Data Point to Amlodipine, Atorvastatin Synergy

Evidence obtained from ASCOT may lead to more aggressive use of statins in hypertensive patients.

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — Combined treatment with the calcium channel blocker amlodipine and atorvastatin appeared to have synergistic effects for cutting the rate of coronary heart disease events in a trial with about 10,000 patients.

A new analysis of data that was collected from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated a "much more dramatic risk reduction in patients treated with amlodipine and atorvastatin, compared with those treated with atenolol and atorvastatin," Peter S. Sever, M.B., said at the annual scientific sessions of the American Heart Association.

The results suggested that physicians may need to be more aggressive about prescribing a statin to hypertensive patients regardless of their baseline serum level of LDL cholesterol.

"In the context of hypertension, you have to ask, why is my patient not on a statin, because the evidence is fairly convincing that most patients would benefit," said Dr. Sever, professor of clinical pharmacology and therapeutics at Imperial College in London.

ASCOT was sponsored by Pfizer Inc., which makes amlodipine (Norvasc), atorvastatin (Lipitor), and a combined formulation of both drugs (Caduet). Dr. Sever served as a consultant to and received honoraria, travel expenses, and research support from Pfizer.

"I think the evidence is very good," said Richard B. Devereux, M.D., professor of medicine at Cornell University in New York. "I use statins a fair amount of time in my patients [with hypertension] and now I'll use it in a few more. I'm sure that the [ASCOT] results will influence some guidelines" to recommend wider use of statins in hypertensive patients, said Dr. Devereux, who was not involved in the ASCOT study and does not have any financial relationship with Pfizer.

"The guideline should be that anyone who needs treatment for hypertension should also be on a statin," said Jay Cohn, M.D., professor of medicine at the University of Minnesota in Minneapolis. The results of the new ASCOT analysis are "very provocative," he said, although he added that the finding needs to be repeated to prove that it's real.

Still, he is convinced that statins, calcium channel blockers like amlodipine, and ACE inhibitors, which were used with amlodipine in ASCOT, "protect the arteries in patients with arterial disease," and that this effect goes beyond simply using these drugs to reach a target blood pressure or level of serum cholesterol. Dr. Cohn was not involved in ASCOT; he has received research support from and served as a consultant to Pfizer.

ASCOT randomized a total of more than 19,000 patients with hypertension to two different antihypertensive treatment strategies. One arm used amlodipine as the primary agent, followed by addition of the ACE inhibitor perindopril in patients who did not reach the target blood pressure. The second arm used the β-blocker atenolol as the primary drug, with the diuretic bendroflumethiazide and potassium added when a second drug was needed.

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DR. COHN

The results of this comparison showed that amlodipine plus perindopril was more effective than atenolol plus the diuretic for reducing coronary heart disease events in this primary prevention population (Lancet 2005;366:895-906).

In addition, 10,305 patients with a nonfasting total serum cholesterol level of 250 mg/dL or lower were subjected to a second randomization to treatment with 10-mg atorvastatin daily or placebo. This aspect of the study showed that the atorvastatin regimen led to a reduction in coronary heart disease events (Lancet 2003;361:1149-58).

The new analysis looked at the interaction between the lipid-lowering and blood pressure–lowering regimens in a 2-by-2 factorial study. This additional analysis was prespecified in the study's original design.

The findings appeared to show an interaction. During almost 6 years of follow-up, 38 patients treated with amlodipine and atorvastatin had the study's primary end point—a nonfatal myocardial infarction or coronary heart disease death—compared with 80 patients with this end point among those who got amlodipine plus placebo, a 53% reduction in the patients on dual therapy compared with monotherapy. Among those treated with atenolol, there were 62 events in those who also received atorvastatin and 74 events in those treated with atenolol plus placebo, a 16% reduction in patients on dual therapy.

The *P* value for an interaction between the two treatments was .025, which was of borderline statistical significance because the threshold for statistical significance in this tertiary analysis was prespecified as .01.

"While this could be a chance finding, there is a plausible biologic explanation for a synergistic effect between amlodipine and atorvastatin for coronary events," Dr. Sever said.

He proposed the hypothesis that vascular smooth-muscle cells in atherosclerotic plaque are stimulated by cytokines to grow and dedifferentiate into synthetic cells that are unresponsive to calcium channel blockers. Statin treatment transforms the synthetic cells back to a differentiated phenotype that is again responsive to calcium channel blockers, he said. ■

Central Pressure Changes May Give Advantage to Amlodipine

BY MITCHEL L. ZOLER
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DALLAS — Brachial blood pressure measurements may not be the best way to assess the effects that antihypertensive drugs have on blood pressure.

An amlodipine-based regimen was much better than atenolol-based treatment for lowering central aortic pressure in a substudy of a trial that involved a total of more than 19,000 patients, Bryan Williams, M.D., said at the annual scientific sessions of the American Heart Association.

The results "demonstrate for the first time in a large, clinical-outcomes trial that blood-pressure lowering drugs have profoundly different effects on central aortic pressures and hemodynamics despite a similar impact on brachial blood pressure," said Dr. Williams, who is a professor of medicine at the University of Leicester (U.K.).

Amlodipine's ability to substantially reduce central aortic pressure is likely a major reason why the clinical results from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that patients treated with an amlodipine-based regimen had a 16% relative reduction in the incidence of total cardiovascular events and procedures, compared with patients treated with an atenolol-based regimen during an average follow-up of 5.5 years (Lancet 2005;366:895-906).

"It's remarkable that we're talking about what these drugs do in the central aorta after years of being completely blind" to these effects, Dr. Williams said. Multiple measures of central aortic pressures were obtained for 2,199 of the patients enrolled in ASCOT. These measures were obtained via a commercially available device that calculates central aortic pressures after transcutaneously measuring the radial artery waveform through an external transducer wand that's placed on a patient's wrist.

"Systolic pressure is not constant throughout the arterial tree, and clinically relevant changes may not be measured by brachial-cuff blood pressure," commented Joseph L. Izzo Jr., M.D., professor of medicine and pharmacology at the State University of New York at Buffalo. "We now have a mandate to look beyond blood-pressure cuff measurements."

The ASCOT substudy was done at five participating hospitals in the United Kingdom and Ireland. Participating patients had their central aortic pressures measured at baseline and during multiple follow-up examinations using the SphygmoCor Px system. Like all participants in ASCOT, these hypertensive patients were randomized to treatment with either of two regimens: amlodipine, followed by perindopril when a second drug was needed to reach the goal brachial-artery pressure, or atenolol, with the diuretic bendroflumethiazide and potassium added when a second drug was needed.

Throughout treatment, patients on the amlodipine-based regimen maintained a central aortic systolic pressure that averaged 4.3 mm Hg lower than patients treated with the atenolol-based regimen. Central aortic pulse pressure averaged 3.0 mm Hg lower in the amlodipine group, reported Dr. Williams. Both cuts in pressure were statistically significant. In contrast, systolic pressure measured by brachial cuff averaged 0.7 mm Hg lower in the amlodipine group, compared with the atenolol group, and diastolic blood pressure averaged 1.6 mm Hg lower with amlodipine.

Dr. Williams and his associates analyzed the role of central aortic pressure and other measured variables on the incidence of 305 cardiovascular events, procedures, or episodes of renal impairment that occurred among the 2,199 patients during follow-up. In a multivariate analysis, central aortic pulse pressure was the only factor that produced a significant, independent effect on the rate of these outcomes.

Central aortic pressure is produced by a combination of the main, outgoing pressure wave and a wave that's reflected back from the arms. Amlodipine causes peripheral vasodilation that reduces the reflected wave and shifts it away from the heart; atenolol causes peripheral vasoconstriction that boosts the reflected wave and brings it closer to the heart, Dr. Williams said.

The ASCOT study and substudy were sponsored by Pfizer Inc. which markets amlodipine (Norvasc). Dr. Williams has been a consultant to and has received research grants from Pfizer. ■

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'These things happen, and to draw the line and expect to hear about every single malfunction by notification or letter, you'd be very, very busy.'

Dr. William Maisel, on malfunctions of implantable cardioverter defibrillators, p. 48