis" and that extensive preapproval and ongoing clinical trial–safety experience indicates that rosuvastatin's muscle safety is comparable to that of other statins.

—Mark S. Lesney