# *Aliskiren Safe, Effective in Lowering Blood Pressure*

## *Unlike other antihypertensives, the investigational drug appears to block the entire RAAS system.*

BY MITCHEL L. ZOLER
*Philadelphia Bureau*

ATLANTA — Treatment with aliskiren, a drug from a new class of antihypertensive agents, led to safe and effective lowering of blood pressure in a phase III study with 672 patients.

"Aliskiren has the potential to be an important new treatment for hypertension, with placebolike tolerability and sustained, 24-hour action," Dr. Byung-Hee Oh said in a poster presentation at the annual meeting of the American College of Cardiology.

But what some experts find even more compelling is the potential that aliskiren might have for preventing end-organ damage because it works by blocking renin, the rate-limiting enzyme for the entire renin-angiotensin-aldosterone system (RAAS). Two existing classes of antihypertensive drugs, ACE inhibitors and angiotensin-receptor blockers (ARBs), also act by inhibiting elements of the RAAS.

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**DR. GILES**

"As good as the ACE inhibitors and ARBs have been, there is still some unfulfilled promise. It may be that we need to inhibit the whole RAAS rather than one or two components. The hope is that renin inhibitors can do what the other RAAS-active drugs do, but do it even better," said Dr. Thomas D. Giles, a professor of medicine at Louisiana State University, New Orleans, and president of the American Society of Hypertension Inc.

Clinical studies are planned to test aliskiren's efficacy for preventing end-organ damage, such as heart or renal failure, in patients with hypertension. In the meantime, Novartis, the company developing aliskiren, has filed a new drug application with the Food and Drug Administration. The company is seeking an indication of blood pressure lowering, based on the study results reported by Dr. Oh and findings from other studies, said a company spokeswoman.

The study run by Dr. Oh and his associates enrolled patients with mild to moderate hypertension (defined as an average diastolic blood pressure of 95-109 mm Hg and an average systolic blood pressure of less than 180 mm Hg) at 68 centers in five countries, including the United States. Patients were randomized to daily treatment with placebo or one of three dosages of aliskiren: 150 mg, 300 mg, or 600 mg once daily. Treatment continued for 8 weeks, and 608 patients completed the full study course.

After 8 weeks of treatment, systolic blood pressure fell by an average of 13.0, 14.7, and 15.8 mm Hg in patients taking 150 mg, 300 mg, and 600 mg of aliskiren, respectively, compared with an average drop of 3.8 mm Hg in the placebo group. Diastolic pressure fell by an average of 10.3, 11.1, and 12.5 mm Hg in the three aliskiren arms, compared with a 4.9 mm Hg decline in the placebo group, reported Dr. Oh, chief of the division of cardiology at Seoul (South Korea) National University.

Substantial reductions in blood pressure were seen after 2 weeks of treatment, and the drops in pressure reached near-maximal levels after 4 weeks and then were maintained out to week 8.

Between 59% and 69% of the patients who were treated with aliskiren had a drop of at least 10 mm Hg in their diastolic pressure or reached a pressure of less than 90 mm Hg, compared with 36% of patients having this level of decline while on placebo.

Laboratory analyses of serum specimens showed that plasma renin activity fell by an average of 75%-81% in patients treated with aliskiren, compared with a 20% rise in the control group. Despite these drops in activity, the level of plasma renin rose substantially, by 52%-229%, in patients taking aliskiren.

Treatment with aliskiren was generally well tolerated; the overall rate of all reported adverse effects was roughly similar in all four treatment groups. The incidence of serious adverse events was 0, 2.4%, and 1.8% in the three groups taking aliskiren, compared with 0.6% in the placebo group.

Fewer patients discontinued aliskiren because of adverse effects, compared with patients in the placebo group. The most common adverse event associated with aliskiren use was diarrhea, which occurred in 11.8% of patients taking 600 mg daily, compared with rates of 1.2%-1.8% in the other two dosage groups and in patients who received placebo.

Based on these results, aliskiren's side effect profile is "distinctly better than [that of] a lot of other antihypertensive drugs," said Dr. Giles in an interview. As a result, once aliskiren gets FDA approval, some physicians will probably use it for patients who have not adequately responded to other drugs, and some may be attracted to trying aliskiren as a first-line agent because of its efficacy and good adverse effect profile, said Dr. Giles, who did not collaborate on this study but has been a consultant to, a speaker for, and received research support from Novartis. ■

# Latest Research Brings New Focus to Hypertension Tx

BY MITCHEL L. ZOLER
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ATLANTA — A new hormone therapy for postmenopausal symptoms also has a significant antihypertensive effect; the popular β-blocker carvedilol comes in a once-daily formulation; and an analysis of more than 600 patients with hypertension quantified the potential for reducing coronary heart disease by controlling blood pressure and serum lipids. These three poster reports were among the hypertension studies presented at the annual meeting of the American College of Cardiology.

### New Progestin Lowers Blood Pressure

Drospirenone is a new progestin with antialdosterone effects that is being developed for use with 17-β estradiol to treat postmenopausal symptoms. The effect of drospirenone and estradiol on blood pressure was assessed in a dose-ranging study with 750 women. All participants were postmenopausal women with mild to moderate hypertension, with a systolic pressure of 140-179 mm Hg and a diastolic pressure of 90-109 mm Hg when off treatment.

The women were randomized to treatment with estradiol alone; estradiol plus 1 mg, 2 mg, or 3 mg of drospirenone daily; or placebo. After 8 weeks of treatment, average clinical BP readings in the placebo group had fallen by 8.7 mm Hg (systolic) and by 5.0 mm Hg (diastolic), compared with baseline. Estradiol treatment alone produced no significant reduction in BP, compared with the placebo effect.

Women treated with 1 mg of drospirenone daily had an average additional systolic pressure reduction of 0.9 mm Hg and a diastolic pressure reduction of 2.0 mm Hg, compared with the placebo group; this was of borderline statistical significance. The higher dosages of drospirenone had a more marked effect. Women taking a 2-mg daily dosage had an average additional fall in systolic pressure of 3.4 mm Hg and in diastolic pressure of 4.0 mm Hg, compared with the placebo group, which were statistically significant declines, reported Dr. William B. White, chief of the section of hypertension and clinical pharmacology at the University of Connecticut, Farmington, and his associate. Similar drops in pressure were also seen in women who received 3 mg of drospirenone daily.

All three dosages of drospirenone were "well tolerated, with modest subjective or objective adverse events," said Dr. White and his associate in their poster. The percentage of patients who developed hyperkalemia while on treatment was similar in all five treatment groups. Other details of adverse effects were not reported. The study was sponsored by Berlex, which is developing drospirenone.

### Once-Daily Dosing of Carvedilol

Carvedilol is a widely used β-blocker that is effective for lowering blood pressure and is especially popular for treating patients with heart failure. The only available formulation of carvedilol requires twice-daily dosing. A placebo-controlled, dose-ranging study with a total of 338 patients was done to assess the BP-lowering effects of a controlled-release (CR) once-daily formulation of carvedilol.

The study enrolled patients with diastolic blood pressures of 90-109 mm Hg. Patients were randomized to treatment with 20 mg, 40 mg, or 60 mg of carvedilol CR or placebo once daily for 6 weeks. The study's primary end point was the change in mean diastolic BP, measured by ambulatory BP monitoring, in the treatment groups, compared with those on placebo.

Placebo use led to an average 0.4 mm Hg decline in mean, 24-hour diastolic pressure. The three dosages of carvedilol CR led to significantly larger declines in a dose-dependent manner. The average falls in diastolic pressure were 4.4 mm Hg, 7.9 mm Hg, and 9.6 mm Hg in the 20-mg, 40-mg, and 60-mg groups, respectively, reported Dr. Michael A. Weber, professor of medicine at the State University of New York, Brooklyn, and his associates. Similar drops were also seen in systolic pressure. Blood pressure control was maintained for 20-24 hours after a dose of carvedilol CR.

The rates of adverse effects and of adverse effects leading to withdrawal from treatment were similar in all four treatment groups.

GlaxoSmithKline is developing carvedilol CR (Coreg CR), and submitted a new drug application to the Food and Drug Administration last year to have carvedilol CR approved as hypertension treatment.

### CHD Risk Tied to Hypertension and Lipids

In patients with hypertension, a third to a half of their coronary heart disease events could be prevented by reductions in their BP and improved serum levels of LDL and HDL cholesterol. Three-quarters of their events could be prevented by optimal control of these parameters, Dr. Nathan D. Wong and associates reported in a poster.

They made these estimates by analyzing data collected for 1,921 people in the National Health and Nutrition Examination Survey (NHANES) 2001-2002. The study, sponsored by Pfizer Inc., focused on the 676 people from this group who had hypertension, defined as a BP of at least 90 mm Hg diastolic or 140 mm Hg systolic, or at least 80 mm Hg diastolic or 130 mm Hg systolic in patients with diabetes.

Using the Framingham risk formula for the 10-year risk of coronary heart disease events, Dr. Wong and his associates calculated the projected number of events expected for these 676 people on the basis of their clinical characteristics at the time of the survey. They also calculated the projected number of events if their blood pressures and serum levels of LDL and HDL cholesterol were treated to achieve either nominal control or optimal control.

The calculations also showed that more events would be prevented by combined control of blood pressure and serum lipids than by the additive effect of controlling each of these parameters alone, said Dr. Wong, director of the heart disease prevention program at the University of California, Irvine. ■