Analysis Backs Benazepril-Amlodipine Combo

BY SHERRY BOSCHERT

SAN FRANCISCO — A new analysis supports a controversial study that challenged the favored role of diuretics in combination therapy for hypertension, but some experts remain skeptical.

Dr. Kenneth Jamerson, lead investigator of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, said the results of a substudy he presented at the annual meeting of the American Society of Hypertension confirm that the main trial constitutes a paradigm shift in treating hypertension. His coinvestigator, Dr. George Bakris, director of the hypertension center and professor of medicine at the University of Chicago, echoed that assessment at a press conference.

The ACCOMPLISH trial's conclusion that a fixed-dose combination of an ACE inhibitor and a calcium channel blocker was superior to a combination of an ACE inhibitor and a diuretic for initial antihypertensive therapy "has huge implications for the millions of patients that are taking blood pressure medication," said Dr. Jamerson, professor of medicine at the University of Michigan, Ann Arbor.

Other experts on a separate panel at the meeting were not convinced. Dr. William C. Cushman, chief of preventive medicine at the Memphis Veterans Affairs Medical Center and professor of preventive medicine at the University of Tennessee, Memphis, said the literature supports three drug classes as the mainstays of combination therapy for hypertension: diuretics, blockers of the renin-angiotensin-aldosterone system (RAAS), and calcium channel blockers.

"Based on all the data that we have, I would still put diuretics in a very favorable position in any combinations of these," Dr. Cushman said.

Here's the back story: Diuretics have been a mainstay of antihypertensive therapy for half a century. Recent guidelines have promoted the use of combination therapy to treat hypertension rather than starting with a single agent in higher-risk patients. The double-blind, industry-sponsored ACCOMPLISH trial was the first to compare two antihypertensive combinations as initial therapy.

The study randomized 11,506 patients with hypertension who were at high risk for cardiovascular events to receive fixed-dose pills containing either the ACE inhibitor-diuretic combination of benazepril-hydrochlorothiazide (HCTZ) or benazepril plus amlodipine, a calcium channel blocker. After 36 months, the risk of cardiac events was significantly lower in the benazepril-amlodipine group (9.6%) compared with the benazepril-HCTZ group (11.8%), a 20% relative risk reduction (N. Engl. J. Med. 2008;359:2417-28).

Critics pounced on several aspects of the study, including the fact that the 0.9-mm Hg difference between groups in systolic blood pressure results was based on clinic measurements, which are less accurate than ambulatory blood pressure monitoring (N. Engl. J. Med. 2009;360:1147-50).

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The findings have "huge implications" for millions taking BP medication, Dr. Kenneth Jamerson said.

A new substudy of 573 ACCOMPLISH subjects who underwent 24-hour ambulatory blood pressure monitoring, however, showed good blood pressure control that was similar between groups and, if anything, may have been slightly better in the benazepril-HCTZ group, with a nonsignificant 1.6-mm Hg difference in mean 24-hour systolic pressures between groups, Dr. Jamerson reported at the meeting. (See box.)

The substudy confirms that the reduced cardiovascular risk seen with benazepril-amlodipine was due to other beneficial characteristics of this combination therapy and not driven by differences in blood pressures between groups, Dr. Jamerson said.

He has received funding from, or been a consultant and speaker for, Novartis Pharmaceuticals and other drug companies, and as president of the International Society of Hypertension in Blacks, he sought industry support for the organization. Novartis markets trade versions of the benazepril-amlodipine and benazepril-HCTZ combinations, and both combinations have generic versions on the market.

European guidelines on hypertension treatment favor combination therapy and suggest that combinations of ACE inhibitor with a diuretic or a calcium channel blocker are equally good. "We show evidence that they're not," Dr. Jamerson said.

"They very likely may have to rethink their guidelines." U.S. guidelines generally prefer combinations that include a diuretic, he added. "I think this directly challenges that. I consider it a paradigm shift. It's up to the entire community to decide."

Dr. Bakris said that the subanalysis should pave the way for a change in recommendations. As editor of the hypertension portion of the electronic clinical resource tool UpToDate, he will be dropping a caveat about the ACCOMPLISH results and UpToDate will recommend the benazepril-amlodipine combination for initial therapy. Dr. Bakris has been a consultant, speaker, or adviser for Novartis and other pharmaceutical companies.

"The results of ACCOMPLISH *may* challenge current diuretic-based guidelines. I don't think this is absolutely clear," Dr. Angela L. Brown said in the panel discussion. "I don't think we really know that yet just from this one trial," said Dr. Brown of Washington University, St. Louis. She has been a consultant, adviser, or lecturer for Novartis, Boehringer Ingelheim, and Forest Laboratories.

The HCTZ dosage used in the ACCOMPLISH trial (12.5-25 mg/day) was lower than were dosages used in placebo-controlled studies that established the antihypertensive benefits of HCTZ, Dr. Cushman noted. Also, if the combined end points of death from cardiovascular causes, nonfatal MI or stroke, resuscitation after sudden cardiac arrest, hospitalization for angina, and coronary revascularization were reconfigured to exclude the angina and revascularization outcomes, there would have been no significant difference between groups in the primary combined outcome, he said.

One could interpret the ACCOMPLISH results to suggest that HCTZ doses of 25 mg/day or less are not as effective in preventing cardiovascular events as are full doses of amlodipine monotherapy or doses of diuretics used in previous trials, suggested Dr. Cushman, who has been a consultant, adviser, or lecturer for Novartis.

Dr. Louis Kuritzky suggested that results might have been different had ACCOMPLISH used the more potent diuretic chlorthalidone instead of HCTZ. In addition, it's unclear whether the results of the trial are generalizable, because the ACCOMPLISH cohort was older and more likely to have diabetes, dyslipidemia, and left ventricular hypertrophy than was the hypertensive population as a whole, said Dr. Kuritzky of the University of Florida, Gainesville.

He has been a consultant or speaker for Novartis and other drug companies but has no association with the company that markets chlorthalidone.

The ACCOMPLISH investigators chose HCTZ because it's the dominant diuretic used for hypertension. Choosing a different diuretic to combine with an ACE inhibitor would not provide the mechanistic synergy of a combined ACE inhibitor and calcium channel blocker that provides an antiatherosclerotic effect, Dr. Jamerson and his associates noted.

"It really does matter what agent you use," he said. ■

Ambulatory Monitoring Supports ACCOMPLISH Results

The initial analysis of ACCOMPLISH results reported mean systolic blood pressures of 131.6/73.3 mm Hg in the benazepril-amlodipine group and 132.5/74.4 mm Hg in the benazepril-HCTZ group using measurements taken predominantly in clinics.

The new analysis by Dr. Jamerson and associates studied 24-hour ambulatory blood pressure monitoring results in a subgroup of 573 patients, to provide a more accurate look at treatment effects on blood pressure.

After 2 years, the treatment groups did not differ significantly in 24-hour mean, daytime, or nighttime blood pressure levels. More than 80% in both groups achieved 24-hour blood pressure control (a mean systolic pressure less than 135 mm Hg over 24 hours). Rates of escape from control, morning surge in blood pressure, or dipping status did not differ significantly between groups, he reported.

Comparing the 288 patients on benazepril-amlodipine and 185 on benazepril-HCTZ, mean systolic pressures in clinic were 129.7 vs. 130.3 mm Hg and mean 24-hour measurements were 123.9 vs. 122.3 mm Hg, respectively. Mean daytime systolic pressures were 125.9 mm Hg vs. 124.1 mm Hg, and nighttime pressures were 118.1 vs. 116.9 mm Hg, respectively.

The proportion with a.m. dipping of systolic pressure comprised 29% of the benazepril-amlodipine group and 32% of the benazepril-HCTZ group, and 24-hour blood pressure control was achieved in 81% and 85%, respectively. Ten percent and 12% of the respective groups had any hourly mean systolic pressure above 160 mm Hg. Nighttime hypertension was seen in 19% on benazepril-amlodipine and 17% on benazepril-HCTZ. An a.m. surge (defined as greater than a 55-mm Hg rise between 6 and 10 a.m. compared with the lowest nighttime hourly mean) occurred in 3% and 4%, respectively.

The benazepril-amlodipine dosing was 20/5 mg once daily for 1 month, then 40/5 mg, followed by 40/10 mg if needed to achieve blood pressure goals. The benazepril-HCTZ group started with 20/12.5 mg once daily for 1 month, then 40/12.5 mg, followed by 40/25 mg if needed.