Carvedilol Beats Metoprolol

Microalbuminuria *from page 1*

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 already 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% of 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 uptitrated 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 rise in the ratio of 2.5% among 542 patients treated with metoprolol. The difference was statistically significant.

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.

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

Rimonabant Weight Loss Sustained at 2 Years

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — The outstanding weight loss and cardiovascular-risk reduction previously reported after 1 year of rimonabant therapy were maintained after 2 years of treatment in the phase III Rimonabant in Obesity–Europe trial, Luc Van Gaal, M.D., reported at the annual meeting of the American College of Cardiology.

The safety and tolerability profiles of rimonabant, the first in a new class of selective endocannabinoid type 1–receptor blockers, also remained reassuring after 2 years' treatment, added Dr. Van Gaal, professor of diabetology, metabolism, and clinical nutrition at the University of Antwerp (Belgium) and principal investigator for Rimonabant in Obesity (RIO)–Europe.

The 57% decrease in prevalence of metabolic syndrome was particularly impressive in terms of CVD and diabetes prevention.

The new 2-year study results are virtually superimposable on the 2-year outcomes of the phase III RIO–North America trial presented last fall at the annual scientific sessions of the American Heart Association (INTERNAL MEDICINE NEWS, Jan. 15, 2005, p. 52).

Armed with data from over 6,600 overweight and obese participants in the two trials, plus two Sanofi-Aventis–sponsored 1-year phase III trials, the company plans to file before midyear for Food and Drug Administration and European Commission approval of rimonabant 20 mg/day for weight loss, a spokesman told this newspaper. Simultaneously, Sanofi-Aventis will file for a smoking cessation indication, the subject of another extensive phase III rimonabant clinical trials program.

RIO–Europe was a randomized, double-blind, placebo-controlled study involving 1,507 overweight or obese patients with a mean baseline body mass index (BMI) of 37 kg/m^2 and a mean age of 45 years. As is typical in weight loss trials, 80% were women. Participants were strongly encouraged by dietitians and counselors to adopt a 600-kcal/day–deficit diet and increase their physical activity.

In RIO–Europe, 20 mg/day of rimonabant resulted in a mean 7.2-kg weight loss among those who completed 2 years of treatment, compared with a mean 2.5-kg loss in those taking placebo. In an intent-to-treat analysis, the mean weight loss was 5.5 kg in the rimonabant arm and 1.2 kg with placebo.

At baseline, more than 42% of study participants met National Cholesterol Education Program criteria for metabolic syndrome. After 2 years on rimonabant 20 mg/day, the prevalence of metabolic syndrome fell by 57%, compared with a 34% drop with placebo.

Mean waist circumference—a measure of intraabdominal obesity—was reduced by 7.5 cm after 2 years on rimonabant, from a baseline of 110 cm, and by 3.4 cm in the placebo group. More than 32% of patients who completed 2 years of rimonabant treatment lost at least 10% of their baseline body weight—a medically meaningful threshold—as compared with 11% on placebo. HDL-cholesterol levels climbed by 28.2%, compared with 16.8% with placebo. Triglycerides fell by an average of 8.8% with rimonabant while rising 6.3% in the placebo group.

Rimonabant also significantly improved insulin sensitivity. Only about half of the observed improvement in lipids could be explained by the weight loss, implying that rimonabant exerts direct metabolic effects beyond weight loss, Dr. Van Gaal continued.

As was the case after 1 year, rimonabant resulted in no significant changes in heart rate, blood pressure, or QT interval at the 2-year mark. The most common treatment side effects were nausea and other GI symptoms and dizziness, all of which were more frequent in year 1 and mostly mild.

Discussant Julius M. Gardin, M.D., called RIO–Europe "a remarkable study—really a landmark study in the field of obesity."

He singled out the 57% decrease in prevalence of metabolic syndrome as particularly impressive in terms of future likely cases of cardiovascular disease and diabetes prevented. He also called the 2-year safety data "heartening." 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 philosophical 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 million prescriptions out there, and we get all of the wonderful positive effects described in the study—but it turns out one person per million dies related to the drug? What should reasonable people do about this? Should they say that's an acceptable risk-benefit ratio? Or should we handle it the way previous anorexigens were handled, with punitive measures?" asked Dr. Gardin, chief of cardiology at St. John Hospital and Medical Center, Detroit.

Another societal issue is whether rimonabant should be considered in anyone who meets a BMI criterion, or if additional risk factors ought to be required. "I would hate to see prescription of a medication subvert efforts … to encourage prudent eating, reduction of calories, exercise, and other healthful lifestyle measures," Dr. Gardin said. ■

Dx of Metabolic Syndrome Often Missed in Women

ORLANDO, FLA. — Middle-aged women should routinely be assessed for metabolic syndrome, Ana M. Schaper, Ph.D., said at an international conference on women, heart disease, and stroke.

In a chart review including 147 women under 65 years who were treated for MI in a rural midwestern community, Dr. Schaper found that 113 (77%) had no history of coronary artery disease (CAD), but many had risk factors: a history of smoking in 70%, high blood pressure in 63%, a family history of CAD in 52%, and obesity or overweight in 70%.

Sufficient data were available for 80 of the women with no history of CAD to allow risk stratification based on National Cholesterol Education Program guidelines. Of these women, only 10% would have qualified for medical management under the guidelines, and only 18% would have qualified for therapeutic lifestyle changes, but 49% had metabolic syndrome, said Dr. Schaper of Gundersen Lutheran Medical Foundation, La Crosse, Wis., in a news conference at the meeting.

Of the 135 patients who survived their initial hospitalization, 54 were readmitted within a year for chest pain, myocardial infarction, or for a revascularization procedure. All women who were discharged on an ACE inhibitor or angiotensin receptor blocker, and lipid therapy, and 90% of those discharged on a -blocker, remained on their medications at 1-year follow-up.

At that time, total- and LDL-cholesterol levels were lower, and HDL-cholesterol levels were higher. Triglyceride levels were unchanged, Dr. Schaper said.

The findings suggest that all components of metabolic syndrome in younger women should be identified and treated aggressively, she said.

—Sharon Worcester