Microalbuminuria Risk Drops With Carvedilol

BY MITCHEL L. ZOLER
Philadelphia Bureau

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 β-blockers and perhaps over other classes of antihypertensive medications as well, according to George L. Bakris, M.D., said at the annual meeting of the American College of Cardiology.

The 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.

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 β-blocker or other antihypertensive regimen should be switched to carvedilol.

The new findings came from a pre-specified 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. Ninety-one 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 titrated up 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. 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 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 Tt 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, with a statistically significant difference in risk of cardiac death, myocardial infarction, and stroke.

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,” said Dr. Bakris.

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 rosvastatin 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, rosvastatin (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 levels with the 20-mg dose.”

All statins are known to create a risk of rhabdomyolysis and the original Crestor product label included a warning that patients 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

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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 rosvastatin 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 rosvastatin 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 rosvastatin 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 a unacceptable risk of rhabdomyolysis and that extensive preapproval and ongoing clinical monitoring indicates that rosvastatin’s muscle safety is comparable to that of other statins.”

—Mark S. Lesney