# Aliskiren Bests Ramipril for Diabetic Hypertension

BY ERIK GOLDMAN
*Contributing Writer*

MADRID — Aliskiren, the novel renin-blocking drug, improved 24-hour blood pressure control and showed greater systolic pressure reductions, compared with ramipril, in diabetics with uncontrolled hypertension, according to data presented at the annual meeting of the European Society of Hypertension.

Aliskiren also can be safely combined with the ACE inhibitor in this population, the combination giving the greatest degree of pressure.

Aliskiren works by blocking the renin-regulated conversion of circulating angiotensinogen to angiotensin-1. The new drug, also known by the brand name Rasilez, is the first of what may soon be a burgeoning class of renin blockers. It is being considered for approval by regulatory authorities in Europe and the United States.

Dr. Yagiz Uresin, professor of clinical pharmacology at Istanbul (Turkey) University, presented a multicenter international study of 837 patients with diabetes and hypertension. At baseline, the patients had blood pressures of over 155 mm Hg systolic and 98 mm Hg diastolic.

After a washout period and a 2-4 week placebo run-in, the patients were randomized to aliskiren monotherapy, 150 mg/day; ramipril monotherapy, 5 mg/day; or a combination of 150 mg aliskiren plus 5 mg ramipril per day. After 4 weeks, the investigators doubled the doses in all study groups.

**The difference in blood pressure control between renin blockade and ACE inhibition was greatest in the early morning hours, at 21-24 hours post dose.**

After 8 weeks, aliskiren gave mean pressure reductions of 14.7 mm Hg systolic and 11.3 mm Hg diastolic. This was significantly better than the 12.0- and 10.7-mm Hg reductions obtained with ramipril alone. In combination, the two drugs gave mean pressure reductions of 16.6 mm Hg systolic and 12.8 mm Hg diastolic.

Using a target pressure of 130/80 mm Hg, slightly over 8% of the patients in the monotherapy arms could be considered well controlled by the end of the study. Combination therapy bumped this up to 13%. This low rate of response reflects the difficulty of treating longstanding hypertension in diabetic patients, said Dr. Uresin.

A separate subgroup analysis drawn from the same international cohort showed that aliskiren alone and in combination with ramipril gave significantly better round-the-clock diastolic pressure control than did ramipril alone.

A total of 173 patients, 55 on ramipril alone, 57 on aliskiren alone, and 61 on the combination, underwent 24-hour ambulatory monitoring. Using the smoothness index, a scale that measures the consistency of pressure control over a 24-hour period, the investigators found that aliskiren alone and in combination with ramipril provides significantly greater consistency over the course of a day. Smoothness index scores correlate with reversal of left ventricular hypertrophy and carotid artery wall thickening.

The difference between renin blockade and ACE inhibition was greatest in the early morning hours. At 21-24 hours post dose, the renin blocker alone and in combination with ramipril gave significantly better pressure control than did ramipril alone. Systolic pressures remained between 4 and 12 mm Hg below baseline in patients on aliskiren or aliskiren plus ramipril. In the ramipril group, systolic pressure rose to near baseline levels at the end of the 24-hour dosing cycle.

Adverse effects in the new study were similar to those found in earlier trials showing aliskiren as having a low side-effect profile. The impact of side effects was low in all treatment groups, said Dr. Uresin. About one-third of the patients in each monotherapy group had some untoward effects, the most common being headache, cough, nasopharyngitis, and diarrhea. These were mild and self-limiting in the vast majority. Just over 2% of the ramipril monotherapy group and just under 3% of the aliskiren group had serious side effects; the incidence was reduced to 1.4% for the combination.

The addition of aliskiren to ramipril can cut the incidence of coughing, which is the most common reason patients quit ACE inhibitor therapy. Dr. Uresin pointed out that incidence of cough was just under 5% in the ramipril-alone group, and just over 2% for aliskiren. The rate was 1.8% among those taking the combination. The difference was statistically significant.

"This was definitely not expected," said Dr. Uresin. It may have to do with reduced bradykinin levels following renin blockade, he said. ■

# Rimonabant Linked to Blood Pressure Reduction in Hypertensive Obese Patients

BY ERIK GOLDMAN
*Contributing Writer*

MADRID — Rimonabant, the novel cannabinoid type 1 receptor–blocking drug that has been shown to induce weight loss, improve glucose metabolism, raise HDL cholesterol, and lower triglycerides, also appears to lead to small but meaningful reductions in blood pressure in hypertensive obese patients.

That finding comes from a new analysis of pooled data from the four major rimonabant trials involving over 6,600 patients. Among patients with elevated BP at baseline (greater than 143/89 mm Hg for nondiabetics, and greater than 130/85 mm Hg for diabetics), the use of 20 mg/day of rimonabant was associated with a mean systolic pressure reduction of 7.5 mm Hg and a mean diastolic reduction of 5.2 mm Hg. This compares favorably with the mean reductions of 4.7 mm Hg and 3.0 mm Hg, respectively, in patients who received placebo, Dr. Luc Van Gaal reported at the annual meeting of the European Society of Hypertension.

This is the first indication that the cannabinoid receptor blocker may have a role in blood pressure reduction, and it is clearly good news for the treatment of obese or overweight patients who have multiple cardiovascular risk factors.

But the drug should not be misconstrued as being an antihypertensive agent per se. The observed reduction in blood pressure "is mediated by weight loss only, with the drug having no direct effect on blood pressure at this dose level," stressed Dr. Van Gaal, head of diabetology, metabolism and clinical nutrition at the University Hospital of Antwerp, Belgium.

Rimonabant, which is being developed by Sanofi-Aventis, is under review by the Food and Drug Administration.

The Rimonabant in Obesity and Related Metabolic Disorders (RIO) trial series comprises four distinct international multicenter trials looking at the effects of the drug in nonoverlapping populations.

RIO-North America involved 3,040 obese or overweight patients without comorbidities in the United States and Canada; RIO-Europe looked at a similar population of 1,507 European patients; RIO-Lipids involved 1,033 obese people with untreated dyslipidemia; RIO-Diabetes involved 1,045 obese or overweight patients with type 2 diabetes.

All four studies included hypertensive and nonhypertensive individuals. Across the RIO trials, the percentage of hypertensive subjects ranged from 13% in RIO-North America to 54% in RIO-Diabetes.

The reduction in blood pressure seen in the aggregate RIO population was most pronounced among those with dyslipidemia who were also hypertensive at baseline. In this cohort, the drug was associated with a mean 11.9-mm Hg reduction in systolic pressure and a mean 5.9-mm Hg reduction in diastolic pressure. In contrast, the placebo group had a 6.3-mm Hg drop in systolic and a 2.0-mm Hg drop in diastolic pressure.

In the RIO-Diabetes trial, rimonabant had little apparent effect on blood pressure in those who were normotensive at baseline. But those who were hypertensive at the outset had a 5.5-mm Hg decrease in systolic and a 4.4-mm Hg reduction in diastolic pressure. These differences were statistically significant, and given that nearly 60% of those who were hypertensive were already on antihypertensive medications, these incremental reductions are clinically meaningful, Dr. Van Gaal said.

A linear regression analysis plotting the blood pressure changes against changes in body weight showed nearly identical curves for rimonabant and placebo. The degree of pressure reduction with rimonabant is equivalent to that seen for placebo in patients matched for the same degree of weight loss.

That said, the observed reduction in blood pressure "adds to the other cardiometabolic benefits demonstrated for rimonabant, such as reduced body weight and waist circumference, improved lipid profile, and improved glycemic control," Dr. Van Gaal said.

Dr. Nick Finer of the Addenbrooke's Hospital, National Health Service Trust, Cambridge, England, commented, "Currently, we use a wide variety of drugs to treat the cardiovascular, inflammatory, endocrine and adipose aspects of the disease of abdominal obesity. Cannabinoid 1 receptor blockade seems to affect all of these areas with one drug. In principle, this could be drug sparing. It is a very exciting development." ■

# *Thiazides and β-Blockers May Up Diabetes Risk*

Both thiazide diuretics and β-blockers taken to treat hypertension appear to raise the risk of type 2 diabetes, reported Dr. Eric N. Taylor of Harvard Medical School, Boston, and associates.

They used data from three large cohort studies to determine whether various antihypertensive agents were associated with incident cases of type 2 diabetes. They analyzed data on more than 14,000 younger women (aged 25-42 years at baseline) in the Nurses' Health Study II, more than 41,000 older women (aged 30-55 at baseline) in the Nurses' Health Study I, and more than 19,000 men (aged 40-75 at baseline) in the Health Professionals Follow-Up Study.

All the subjects were taking medication for hypertension. During follow-ups of 10 years (NHS II participants), 8 years (NHS I participants), and 16 years (HPFS participants), 3,589 of these subjects developed type 2 diabetes.

The use of thiazide diuretics significantly raised the risk of incident diabetes in all three cohorts. The use of β-blockers was not assessed separately from other antihypertensives in the younger women, but it significantly raised the risk of incident diabetes in the older women and in the men, Dr. Taylor and his associates wrote (Diabetes Care 2006;29:1065-70).

There was no association between the use of calcium channel blockers or other antihypertensive medications and diabetes risk.

**—Mary Ann Moon**