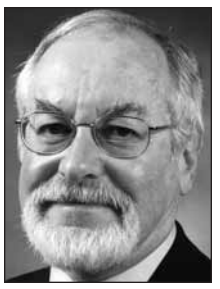
Combination Lipid/BP Treatment Reduces Events

Lower event rates with calcium channel blocker and statin are attributed to improved arterial elasticity.

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Combining a calcium channel blocker and a lipid-lowering drug to treat 847 patients with both hypertension and hyperlipidemia reduced cardiovascular events more than either drug alone or placebo because of improvements in small artery elasticity, said Jay N. Cohn, M.D.

Preliminary results previously reported from the Efficacy and Safety of Atorvastatin Plus Amlodipine Versus Either Agent Alone in Patients with Concomitant Dyslipidemia and Hypertension (AVALON) trial showed a significantly lower rate of cardiovascular events with the combination therapy than with monotherapy or placebo, he said at the annual meeting of the American Society of Hypertension.



New data provide an explanation for the additive effects of the combined therapy. A nested substudy of 667 patients within the AVALON trial sequentially measured arterial wall compliance during treatment and found physiologic changes consistent with significantly greater improvements in small-artery compliance and better endothelial function in the combination therapy group, said Dr. Cohn, professor of medicine and director of the Rasmussen Center for Prevention of Cardiovascular Disease at the University of Minnesota, Minneapolis.

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DR. COHN

Pfizer Inc., which makes both amlodipine and atorvastatin, funded the study. Two of the investigators were Pfizer employees. Dr. Cohn is a consultant to and holds stock in Hypertension Diagnostics Inc., which makes the CV Profiler device that measured arterial compliance.

The CV Profiler uses a transducer placed over the radial artery of a patient at rest to measure pulse waves. A computer analysis of the waveforms assesses arterial stiffness. Separate short-term epidemiologic data suggest that lower small-artery elasticity increases the risk of heart attack, stroke, and other cardiovascular events, he said.

Dr. Cohn extrapolated from the current and previous data to suggest that reduced nitric oxide activity causes small-artery stiffness and that the combination of amlodipine and atorvastatin improves nitric oxide bioactivity. "I'm a firm believer that it's more than blood pressure which is playing a role in arterial health," he said.

The results add to findings from a 10,000-patient substudy within the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showing that amlodipine plus atorvastatin therapy in older hypertensive patients with normal lipid levels reduced the rate of cardiovascular events, compared with monotherapy or placebo (Drugs 2004;2[64 suppl. 2]:43-60). ■

Novel Drug Found Safe, Effective in Pulmonary Arterial Hypertension

BY BRUCE GOLDMAN
Contributing Writer

SAN DIEGO — An investigational drug, sitaxsentan, improved exercise capacity and World Health Organization functional class in patients with pulmonary arterial hypertension in a phase III trial, Robyn J. Barst, M.D., reported at the 100th International Conference of the American Thoracic Society.

The drug also exhibited a favorable safety profile.

STRIDE-2 (Sitaxsentan to Relieve Impaired Exercise) was a 246-patient, 18-week, randomized, double-blind, placebo-controlled clinical trial of sitaxsentan, which is in development by Encysive Pharmaceuticals under the trade name Thelin.

"STRIDE-2 confirmed what its predecessor, STRIDE-1, showed: Sitaxsentan at 100 mg is safe and efficacious, with a low incidence of acute hepatotoxicity," said Dr. Barst, professor of pediatrics at Columbia University, New York, and director of New York Presbyterian Hospital's Pulmonary Hypertension Center.

In the study, conducted at 55 centers around the world, about 60 patients were randomized to once-daily oral doses of 50 mg or 100 mg of sitaxsentan or placebo. An additional 60 patients received twice-daily open-label doses of bosentan (Tracleer, marketed by Actelion Pharmaceuticals), the only currently approved oral medication for pulmonary arterial hypertension (PAH).

PAH is uncommon, affecting an estimated 100,000-200,000 people worldwide, but the prevalence is rising with the advent of noninvasive diagnostic methods and improved treatment. Relentlessly progressive, the disease is characterized by high blood pressure and extensive remodeling of pulmonary arterial walls. Without lung or heart/lung transplantation, PAH is inevitably fatal, with a median survival of about 2.8 years.

One of the hallmarks of PAH is a high level of endothelin in the pulmonary vasculature. Endothelin is a potent mediator of both blood vessel constriction and smooth muscle proliferation. Two endothelin receptor subtypes, designated ET-A and ET-B, reside on pulmonary endothelial and smooth-muscle cells.

Animal and human studies have suggested that, whereas ET-A is strongly implicated in the etiology of PAH, ET-B's role may be beneficial, and therefore that a selective ET-A blocker might be desirable. Bosentan blocks both receptor types, while sitaxsentan is extremely selective for ET-A, Dr. Barst said.

Moreover, bosentan has been associated with relatively high rates of liver-function abnormalities. Sitaxsentan has oral bioavailability exceeding 90% and a relatively long duration of action, permitting dosing on a once-a-day basis, she said.

In the 6-minute walk, the primary end point in STRIDE-2, the sitaxsentan 100-mg group had a statistically significant increase of 31.4 meters over placebo, with open-label bosentan increasing the distance by 29.5 meters over placebo. Among patients on the 100-mg sitaxsentan dose, the 6-minute walk distance appeared on average to continue improving after week 12; bosentan's efficacy appeared to peak at week 12 and then trend downward.

Sitaxsentan at 100 mg, but not open-label bosentan, improved World Health Organization functional class versus placebo. Sitaxsentan at 100 mg, but not at 50 mg, trended toward clinical significance in delaying clinical worsening, Dr. Barst reported.

At 18 weeks, the 100-mg sitaxsentan dose was associated with a 3% rate of liver function abnormality (liver-enzyme elevations to greater than three times the upper limit of normal), compared with 6% for placebo and 11% for bosentan. Liver enzyme abnormalities reversed in all cases. These results are consistent with earlier studies of the two drugs and with bosentan's package insert. Other adverse effects of sitaxsentan didn't appear to have high clinical significance, she said.

About 72% of STRIDE-2 subjects were on warfarin, a blood-thinning agent commonly prescribed for PAH patients. Sitaxsentan inhibits, and bosentan enhances, the metabolism of warfarin, whose levels must therefore be monitored and in many cases decreased when sitaxsentan is coadministered. In this trial, bosentan necessitated about the same number of per-patient warfarin dose adjustments as did sitaxsentan, but in the opposite direction, Dr. Barst reported. ■

Adherence Better With Home BP Monitoring

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — New data for the first time support the assumption that home monitoring improves blood pressure control because of better adherence to antihypertensive therapy, Gbenga Ogedegbe, M.D., said at the annual meeting of the American Society of Hypertension.

Previous reports showed better control in hypertensive patients performing home blood pressure monitoring, compared with patients monitored in physicians' offices, and clinicians assumed this was due to better adherence to therapy with home monitoring.

The current data—part of a larger and longer study—came from patients with uncontrolled blood pressure on one or more antihypertensive medications who were randomized to home blood pressure monitoring (118 patients) or usual care in offices (60 patients) for 12 weeks.

Investigators assessed adherence to therapy using the well-validated Morisky questionnaire, said Dr. Ogedegbe of Columbia University, New York.

At baseline, 47% of patients in the home monitoring group and 65% of those in the usual care group reported being adherent to therapy, a difference that was not statistically significant.

In the home monitoring group, patients took their blood pressure three times per week on average, usually at different times of the day, using a "life-link" monitoring system that gave them immediate feedback on their blood pressure control (or lack of it) and electronically sent a report to their physicians.

At follow-up 12 weeks later, patients were asked four questions that have been shown to predict the likelihood of blood pressure control: In the past 4 weeks, have you been careless about taking your blood pressure medication? In the past 4 weeks, have you forgotten to take your blood pressure medication? Do you stop taking the medication when you feel better? Do you stop taking the medication when you feel worse, from side effects? Patients who answered "yes" to any of the questions were considered nonadherent to therapy.

In the home monitoring group, 31% went from being nonadherent at baseline to adherent with therapy at 12 weeks, compared with 12% of patients in the usual care group, a significant difference.

Patients in the home monitoring group were less likely to move from adherent to nonadherent (12%), compared with those in the usual care group (18%). The rest of the patients did not change adherence patterns.

The study was not large enough to detect any significant changes in blood pressure, Dr. Ogedegbe said. ■