Diuretics' Role in Hypertension Tx Challenged

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 who 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," said Dr. Cushman, who has been a consultant, adviser, or lecturer for Novartis.

The findings have 'huge implications for the millions of patients who are taking blood pressure medication.'

DR. JAMERSON

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).

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 may have been better in the benazepril-HCTZ group, with a nonsignificant 1.6–mm Hg difference in mean 24-hour systolic pressures, Dr. Jamerson reported at the meeting.

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, he said.

Dr. Jamerson 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 the subanalysis should lead to a change in recommendations. Dr. Bakris has been a consultant, speaker, or adviser for Novartis and other pharmaceutical companies.

'Based on all the data that we have, I would still put diuretics in a very favorable position in any combinations.'

DR. CUSHMAN

"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. ■

Meta-Analyses Spot Best HT Therapies for Stroke Prevention

BY SHERRY BOSCHERT

SAN FRANCISCO — Initial therapy with any antihypertensive medication is significantly better than placebo at preventing stroke, and any antihypertensive except an angiotensin receptor blocker is better than placebo for preventing heart disease, results of new meta-analyses show.

"Don't let patients tell you, 'I just read someplace that this drug is not good at preventing stroke,'" Dr. William J. Elliott said at the annual meeting of the American Society of Hypertension. "All the drugs, in fact, are superior to placebo" in preventing stroke, he said.

For heart disease prevention, angiotensin receptor blockers (ARBs) may have fallen short of superiority to placebo in patients with hypertension for reasons related to statistical power, he hypothesized. "ARBs have not been around as long as some of our more tried-and-true drugs" and thus have had fewer trials as initial hypertensive agents, and fewer people in those trials develop coronary heart disease, said Dr. Elliott, professor of preventive medicine at Rush Medical College, Chicago.

Antihypertensives are superior to placebo in stroke prevention, but ARBs fall short for heart disease prevention.

DR. ELLIOTT

The last major meta-analysis in 2003 of cardiovascular outcomes in hypertension treatment provided the basis for recommendations of low-dose diuretics as first-line antihypertensives to prevent cardiovascular disease in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Since then, at least 25 more trials have been published, with stroke data on 269,180 more subjects and heart disease data on 276,396 more subjects who were included in the current meta-analyses.

Dr. Elliott and his associates conducted two types of meta-analyses on data from all published outcome-based clinical trials with a minimum 1-year follow-up in which all subjects had hypertension and in which a drug was the initial antihypertensive therapy. Results of both the "network" and "Bayesian" meta-analyses were strikingly consistent, he said

For stroke prevention, initial treatment for hypertension with a diuretic was no better than was a calcium channel blocker (CCB) or ARB. All three were slightly but significantly better than a beta-blocker or ACE inhibitor in preventing stroke, Dr. Elliott said. The risk for stroke was 56% higher on placebo than on a diuretic or a CCB. There were 9,351 strokes among subjects in 144 randomized arms in the trials.

Initial treatment with an ACE inhibitor was about 8% more effective than was a diuretic in reducing coronary heart disease events, though the difference was not statistically significant.

The finding is consistent with other suggestions in the literature that ACE inhibitors are better than diuretics at preventing heart disease, Dr. Elliott said.

Calcium channel blockers appeared to be as effective as diuretics for preventing heart disease, and beta-blockers were just behind. Both ARBs and placebos were statistically inferior to ACE inhibitors, diuretics, CCBs, and beta-blockers for preventing heart disease. The risk for coronary heart disease was 26%-28% higher on placebo than on an ACE inhibitor. There were 11,122 coronary heart disease events among subjects in 136 arms in the trials.

Dr. Elliott has been a consultant or speaker for Novartis Pharmaceuticals, Pfizer, Bristol-Myers Squibb/Sanofi-Synthelabo Partnership, and Sanofi-Aventis, some of which market antihypertensive drugs. He also has received royalties from Elsevier, which owns this news organization. ■