Carvedilol Beats Metoprolol
Microalbuminuria from page 1

The new findings came from a pre-specified subanalysis of the Glycemic Ef-fects in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives (GEMINI) trial, sponsored by Glaxo-SmithKline, 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 already on other antihypertensive drugs, such as an ACE in-hibitor or an angiotensin receptor block-er. 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—inulin resistance, body weight, total cholesterol, and triglyc erides—compared with metoprolol-treat ed patients (JAMA 2004;292:2227-36). A pre-specified subanalysis of the study focused on the 88% of patients who had al uminuria at enrollment. The vast major ity of these patients had a modest level of microalbuminuria, defined as a 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 cardio vascular 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.

In the study, the effects of both 1-year rimonabant 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 rimonabant treatment began at a daily maximum of 25 mg b.i.d. Meto prolol was begun at 50 mg b.i.d and was raised to a maximum dosage of 200 mg in 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 pa tients treated with carvedilol had an aver age drop in their urinary albumin-to-cre atinine ratio of 14%, compared with an average rise in the ratio of 2.5% among 542 patients treated with metoprolol. The difference was statistically significant. Among the patients who began the tri al 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 the metoprolol—a statistically significant difference.

Treatment with carvedilol cut the risk of developing microalbuminuria by 47%, compared with placebo and with rimonabant. Carvedilol was also more effective than metoprolol for cutting urinary albumin levels in patients who were normal al metabolic syndrome or patients who were overweight or obese. The protective effect of carvedilol, compared with metoprolol, was independent of the drugs' antihypertensive effects. The achieved blood pressure ranges among the pa tients in both treatment groups were es sentially identical. This led Dr. Bakris to speculate that carvedilol's ability to pre vent microalbuminuria was due to the drug's antioxidant properties.

Dr. Bakris cautioned that reductions in microalbuminuria have not yet been proved to cut the rate of cardiovascular events, but he hoped that such a causal link will probably exists.

The 57% decrease in prevalence of metabolic syndrome was particularly impressive in terms of future likely cases of cardiovascular disease and diabetes prevented. He also called the 2-year safety data “hearing.” But he sounded a note of caution: “If you look at the weight-loss data, at 2 years the curves are starting to head upward. And we all know that obesity is not just a 2-year problem. We’ll want to see post marketing studies to see if this effect is maintained long term.”

Dr. Gardin also raised several philo sophical issues that have been on the minds of many physicians who endured the litigious frenzy that followed the fen-phen (fenfluramine-phentermine) controversy. Hypothetically, what if rimonabant is approved, hits the market, we have 5 mil lion prescriptions out there, and we get all of the wonderful positive effects described in the study—but it turns out one person who meets a BMI criterion, or if addi tions at 1-year follow-up.

At that time, total- and LDL-choles terol levels were lower, and HDL-cho lesterol levels were higher. Triglyceride levels were unchanged. Dr. Schaper said. The findings suggest that allcomponents of metabolic syndrome should be identified and treated aggressively, she said.

—Sharon Worcester